NICOLAE TESTEMITANU
STATE UNIVERSITY
OF MEDICINE AND PHARMACY
OF THE REPUBLIC OF MOLDOVA

MJHS Moldovan Journal of Health Sciences

REVISTA DE ȘTIINȚE ALE SĂNĂTĂȚII DIN MOLDOVA

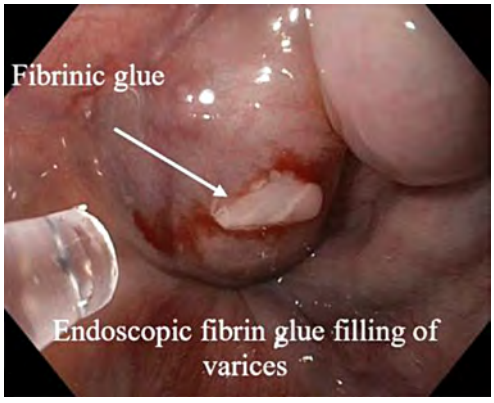
Vol. 11
Issue 3,
September 2024

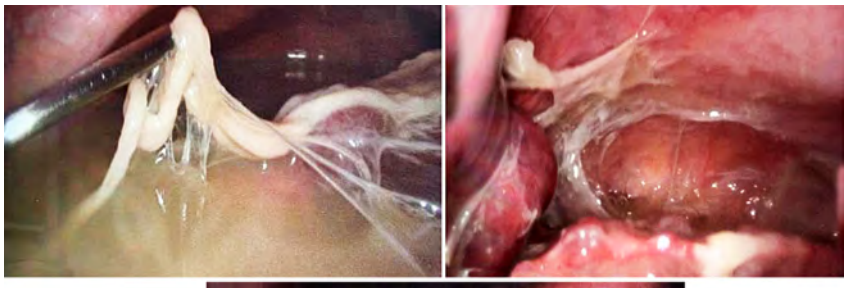
Category B

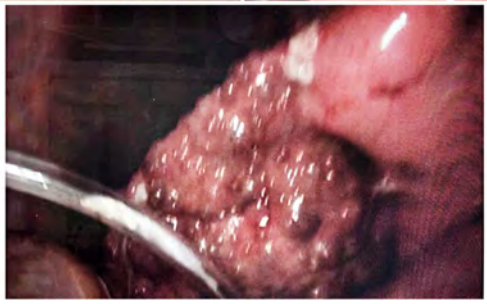
CONTENT HIGHLIGHTS:

Gheorghe Anghelici, Tatiana Zugrav, Sergiu Pisarenco, Oleg Crudu, Gheorghe Lupu, Ana Apascaritei

Laparoscopic peritoneal lavage – a new treatment strategy in spontaneous bacterial peritonitis and liver cirrhosis







9 772345 146002

ISSN 2345-1467

AIRTAL®

aceclofenac

DUREREA SUB CONTROL TOTAL!

RAPID

UȘOR

DE DURATĂ

DENUMIREA COMERCIALĂ A MEDICAMENTULUI: AIRTAL 100 mg comprimate filmate. **COMPOZIȚIA CALITATIVĂ ȘI CANTITATIVĂ:** Fiecare comprimat filmat conține aceclofenac 100 mg. **FORMA FARMACEUTICĂ:** Comprimate filmate. **INDICAȚII TERAPEUTICE:** În caz de osteoartrită, artrita reumatoidă și spondilita anchilozantă, precum și alte sindroame dureroase ale aparatului locomotor (de exemplu, periartrita scapulo-humerală și reumatism extraarticular). Pentru tratamentul stărilor dureroase (inclusiv dureri lombare sau dentare și dismenoree primară). **DOZE ȘI MOD DE ADMINISTRARE:** AIRTAL 100 mg comprimate filmate se administrează pe cale orală și trebuie înghițite cu o cantitate suficientă de lichid. Airtal 100 mg comprimate filmate pot fi administrate în timpul meselor. Adulți: Doza maximă recomandată este de 200 mg pe zi, administrată în două prize separate de 100 mg (un comprimat dimineața și unul seara). **CONTRAINDICAȚII:** Aceclofenacul este contraindicat în următoarele situații: Hipersensibilitate la substanța activă sau la oricare dintre excipienți; La pacienții la care administrarea substanțelor cu acțiune similară (de exemplu, acid acetilsalicilic sau alte AINS) precipită crizele de astm bronșic, bronhospasmul, rinita acută sau urticaria sau hipersensibilitate la aceste substanțe; Pacienți cu antecedente de sângerare sau perforație gastrointestinală legate de tratamentul anterior cu AINS. Ulcer peptic/hemoragie active sau recidivante în antecedente (două sau mai multe episoade distincte de ulcerație sau sângerare dovedită); Pacienți cu sângerare activă sau tulburări de sângerare sau tulburări de coagulare (hemofilie); Pacienți cu insuficiență cardiacă congestivă diagnosticată (clasa II-IV NYHA), boală cardiacă ischemică, arteriopatie periferică și/sau boală cerebrovasculară; Pacienți cu deteriorare severă a funcției hepatice sau renale; Sarcină, în special în al treilea trimestru de sarcină, doar dacă sunt motive care să impună acest lucru. **ATENȚIONĂRI ȘI PRECAUȚII SPECIALE:** Utilizarea Airtal concomitent cu alte AINS, inclusiv inhibitorii selectivi de ciclooxigenază-2, trebuie evitată. Reacțiile adverse pot fi reduse la minimum prin utilizarea celei mai mici doze eficace pentru cea mai scurtă perioadă necesară controlării simptomelor. Riscul de sângerare gastrointestinală, ulcerație sau perforație este mai mare la creșterea dozelor de AINS la pacienții cu antecedente de ulcer, în special cei complicați cu hemoragie sau perforație. La pacienții cu antecedente de hipertensiune arterială și/sau insuficiență cardiacă congestivă ușoară până la moderată, sunt necesare monitorizare și recomandări adecvate, deoarece au fost raportate retenție lichidiană și edem în legătură cu tratamentul cu AINS. **REACȚII ADVERSE:** Tulburări gastrointestinale: reacțiile adverse cel mai frecvent observate sunt cele de natură gastrointestinală. Ulcere peptice, perforație sau sângerare GI uneori fatală, mai ales la vârstnici, pot apărea în utilizarea AINS. Pe parcursul administrării de AINS, au fost raportate grețuri, vărsături, diaree, flatulență, constipație, dispepsie, durere abdominală, melenă, hematemeză, stomatită ulcerativă, exacerbare a colitei și boală Crohn. A fost observată mai puțin frecvent gastrita. Reacțiile adverse raportate în asociere cu tratamentul cu AINS au fost edemul, hipertensiunea arterială și insuficiența cardiac. Alte reacții adverse raportate legate de administrarea AINS sunt: Foarte rare (<1/10.000): Tulburări renale și ale căilor urinare: nefrită interstițială. Afecțiuni cutanate și ale țesutului cutanat: reacții buloase, inclusiv sindromul Stevens-Johnson și necroliza epidermică toxică. Clasificare: Grupul II: Acest medicament se eliberează pe bază de prescripție medicală. **DEȚINĂTORUL CERTIFICATULUI DE ÎNREGISTRARE:** Gedeon Richter Plc. Gyömrői út 19-21. 1103 Budapest, Ungaria. **NUMĂRUL CERTIFICATULUI DE ÎNREGISTRARE:** 25086. **DATA AUTORIZĂRII:** 29.10.2018. **DATA REVIZUIRII TEXTULUI:** August 2021. ***Acest material publicitar este destinat persoanelor calificate să prescrie, să distribuie și/sau să elibereze medicamente. Pentru informații complete vă rugăm să consultați rezumatul caracteristicilor produsului. Informații detaliate privind acest medicament sunt disponibile pe site-ul Agenției http://nomenclator.amdm.gov.md/***

DENUMIREA COMERCIALĂ A MEDICAMENTULUI: AIRTAL 15 mg/g cremă. COMPOZIȚIA CALITATIVĂ ȘI CANTITATIVĂ: Un gram de cremă conține aceclofenac 15 mg. **FORMA FARMACEUTICĂ:** Cremă albă. **INDICAȚII TERAPEUTICE:** Tratamentul local al tuturor tipurilor de dureri și inflamații cu diferite cauze locomotorii, incluzând leziuni traumatice. Medicamentul poate fi utilizat pentru ameliorarea inflamațiilor tendoanelor, ligamentelor, mușchilor și articulațiilor, în cazul luxațiilor, entorselor sau contuziei, precum și în tratamentul lumbago, torticolisului și periartritei. **DOZE ȘI MOD DE ADMINISTRARE:** Airtal cremă trebuie aplicat de trei ori pe zi, prin masare ușoară pe zona afectată. Doza aplicată depinde de dimensiunea zonei afectate: 1,5-2g Airtal cremă (aproximativ 5-7 cm). Atenționați pacienții că durata tratamentului fără prescripție medicală în cazul leziunilor musculare și articulare (luxații, entorse, contuzii) și în cazul tendinitelor nu trebuie să depășească 2 săptămâni. Tratamentul fără prescripție medicală în cazul artritei poate fi continuat pentru o perioadă de până la 3 săptămâni. Dacă simptomele se agravează sau nu se ameliorează după 7 zile, pacientul trebuie să se adreseze unui medic pentru o evaluare mai detaliată. Administrare cutanată: Acest medicament este destinat exclusiv uzului extern și nu trebuie utilizat în bandaje ocluzive. După aplicare este necesară spălarea mâinilor, cu excepția cazului când zona tratată este la nivelul mâinilor. Trebuie manifestată prudență astfel încât crema să nu intre în ochi sau în gură. Airtal cremă trebuie utilizat doar pe piele intactă. **CONTRAINDICAȚII:** Hipersensibilitate la substanța activă sau la oricare dintre excipienți. Nu trebuie administrat la pacienții care au prezentat hipersensibilitate la alte AINS. Deși nu a fost stabilită posibila hipersensibilitate încrucișată cu diclofenacul, nu se recomandă aplicarea la acei pacienți care au prezentat hipersensibilitate la diclofenac. Similar altor medicamente antiinflamatoare, aceclofenacul este contraindicat la pacienții la care acidul acetilsalicilic sau alte medicamente antiinflamatoare nesteroidiene produc crize de astm bronșic, urticarie sau rinită acută. **ATENȚIONĂRI ȘI PRECAUȚII SPECIALE:** Dacă utilizarea Airtal cremă produce simptome de iritație locală, administrarea trebuie întreruptă și trebuie inițiat un tratament corespunzător. Nu trebuie utilizat pentru tratamentul plăgilor deschise, mucoaselor sau a pielii iritate (cu eczeme) sau în situații în care zona de aplicare cuprinde orice altă afecțiune cutanată. Trebuie evitată expunerea fără protecție a zonei tratate la radiații solare puternice, pentru a preveni reacțiile de fotosensibilitate. **REACȚII ADVERSE:** Airtal cremă a demonstrat o toleranță locală bună. În anumite cazuri au fost observate iritații locale ușoare sau moderate, însoțite de înroșire a pielii și prurit, aceste simptome dispărând odată cu întreruperea tratamentului. În mod excepțional, în cazul varicelei a fost raportată apariția de complicații infecțioase grave la nivelul pielii și țesuturilor moi în legătură cu utilizarea AINS. Au fost raportări ocazionale de reacții de fotosensibilitate (≥1/1.000 și <1/100) atunci când zona de piele tratată a fost expusă fără protecție adecvată la radiații solare puternice. **DEȚINĂTORUL CERTIFICATULUI DE ÎNREGISTRARE:** Gedeon Richter Plc., Gyömrői út 19-21. 1103 Budapest, Ungaria. **NUMĂRUL CERTIFICATULUI DE ÎNREGISTRARE:** 27870 din 27.05.2022. **DATA REVIZUIRII TEXTULUI**: Mai 2022. **STATUT LEGAL:** Se eliberează fără prescripția medicului. ***Acest material publicitar este destinat persoanelor calificate să prescrie, să distribuie și/sau să elibereze medicamente. Pentru informații complete vă rugăm să consultați rezumatul caracteristicilor produsului. Informații detaliate privind acest medicament sunt disponibile pe site-ul Agenției http://nomenclator.amdm.gov.md/***

Reprezentanța în Republica Moldova, Chișinău, str. A. Puşkin, 47/1, bl. A, of.1;
Tel./Fax: 22-14-49; 22-26-71; www.gedeonrichter.md

GEDEON RICHTER

MJHS
Moldovan Journal of Health Sciences
Revista de Ştiinţe ale Sănătăţii din Moldova
2024;11(3)

CONTENT

RESEARCH ARTICLES

3 **Gheorghe Anghelici, Tatiana Zugrav, Sergiu Pisarenco, Oleg Crudu, Gheorghe Lupu, Ana Apascaritei**
Laparoscopic peritoneal lavage – a new treatment strategy in spontaneous bacterial peritonitis and liver cirrhosis

10 **Rodica Scutelnic, Larisa Spinei**
Childbirth at advanced reproductive age: the impact of biopsychosocial factors on the mode of delivery

22 **Nadejda Codreanu, Elena Ivanova**
Deep endometriosis – impact on infertility, endometriosis fertility index, and reproductive prognosis (comparative study)

27 **Natalia Belîi, Cătălina Lozan**
Postoperative urinary retention - prevalence and risk factors: prospective, cohort study

34 **Natalia Cernei, Serghei Şandru, Serghei Cobîleţchi, Ivan Cîvîrjîc, Ion Chesov, Ruslan Baltaga**
The impact of ozone therapy on the progression of COVID-19 patients

42 **Victoria Seu, Oxana Malîga**
Comparative analysis of imaging data in sensory and motor disorders in lumbar neurocompressive syndrome

48 **Mariana Ceban, Victor Ceban, Vitalie Pântea**
Temporary splinting in periodontally mobile teeth: review before application

REVIEW ARTICLES

54 **Cristina Şcerbatiuc**
Management of diabetic retinopathy in pregnancy

CASE STUDIES

59 **Vera Chirca, Serghei Popa, Svetlana Agachi, Lucia Dutca, Valeriu Corotaş**
Acute autoimmune hemolytic anemia in a patient with systemic lupus erythematosus

Moldovan Journal of Health Sciences
Revista de Ştiinţe ale Sănătăţii din Moldova

Ediţie în limba engleză

Fondator:
Instituţia Publică Universitatea de Stat de Medicină şi Farmacie „Nicolae Testemiţanu" din Republica Moldova

Redactor-şef:
Serghei Popa, dr. şt. med. conferenţiar universitar.

Colectivul redacţiei:
Dorian Sasu, redactor stilist
Sergiu Iacob, redactor stilist
Ana Orlic, redactor stilist
Irina Gangan, redactor

Adresa redacţiei:
biroul 303, blocul Administrativ, Universitatea de Stat de Medicină şi Farmacie „Nicolae Testemiţanu" bd. Ştefan cel Mare şi Sfânt, 165, Chişinău, Republica Moldova, MD-2004

Editat: Editura „Lexon-Prim"
Tiraj: 200 ex.

Înregistrată la Ministerul Justiţiei al Republicii Moldova (nr. 250 din 01.08.2014).

Categoria B acordată de Agenţia Naţională de Asigurare a Calităţii în Educaţie şi Cercetare (decizia nr. 2 din 04.11.2022)

English edition

Founder:
Public Institution *Nicolae Testemitanu* State University of Medicine and Pharmacy from Republic of Moldova

Editor-in-chief:
Serghei Popa, PhD.
university associate professor.

Editorial staff:
Dorian Sasu, editor
Sergiu Iacob, editor
Ana Orlic, editor
Irina Gangan, editor

Address of Editorial Office:
office 303; Administrative building, *Nicolae Testemitanu* State University of Medicine and Pharmacy
165, Ştefan cel Mare şi Sfânt blvd., Chisinau, Republic of Moldova, MD-2004

Editorial board

https://doi.org/10.52645/MJHS.2024.3.01

UDC: [616.381-002-022+616.36-004]-089.48-072.2

RESEARCH ARTICLE

Laparoscopic peritoneal lavage – a new treatment strategy in spontaneous bacterial peritonitis and liver cirrhosis

Gheorghe Anghelici[1,2], Tatiana Zugrav[1,2*], Sergiu Pisarenco[1], Oleg Crudu[2], Gheorghe Lupu[2], Ana Apascaritei[1]

[1]Surgery Department No.2, *Nicolae Testemițanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova
[2]Department of General Surgery No.2, *Holy Trinity* Clinical Municipal Hospital, Chisinau, Republic of Moldova

ABSTRACT

Introduction. Bacterial infections in cirrhotic patients represent a major clinical problem, occuring 4-5 times more frequently compared to the general population and increasing mortality by leading to acute on chronic liver failure, subsequent decompensation, and multiorgan failure. The study's purpose is to determine the possibilities of laparoscopy in the treatment of spontaneous bacterial peritonitis with decompensated liver cirrhosis.

Materials and methods. A retrospective descriptive study was conducted on 82 patients diagnosed with liver cirrhosis and spontaneous bacterial peritonitis, who were admitted to the *Constantin Tibirna* Surgery department No2, *Holy Trinity* Municipal Clinical Hospital and the Scientific Research Laboratory of Hepatic Surgery, *Nicolae Testemițanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova, between January 2012 and December 2021. Patients who underwent surgical drainage of the abdominal cavity by laparoscopy with postoperative peritoneal lavage with antibiotics were selected. All patients received standard treatment for the correction of liver function and complications of portal hypertension. The data were extracted from the medical records of the hospital archive, and the patient database was compiled. Data analysis was performed using simple statistical calculations.

Results. Positive ascitic fluid bacterial culture was in 29.2% (24 patients), while 70.7% (58 patients) had culture-negative ascites and peritonitis. The most frequent bacterial species was E. coli, present in 54.1% (13 patients). Mortality was 8.5% (7 patients) due to progressive liver failure. Recurrence of ascites and peritonitis at 1 month was 6.0% (5 patients).

Conclusions. The laparoscopic approach in spontaneous bacterial peritonitis in patients with decompensated liver cirrhosis allows for better sanitation of the abdominal cavity, improves peritoneal absorption, and deserves establishment as clinical practice for patients with ascites and peritonitis and cirrhosis.

Keywords: cirrhosis, laparoscopy, spontaneous bacterial peritonitis.

Cite this article: Anghelici G, Zugrav T, Pisarenco S, Crudu O, Lupu G, Apascaritei A. Laparoscopic peritoneal lavage – a new treatment strategy in spontaneous bacterial peritonitis and liver cirrhosis. Mold J Health Sci. 2024;11(3):3-9. https://doi.org/10.52645/MJHS.2024.3.01.

Manuscript received: 31.05.2024

Accepted for publication: 05.09.2024

Published: 20.09.2024

***Corresponding author:** Tatiana Zugrav, MD, PhD fellow,
Surgery Department No.2,
Nicolae Testemițanu State University of Medicine and Pharmacy,
165, Stefan cel Mare si Sfant blvd., Chisinau, Republic of Moldova, MD2004,
e-mail: zugravtatiana@yahoo.com

Authors' ORCID IDs
Gheorghe Anghelici – https://orcid.org/0009-0003-1063-2802
Tatiana Zugrav – https://orcid.org/0000-0002-5205-5471
Sergiu Pisarenco – https://orcid.org/0009-0003-6516-1630
Oleg Crudu – https://orcid.org/0009-0003-8616-7222
Gheorghe Lupu – https://orcid.org/0009-0004-0901-0341
Ana Apascaritei – https://orcid.org/0009-0007-3666-6794

Key messages

What is not yet known on the issue addressed in the submitted manuscript

The diagnosis of spontaneous bacterial peritonitis in patients with liver cirrhosis is based on standard analyzes of the ascitic fluid for bacterial flora and the number of PMN cells. However, many questions remain unanswered, leading to delayed diagnosis of ascites and peritonitis and late initiation of treatment, which increases the mortality rate to up to 90% in undiagnosed patients.

The research hypothesis

The laparoscopic approach as surgical treatment for spontaneous bacterial peritonitis in patients with decompensated liver cirrhosis should lead to good sanitation of the peritoneal cavity and improve peritoneal absorption.

The novelty added by manuscript to the already published scientific literature
Conservative treatment of ascites and peritonitis with combined antibiotic therapy and evacuation laparocentesis is currently the only approach for these patients. This manuscript shows that laparoscopy is a safe and optimal treatment for spontaneous bacterial peritonitis by increasing parietal peritoneum absorption.

Introduction

Worldwide, 844 million people suffer from chronic liver disease, with a mortality rate of two million deaths per year, including one million deaths from complications of cirrhosis. According to the National Bureau of Statistics in the Republic of Moldova, over 10000 patients with liver cirrhosis were registered in 2019, and 8962 in 2021 [1]. The main causative factors of liver cirrhosis are hepatitis B and C viruses, followed by non-viral causes, excessive alcohol consumption, and lipid dystrophy of the liver. As liver cirrhosis is often asymptomatic until decompensation occurs, many patients remain undiagnosed until complications arise. The main complications include ascites, spontaneous bacterial peritonitis (SBP), digestive bleeding from esophagogastric varices, and hepatic encephalopathy [2].

Bacterial infections in cirrhotic patients represent a major clinical problem, occurring 4-5 times more frequently compared to the general population. These infections can increase mortality by leading to acute-on-chronic liver failure, subsequent decompensation, and multiorgan failure. Sudden-onset spontaneous bacterial infections without an obvious source are specific to patients with decompensated liver cirrhosis and include spontaneous bacterial peritonitis, spontaneous bacteremia, and spontaneous bacterial empyema (infected hepatic hydrothorax). Despite advances in intensive care and prophylactic antibiotic usage, SBP remains the most common and significant bacterial infection in cirrhotic patients with ascites due to its considerable morbidity and mortality [3]. Spontaneous bacterial ascitic peritonitis occurs in 9% of hospitalized patients with liver cirrhosis and ascites and accounts for 25% of all infections in patients with liver cirrhosis [4]. Mortality due to untreated spontaneous bacterial peritonitis can reach up to 90% in patients with decompensated hepatic cirrhosis, but it decreases significantly, by up to 20%, with early diagnosis and prompt initiation of treatment [5].

In this article, the early initiation of treatment will be discussed using a patented procedure developed at the Scientific Research Laboratory of Hepatic Surgery, *Nicolae Testemițanu* State University of Medicine and Pharmacy for patients with cirrhosis.

The aim of the research is to determine the possibilities of laparoscopy with sanitation and drainage of the abdominal cavity, combined with postoperative peritoneal lavage with antibiotics, in the treatment of spontaneous ascitic peritonitis in patients with decompensated liver cirrhosis.

Materials and methods

We conducted a retrospective descriptive study on patients admitted with decompensated liver cirrhosis and ascites, and peritonitis between January 2012 and December 2021. Patients who underwent surgical drainage of the abdominal cavity by laparoscopy with postoperative peritoneal lavage with antibiotics were selected. The patients were treated at the *Constantin Tibirna* Surgery Department No.2, *Holy Trinity* Municipal Clinical Hospital, and the Scientific Research Laboratory of Hepatic Surgery, *Nicolae Testemițanu* State University of Medicine and Pharmacy. The data were extracted from the medical records of the hospital archive, and a patient database was compiled. Data analysis was performed using simple statistical calculations.

The study consists of analyzing the role of laparoscopic sanitation of the abdominal cavity in patients with liver cirrhosis and spontaneous bacterial ascites. The study was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy - Minutes no. 15 from 28.02.2022. The project was funded by the National Agency for Research and Development of the Republic of Moldova and conducted at a large tertiary medical center – the *Holy Trinity* Municipal Clinical Hospital. Patients with non-cirrhotic ascites were not considered for evaluation.

All patients underwent a diagnostic algorithm consisting of:

- Chest radiography to evaluate pleuritis.
- *Esophagogastroduodenoscopy* to prevent possible bleeding. Preoperative endoscopic fibrin glue filling of the esophageal and gastric varices was performed on 49 patients (60%) (Figure 1).
- Laboratory analysis of ascitic fluid, including ascitic neutrophil count and ascitic fluid culture.
- General analysis of urine and blood.
- Ultrasonography of the abdomen and pelvis.
- The diagnosis of SBP was based on criteria recommended by the International Ascites Club and published in 2000 [6].

Preoperative management

All patients received thorough preoperative preparation, including evaluation and correction of hepatic status, thoracocentesis, and dosed preoperative microlaparocentesis (Figure 2), with perfusion of albumin to avoid post-paracentesis circulatory dysfunction and to reduce acute hepatic failure.

Dosed microlaparocentesis consisted of abdominal cavity puncture on the abdominal flank with a 14G vein cannula under local anesthesia with 2% lidocaine solution (2 ml) to

evacuate ascitic fluid through the perfusion drainage system in a dosed manner. This avoids circulatory dysfunction post-paracentesis. During the same session, albumin (6-8 g/l), hepatoprotective drugs, and prokinetic drugs were administered according to the national protocol for ascites in cirrhotic patients [7].

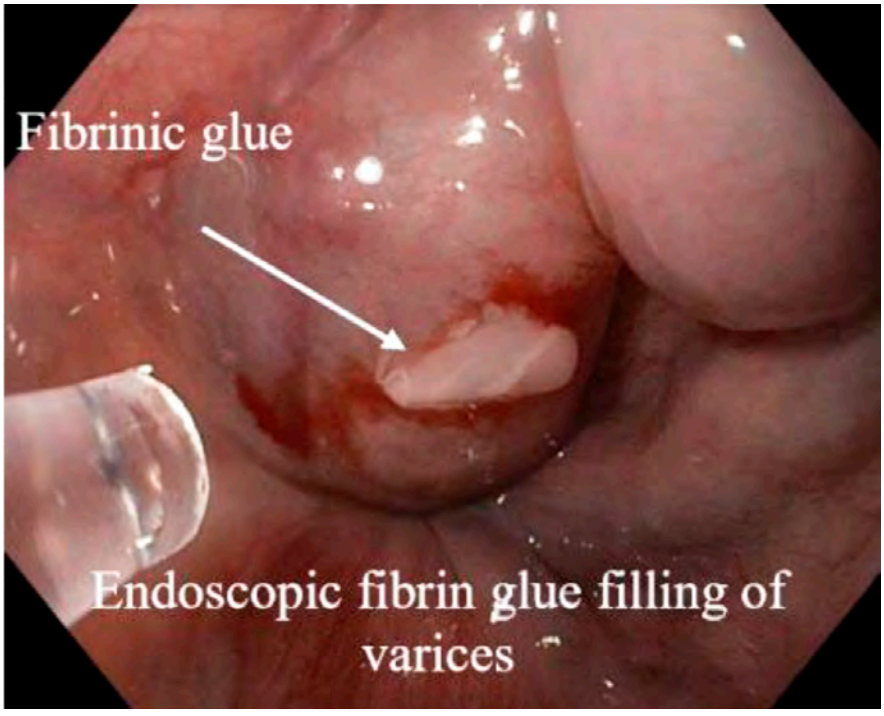


Fig. 1 Preoperative management of patients with decompensated liver cirrhosis and ascites complicated by spontaneous bacterial peritonitis – preoperative endoscopic fibrin glue filling of the esophageal and gastric varices.

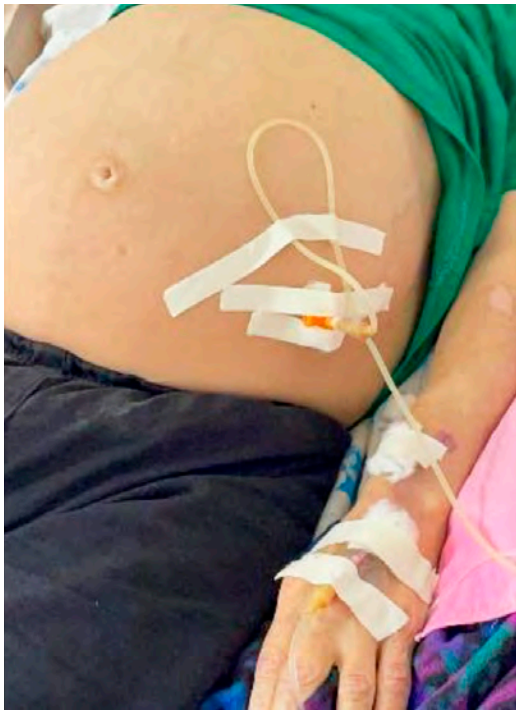


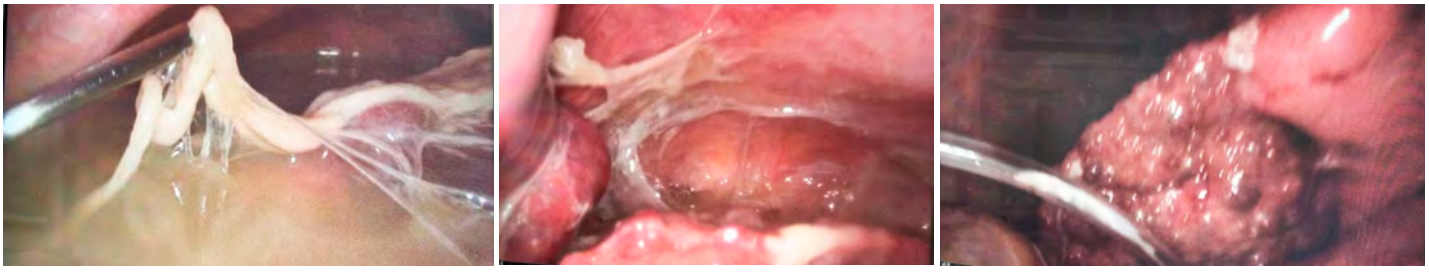
Fig. 2 Preoperative management of patients with decompensated liver cirrhosis and ascites complicated by spontaneous bacterial peritonitis – dosed microlaparocentesis with a 14G venous catheter.

Minimally invasive surgical treatment of SPB

The minimally invasive surgical treatment of patients with cirrhosis and SPB includes two stages:

1. Laparoscopic complete evacuation of ascitic fluid with peritoneal lavage and drainage of the abdominal cavity.
2. Under general anesthesia, the first, optical, trocar was placed through the umbilical site. The working trocar, 5 mm in size, was placed on the right flank. Through the working trocar, the entire abdominal cavity was reviewed, and all the ascitic fluid from all spaces was evacuated, allowing for the inspection of abdominal organs (Figure 3).

The next step is to debride all fibrinous smudges and adhesions from the intraperitoneal cavity (Figure 3A) and the parietal peritoneum and diaphragm (Figure 3B). Then, lavage is carried out with 1.0–2.0 L of saline, which is completely aspirated. A mixture containing hyaluronidase (640-1080 CU) dissolved in 200-400 ml of saline and ceftriaxone (2-4 g) is then introduced simultaneously. Drainage tubes are placed in the Douglas pouch and right subdiaphragmatic space (Figure 3C).



A **B** **C**

Fig. 3 Laparoscopic sanitation and drainage of the peritoneal cavity in a patient with decompensated liver cirrhosis and spontaneous bacterial peritonitis.
A. and B. – Fibrin debridement and sanitation of the peritoneum; C – Drainage placement in the abdominal cavity.

Post-operative irrigation of the abdominal cavity

In the postoperative period, third-generation cephalosporins and ciprofloxacin, along with the hyaluronidase enzyme and 2-3 L of saline solution, were introduced daily through the drainage tubes and removed after several hours. This procedure, called post-operative irrigation of the abdominal cavity, was performed daily for 5 days.

Postoperative lavage of the peritoneal cavity removes residual fibrin and infections, decreases peritoneal edema, and improves its absorbent properties.

82 patients with decompensated liver cirrhosis and ascites for more than one month prior, and SBP indicated by an ascitic neutrophil count >250 cells/mm^3 in the absence of an intra-abdominal and surgically treatable source of sepsis were analyzed. These patients underwent diagnostic-therapeutic laparoscopy with sanitation and drainage of the abdominal cavity, followed by postoperative lavage and antibiotics.

Inclusion criteria: decompensated liver cirrhosis with ascites for more than one month prior; SBP indicated by an ascitic neutrophil count >250 cells/mm^3 or patients with positive bacteriological examination of ascitic fluid.

Exclusion criteria: absence of any other sources of infections, such as pneumonia, renal infections, surgical treated source of intrabdominal infections; encephalopathy; any states that serves as contraindication for pneumoperitoneum; patients with non-cirrhotic ascites; pleuritis; patients with pneumonia.

Results

Patients' characteristics are shown in Table 1. The mean MELD (Model for End-Stage Liver Disease) score in this group was 21. Most of the patients had liver cirrhosis of viral etiology, primarily of HCV origin (Figure 4).

Table 1. Demographic and clinical data

No.	82
Gender Male Female	 49 (60 %) 33 (40 %)
Age	53.9 (range, 28 – 71)
Child-Pugh Class C	82 (100%)
MELD score	21 (9-31)
Serum bilirubin (mg/dL)	40 (26-38)
Serum albumin (g/dL)	20 (14-24)
Prothrombin time (%)	58 (40-65)
Serum creatinine (mg/dL)	93 (70-120)
Prophylactic endoscopic sealing of eso-gastric varices	49 (60 %)
Time of diagnosis establishment from admission to hospital	72 h
Time of onset of ascites	15 months
Recent evacuation laparocentesis, 1 month	9

Following the analysis of the patient group, it was observed that patients with liver cirrhosis and decompensated ascites who were diagnosed with SBP through the analysis of ascitic fluid by diagnostic laparocentesis did not present a specific clinical picture, nor did they have significant complaints. A classic clinical picture that would clearly indicate a diagnosis of SBP was present in only 24 patients, specifically those with bacteriascites. Most patients exhibited general symptoms, such as general asthenia and intestinal motility disorders. Some patients had nonspecific abdominal symptoms, such as mild abdominal pain, constipation, or frequent semi-formed stools, and only 10 out of 82 patients with spontaneous bacterial peritonitis experienced abdominal pain with signs of peritonism (Table 2).

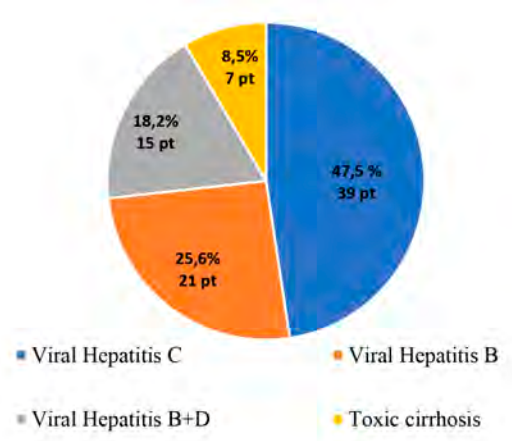


Fig. 4 Major etiological factors of liver cirrhosis.

Table 2. Symptoms and signs of spontaneous bacterial peritonitis and its variants

Symptoms and signs	SBP 82 pt (100%)	Bacteriascites 24 pt (29.2%)	CNNA 58 pt (70.7%)
Abdominal pain	14 (17 %)	12 (85.7)	2 (14.2)
Abdominal tenderness	46 (56 %)	24 (52.1)	22 (47.8)
Rebound	10 (19 %)	7 (70%)	3 (30%)
Nausea	34 (41.4%)	20 (58.8)	14 (41.1)
Fatigue	67 (81.7 %)	24 (35.8)	43 (64.1)
Vomiting	17 (20.7 %)	9 (52.9)	8 (47.0)
Fever	9 (10.9 %)	7 (77.7)	2 (22.2)
Diarrhea	21 (25.6 %)	8 (38.0)	13 (61.9)
Constipation	38 (46.3 %)	30 (78.9)	8 (21.0)
Signs of dynamic ileus	3 (3.6 %)	3	0
Encephalopathy	21 (25.6 %)	18 (85.7)	3 (14.2)
Upper digestive bleeding	17 (20.7 %)	14 (82.3)	3 (17.6)

Note: *SBP - Spontaneous Bacterial Peritonitis; CNNA – Culture-Negative Neutrocytic Ascites.*

The volume of ascitic fluid withdrawn per paracentesis ranged from 8 to 16 L. The ascitic protein content was 14 g/L, and the mean neutrophil count was 290 cells/mm^3. Positive ascitic fluid bacterial culture was detected in 29.2% of patients (24 patients), while 70.7% (58 patients) had culture-negative neutrocytic spontaneous bacterial peritonitis. Ascitic fluid characteristics are shown in Table 3. The variants of SBP in our study population are shown in Figure 4.

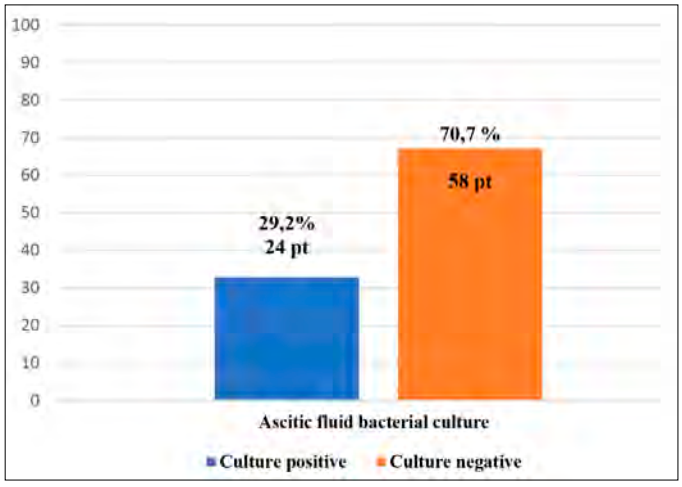


Fig. 4 Positive ascitic fluid bacterial culture was detected in 29.2% of patients (24 patients); 70.7 % (58 patients) had culture-negative spontaneous bacterial peritonitis.

Table 3. Ascitic fluid characteristics.

Average volume of ascitic fluid withdrawn per paracentesis (L) (range)	11 (8-16)
Neutrophil count/ mm^3 (range)	29 0 (180-350)
Total cell count/ mm^3 (range)	370 (280-580)
Protein content (g/L)	14 (5-47)
LDH, U/L	63 (45-90)

Note: *LDH – Lactate Dehydrogenase.*

Based on the bacteriological evaluation, the most frequent bacterial species was E. coli, found in 54.1% of patients (13 patients). No cases of anaerobic infection were registered.

Table 4. Bacterial species detected in ascitic fluid

Microbial agents in ascitic fluid simple	No. of patients (%)
Escherichia coli	13 (54.1)
Staphylococcus aureus	4 (16.6)
Streptococcus haemolyticus	3 (12.5)
Klebsiella pneumoniae	2 (8.3)
Staphylococcus epidermidis	2 (8.3)

In the early postoperative period, patients subjectively reported an improvement in their general condition and did not present complications related to the surgery. Mortality at 1 month was 8.5% (7 patients) due to progressive liver failure. Readmissions for SBP at 1 month were 6% (5 patients).

Discussion

The current theory of the pathogenesis of SBP in patients with cirrhosis and ascites suggests that repeated episodes of bacterial translocation from the intestinal lumen to the mesenteric lymph nodes lead to systemic bacterial inoculation, representing key steps in the development of SBP. However, most episodes of systemic bacteremia remain undetected [8].

Patients with SBP may present with intestinal ileus, fever, diffuse abdominal pain, and a palpable abdomen with diffuse, unclear peritoneal signs. However, up to one-third of patients with spontaneous peritoneal infections may be completely asymptomatic or present with only encephalopathy and/or acute renal failure [9, 10]. The diagnosis of SBP is established by performing laparocentesis on admission, which reveals an absolute neutrophil count in the ascitic fluid greater than 250/mm^3 [11]. Ascites itself is not fatal unless it becomes infected (spontaneous bacterial peritonitis). The infection, in turn, often precipitates hepatorenal syndrome, increases the risk of bleeding from esophageal varices, and, if left untreated, can lead to death [12].

Intestinal permeability dysfunction in patients with decompensated liver cirrhosis is the primary event triggering spontaneous bacterial peritonitis. The passage of infection into the ascitic fluid initiates an inflammatory process, manifested by an increase in the number of neutrophils [2, 13].

According to the 2021 Practice Guideline of the American Association for the Study of Liver Diseases (AASLD), diagnostic laparocentesis should be performed in all patients with ascitic syndrome, even if they do not present obvious clinical signs of infection [14]. The diagnosis of spontaneous bacterial peritonitis in patients with liver cirrhosis and ascites is established based on both the general and bacteriological examination of the ascitic fluid [15].

The bacteriological examination of the ascitic fluid is performed before the initiation of empirical antibacterial therapy [15]. At the patient's bedside, at least 10 ml of ascitic fluid is collected and inoculated into a blood culture test tube, with evaluation done for both aerobic and anaerobic germs. At the same time, the patient's venous blood is collected for blood culture examination. The simultaneous collection of blood and ascitic fluid samples during the bacteriological examination increases the sensitivity of the method for detecting the microorganism involved in triggering SBP by 90% [16].

According to literature data, spontaneous bacterial peritonitis is typically a mono-bacterial infection, most frequently caused by gram-negative bacteria (in 60% of cases). The causative agent is usually specific to the intestinal flora, with Escherichia coli being the most common, followed by Klebsiella pneumoniae, Staphylococcus aureus, Enterococcus faecalis, and Enterococcus faecium [17]. However, there has been a recent increase in cases of SBP caused by gram-positive bacteria, including multidrug-resistant and quinolone-resistant strains. Gram-positive germs involved are Streptococcus spp., Enterococcus spp., and Staphylococcus spp. [18, 19].

Laparocentesis performed more than 48 hours after hospitalization, with the detection of SBP, is considered a nosocomial infection; multidrug-resistant bacteria are most frequently detected. Patients with decompensated liver cirrhosis, due to frequent hospitalizations and repeated exposure to invasive procedures and antibiotic administration,

either for treatment or prophylaxis, often develop infections caused by multidrug-resistant bacteria, accounting for 35% of all infections [19].

With the initiation of antibacterial therapy and the prophylaxis of primary and recurrent SBP using norfloxacin, the detection of quinolone-resistant organisms in ascitic fluid has been increasingly reported, being attributed to nosocomial SBP [20].

Despite the use of high-sensitivity methods for detecting microorganisms in ascitic fluid, bacterial culture remains negative in up to 60% of cases of SBP confirmed by laparocentesis with neutrophils ≥250 cm^3 [6].

According to the bacteriological result of the ascitic fluid and the presence of neutrophils we can differentiate:

- spontaneous bacterial peritonitis (classic) - neutrophils in the ascitic fluid are ≥250/cm^3 and the bacteriological examination is positive, which could be mono-bacterial or poly-bacterial.
- neutrophilic spontaneous peritonitis, culture-negative – neutrophils in the ascitic fluid are ≥ 250/cm^3, and the bacteriological examination is negative.
- spontaneous bacterial peritonitis, or bacteriascites - neutrophils in the ascitic fluid are ≤ 250/mm^3 and the bacterial culture of the ascitic fluid is positive [21].

In the group of patients investigated, the analysis of the protein level in the ascitic fluid showed that, in most cases, the protein level averaged 14 g/L. Runyon demonstrated that cirrhotic patients with protein levels in the ascitic fluid below 1 g/dL are 10 times more likely to develop SBP [22]. Thus, the antibacterial and opsonic activity of ascitic fluid is closely correlated with the protein concentration. Studies have confirmed that the ascetic fluid protein concentration is an essential predictor of the first episode of SBP [23, 24]. However, there were patients with a positive ascitic fluid culture confirming the diagnosis of SBP, but with high protein levels detected in the ascitic fluid, up to 47 g/L. These patients also presented with large fibrin deposits at laparoscopy.

Bacterial infection in patients with liver cirrhosis is the most frequent trigger of acute-on-chronic liver failure [25]. Acute-on-chronic liver failure in cirrhosis is a syndrome characterized by acute decompensation, organ failure, and high mortality [25, 26]. In the analyzed study group, mortality at 1 month was 8.5% (7 patients) due to progressive liver failure. Bacterial infections, especially spontaneous bacterial peritonitis, are a major problem and a significant prognostic factor in patients with acute-on-chronic liver failure [25, 26].

Conclusion

Spontaneous bacterial peritonitis has multiple variants and can be misdiagnosed due to the lack of specific signs and symptoms. In patients with ascites and cirrhosis, SBP may represent a source of latent abdominal sepsis. The laparoscopic approach enables both the diagnosis of latent spontaneous peritonitis and thorough peritoneal lavage, along with the installation of intra-abdominal drains and postoperative lavage of the abdominal cavity to improve peritoneal absorption function. Post-operative fractional lavage of the abdominal cavity facilitates better cleaning, enhancing peritoneal absorption. Thus, minimally invasive laparoscopic access constitutes a safe treatment option for patients with SBP and liver cirrhosis.

Competing interests

None declared.

Authors' contributions

Study conception and design: GA, TZ. Data acquisition: GA, TZ, SP, OC, GL AA. Analysis and interpretation of data: GA, TZ. Drafting of the manuscript: TZ. Significant manuscript review with significant intellectual involvement: TZ, GA. Approval of the final version of the manuscript: GA, TZ, SP, OC, GL AA.

Acknowledgment

The research project was funded by the National Agency for Research and Development of the Republic of Moldova under the State Program 2020-2023 "Pathogenically proven new technologies in minimally invasive complex surgical laparo-endoscopic and endovascular treatment of patients with potentially lethal complications of cirrhosis", No. 15.817.04.37A, Project Code - 20.80009.8007.30.

Patient consent

Obtained.

Ethics approval

The study was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy - Minutes no. 15 from 28.02.2022.

References

1. Paraschiv A. Evoluția situației epidemiologice prin hepatite cronice, ciroze hepatice și cancer hepatic în Republica Moldova [Epidemiological evolution of chronic hepatitis, liver cirrhosis and liver cancer in the Republic of Moldova]. One Health Risck Manag (Chisinau). 2021;(2):83-92. doi: 10/38045/ohrm.2021.2.11. Romanian.
2. Li YT, Huang JR, Peng ML. Current status and prospects of spontaneous peritonitis in patients with cirrhosis. BioMed Res Int. 2020;1:1-12. doi: 10.1155/2020/3743962.
3. Fernandez J, Navasa M, Gomez J, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfl oxacin prophylaxis. Hepatology. 2002;35(1):140-148. doi: 10.1053/jhep.2002.30082.
4. Fiore M, Maraolo AE, Gentile I, et al. Current concepts and future strategies in the antimicrobial therapy of emerging gram-positive spontaneous bacterial peritonitis. World J Hepatol. 2017;9(30):1166-1175. doi: 10.4254/wjh.v9.i30.1166.
5. European Association for the Study of the Liver; Paolo A, Mauro B, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69(2):406-460. doi: 10.1016/j.jhep.2018.03.024.
6. Rimola A, García-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, Inadomi JM. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document.

International Ascites Club. J Hepatol. 2000;32(1):142-53. doi: 10.1016/s0168-8278(00)80201-9.
7. Dumbrava VT, Țurcanu A, Lupașco I, Țurcan S, Hotineanu V, Cazacov V, Tofan-Scutaru L, Berliba E, Maximenco E; Ministry of Health of the Republic of Moldova. Ascita în ciroza hepatică la adult: Protocol clinic national [Ascites in liver cirrhosis in adults: National clinical protocol]. Chisinau: The Ministry; 2009. 44 p. Romanian.
8. Kim JJ, Tsukamoto MM, Mathur AK, Ghomri YM, Hou LA, Sheibani S, et al. Delayed paracentesis is associated with increased in-hospital mortality in patients with spontaneous bacterial peritonitis. Am J Gastroenterol. 2014;109(9):1436-1442. doi: 10.1038/ajg.2014.212.
9. Kasztelan-Szczerbinska B, Słomka M, Celinski K, Serwacki M, Szczerbinski M, Cichoz- Lach H. Prevalence of spontaneous bacterial peritonitis in asymptomatic inpatients with decompensated liver cirrhosis - a pilot study. Adv Med Sci. 2011;56(1):13-17. doi: 10.2478/v10039-011-0010-6.
10. Ruiz-Alcaraz AJ, Martinez-Banaclocha H, Marin-Sanchez P, Carmona-Martinez V, Iniesta-Albadalejo MA, Tristan-Manzano M, et al. Isolation of functional mature peritoneal macrophages from healthy humans. Immunol Cell Biol. 2020;98(2):114-126. doi: 10.1111/imcb.12305.
11. Wong CL, Holroyd-Leduc J, Thorpe KE, Straus SE. Does this patient have bacterial peritonitis or portal hypertension? How do I perform a paracentesis and analyze the results? JAMA. 2008;299(10):1166-1178. doi: 10.1001/jama.299.10.1166.
12. Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology. 1988;8(5):1151-1157. doi: 10.1002/hep.1840080532.
13. Such J, Francés R, Muñoz C, Zapater P, Casellas JA, et al. Detection and identification of bacterial DNA in patients with cirrhosis and culture-negative, nonneutrocytic ascites. Hepatology. 2002;36(1):135-141. doi: 10.1053/jhep.2002.33715.
14. Biggins SW, Angeli P, Garcia-Tsao G, Ginès P, Ling SC, Nadim MK, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the american association for the study of liver diseases. Hepatology. 2021;74(2):1014-1048. doi: 10.1002/hep.31884.
15. Aithal GP, Palaniyappan N, China L, Härmälä S, Macken L, Ryan JM, et al. Guidelines on the management of ascites in cirrhosis. Gut. 2021;70(1):9-29. doi: 10.1136/gutjnl-2020-321790.
16. Runyon BA, Canawati HN, Akriviadis EA. Optimization of ascitic fluid culture technique. Gastroenterology. 1988;95(5):1351-1355. doi: 10.1016/0016-5085(88)90372-1.
17. Piano S, Singh V, Caraceni P, Maiwall R, Alessandria C, Fernandez J, et al. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. Gastroenterology. 2019;156(5):1368-1380.e10. doi: 10.1053/j.gastro.2018.12.005.
18. Dunn DL, Barke RA, Knight NB, Humphrey EW, Simmons RL. Role of resident macrophages, peripheral neutrophils, and translymphatic absorption in bacterial clearance from the peritoneal cavity. Infect Immun. 1985;49(2):257-264. doi: 10.1128/iai.49.2.257-264.1985.
19. Tsiaoussis GI, Assimakopoulos SF, Tsamandas AC, Triantos CK, Thomopoulos KC. Intestinal barrier dysfunction in cirrhosis: Current concepts in pathophysiology and clinical implications. World J Hepatol. 2015;7(17):2058-2068. doi: 10.4254/wjh.v7.i17.2058.
20. Piano S, Fasolato S, Salinas F, Romano A, Tonon M, Morando F, et al. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis: Results of a randomized, controlled clinical trial. Hepatology. 2016;63(4):1299-1309. doi: 10.1002/hep.27941.
21. Huang CH, Lee CH, Chang C. Spontaneous bacterial peritonitis in decompensated liver cirrhosis: a literature review. Livers. 2022;(2):214-232. https://doi.org/10.3390/livers2030018.
22. Runyon BA. Low-protein-concentration ascitic fluid is predisposed to spontaneous bacterial peritonitis. Gastroenterology. 1986;91(6):1343-1346. doi: 10.1016/0016-5085(86)90185-x.
23. Fernández J, Acevedo J, Castro M, Garcia O, de Lope CR, Roca D, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology 2012;55(5):1551-1561. doi: 10.1002/hep.25532.
24. Parsi MA, Saadeh SN, Zein NN, Davis GL, Lopez R, Boone J, et al. Ascitic fluid lactoferrin for diagnosis of spontaneous bacterial peritonitis. Gastroenterology. 2008;135(3):803-7. doi: 10.1053/j.gastro.2008.05.045.
25. Fernández J, Acevedo J, Wiest R, et al.; European Foundation for the Study of Chronic Liver Failure. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut. 2018;67(10):1870-1880. doi: 10.1136/gutjnl-2017-314240.
26. Garcia-Tsao G. Ascites. In: Dooley JS, Lok ASF, Burroughs AK, Heathcote EJ, editors. Sherlock's diseases of the liver and biliary system. 12th ed. Cham: Wiley-Blackwell; 2011. p. 210-133.

https://doi.org/10.52645/MJHS.2024.3.02

UDC: 618.4-053.8

RESEARCH ARTICLE

Childbirth at advanced reproductive age: the impact of biopsychosocial factors on the mode of delivery

Rodica Scutelnic[1,2*], Larisa Spinei[1]

[1]*Nicolae Testemițanu* Social Medicine and Management Department, *Nicolae Testemițanu* State University of Medicine and Pharmacy, Chișinău, Republic of Moldova
[2]Institute of Emergency Medicine, Chișinău, Republic of Moldova

ABSTRACT

Introduction. Contemporary society reflects a clear trend towards delayed motherhood, raising significant concerns in the management of pregnancy and childbirth in women of advanced reproductive age. In this context, the mode of delivery and associated risks for this age category require increased attention. Birth methods have been thoroughly examined to identify risks and influencing factors within this specific cohort.

Material and methods. A descriptive cross-sectional study was conducted on a sample of 528 women. Data were collected using a pre-tested semi-structured questionnaire, and respondents were divided into three groups based on the mode of delivery: vaginal delivery, planned cesarean section, and emergency cesarean section. Sociodemographic, anthropometric, medical, and obstetric characteristics were analyzed using linear regression. Statistical analyses included descriptive and inferential statistics (Chi-square), with a 95.0% confidence interval.

Results. The analysis revealed statistically significant variations in the mode of delivery based on maternal age (p=0.013) and paternal age (p=0.001), with an increased rate of cesarean sections at more advanced ages. Significant variations were also found in relation to area of residence (p=0.003), education level (p=0.001), nature of work (p=0.028), GP appointments (p=0.020), number of GP appointments(p<0.001), number of obstetrician appointments (p=0.032), time of informing on risk factors (p=0.005), parity (p<0.001), multiple pregnancies (p=0.016), mode of first delivery (p<0.001), pregnancy complications (p=0.003), delivery complications (p<0.001), gestational age at birth (p=0.017), Apgar scores at 1 and 5 minutes (p<0.001).

Conclusions. Advanced reproductive age has been associated with a higher risk of cesarean section compared to vaginal delivery. The influence of age is modulated by various sociodemographic, medical, and obstetric characteristics, including area of residence, education level, history of cesarean section, parity, pregnancy and delivery complications, pre-existing chronic conditions, antenatal care and provision of information on risk factors.

Keywords: advanced reproductive age, advanced maternal age, mode of delivery, cesarean section, information, risk factors, antenatal care.

Cite this article: Scutelnic R, Spinei L. Childbirth at advanced reproductive age: the impact of biopsychosocial factors on the mode of delivery. Mold J Health Sci. 2024;11(3):10-21. https://doi.org/10.52645/MJHS.2024.3.02.

Manuscript received: 09.07.2024

Accepted for publication: 5.09.2024

Published: 20.09.2024

[*]**Corresponding author: Rodica Scutelnic,** MD, PhD fellow
Nicolae Testemițanu Social Medicine and Management Department
Nicolae Testemițanu State University of Medicine and Pharmacy
Chișinău, Republic of Moldova
165, Stefan cel Mare **și** Sfânt Blvd., MD-2004
e-mail: rchimirciuc@yahoo.com

Key messages

What is not known yet about the issue addressed in the submitted manuscript

Currently, the relationships between sociodemographic, anthropometric, medical, and obstetric characteristics influencing the mode of delivery in women of advanced reproductive age are not fully understood. Additionally, there are gaps in understanding how these interrelationships affect the increased likelihood of cesare-

Authors' ORCID IDs
Rodica Scutelnic – https://orcid.org/0009-0006-1081-3429
Larisa Spinei – https://orcid.org/0000-0002-5370-9801

an delivery compared to vaginal delivery and influence birth outcomes in this age cohort.

The research hypothesis

Sociodemographic, anthropometric, medical, and obstetric characteristics significantly influence the mode of delivery in women of advanced reproductive age, determining a higher likelihood of cesarean delivery compared to vaginal delivery.

The novelty added to the scientific literature in the field

The scientific novelty of the article lies in the detailed analysis of how biopsychosocial factors influence the mode of delivery in women of advanced reproductive age, highlighting the specific impact of education, area of residence, medical history, and obstetric complications on mode of delivery. This research contributes to a better understanding of the factors determining the mode of delivery in this age group, providing valuable insights for optimizing antenatal care.

Introduction

Globally, the age of motherhood has increased over the previous few decades. According to the report of the Organization for Economic Co-operation and Development, between 1970 and 2021, the average age of women giving birth increased by two to five years in the majority of OECD countries [1]. In numerous high-income countries, the birth rate for women in their late 30s has increased [2].

In 2022, the average age of women at childbirth in Europe varied from 27.8 years in Bulgaria to 32.2 years in Luxembourg, while in Moldova, it was 28 years [3]. Data analysis over the last decade has shown an increase in the birth rate for women aged 35 to 39 in the United States, from 45.9 per 1 000 women in 2010 to 52.7 in 2019. Similarly, there has been an increase in the birth rate for women aged 40 to 44, from 10.2 to 12 per 1 000 [4]. A study conducted in 29 countries across Africa, Asia, the Middle East, and Latin America also revealed that 12.3% of pregnant women fall into the category of advanced maternal age [5]. There is a clear trend of an increasing average age of women at childbirth, partly due to the tendency to delay having their first child [1]. This trend can be explained by women choosing to focus on careers and financial security, thereby postponing maternal age [6]. Furthermore, advances in assisted reproductive technologies have extended the reproductive window, leading to a corresponding increase in the incidence of advanced maternal age [7].

Approximately 21% of total births worldwide, ranging from 6% in low- and middle-income countries to 27% in developed regions, are delivered by cesarean section (CS) [8]. The CS rate continues to rise globally, with reported rates (in 2016) of 24.5% in Western Europe, 32% in North America, and 41% in South America [8, 9]. The reasons for the increasing CS rate are multifactorial, but existing literature suggests that the increase is largely driven by advanced maternal age, especially among nulliparous women [10]. Statistical data indicate higher CS rates among women over 35 years old compared to younger mothers [11]. Additionally, maternal age is considered an independent risk factor for CS or unsatisfactory obstetrical outcomes. Among nulliparous women aged 35 to 39, CS rates are twice as high compared to younger ages and can triple among those over 40 [11, 12]. Consistent research findings have constantly linked increasing maternal age with higher CS rates [13].

Studies have shown that women of advanced maternal age are more likely to have pre-existing chronic diseases (such as chronic hypertension and diabetes) [14], maternal complications (gestational hypertension, gestational diabetes, preeclampsia, placenta previa, and placental abruption) [15], perinatal complications (low birth weight, prematurity, and fetal death) [15], and CS [16]. Additionally, obesity significantly increases the rate of CS, but there is limited evidence in the literature regarding whether elective CS or physiological vaginal delivery (VD) is the optimal mode of delivery for women with morbid obesity [17].

However, unjustified CS can increase short-term and long-term health risks for mothers and their children. Short-term risks include infection, hemorrhage, visceral injuries, placenta accreta, and placental abruption [18]. Long-term risks include asthma and obesity [18]. Additionally, there is a higher likelihood of spontaneous abortion, ectopic pregnancy, and stillbirth in subsequent pregnancies for mothers who have undergone CS [19].

It is important to note that for low-risk women, who typically represent a small proportion of adverse outcomes overall, recovery time after CS is longer compared to VD. Compared to VD, the risk of infection and associated morbidity during a CS can increase by up to 20 times [20]. Therefore, according to the WHO Statement in 2015 regarding CS rates, CS should be performed only when medically necessary [21]. Depending on the location, between 2.5% and 18% of CS performed worldwide are done without medical indications [22, 23].

In low- and middle-income countries, women of advanced reproductive age significantly differ in sociodemo-

graphic characteristics [4], which is reflected in parity and mode of delivery. In this context, this study aims to describe the sociodemographic, anthropometric, obstetric, and medical characteristics of women of advanced reproductive age based on the mode of delivery, as well as to evaluate the influence of the interrelationship among these characteristics on the mode of delivery.

The objective of the study is to examine rates of VD and CS among women of advanced reproductive age based on their sociodemographic, anthropometric, medical, and obstetrical characteristics, and to evaluate the relationships among these factors.

Materials and methods

To achieve the stated objective, a selective cross-sectional observational study was conducted with a sample of 528 participants. The inclusion criteria were as follows: women aged between 35 and 49 years who gave birth during advanced reproductive age. As a research tool, a questionnaire developed by the authors was utilized. Interviews were conducted individually using a set of semi-structured questions to gather detailed information about the medical and social characteristics of the participants, in addition to available medical records. Open-ended questions were employed to capture personal experiences and individual perceptions of the participants.

We divided participants into three groups based on the mode of delivery: vaginal delivery, planned cesarean section, emergency cesarean section, and compared the influence of a series of sociodemographic, anthropometric, medical, and obstetrical characteristics using the linear regression method. Additionally, the modification of the effect was analyzed based on a series of variables whose evaluation showed statistically significant variations.

The collected data were analyzed using IBM SPSS Statistics software, version 26.0, following the documentation available at: IBM SPSS Statistics 26 Documentation. Statistical methods appropriate for the type of variables collected were employed. Tests and correlation analyses were utilized to identify potential relationships between medical and social variables. The significance of the results was assessed at a confidence interval of 95%. This methodological approach allowed for a detailed perspective on the socio-medical characteristics of women of advanced reproductive age, contributing to a deeper understanding of this evolving reality.

Results

In the study, 528 pregnant women were included, of whom 77 or 14.6% (95% CI: 12.0% - 18.0%) were aged between 35 and 39 years, and 451 or 85.4% (95% CI: 82.0% - 88.0%) were aged over 40 years. The mean age of the participants was 37.8 ± 2.5 years, with a median of 37.0 (Min=35.0, Max=49.0, IQR=3). The mean age of their partners was 41.7 ± 3.9 years, with a median of 41.0 (Min=34.0, Max=56.0, IQR=7.0) (95% CI: 41.0% – 42.0%).

Primigravidae accounted for 18.9% (95% CI: 16% - 22%), while primipara represented 25.1% (95% CI: 21% - 29%) of the participants. The mean number of pregnancies was 3.2±1.6 pregnancies, with a median of 3.0 (Min=1.0, Max=7.0, IQR=2.0) (95% CI: 3.0 – 3.3%), and the mean number of births was 1.6±1.4 births, with a median of 2.0 (Min=0.0, Max=6.0, IQR=1.3) (95% CI: 1.5% - 1.8%).

The first pregnancy resulted in birth for 66.5% (95% CI: 62% - 71%) of participants, of which 8% (95% CI: 5.6% - 10%) were via Cesarean section (CS). Complicated obstetrical history was reported in 42.0% (95% CI: 38% - 46%) of participants, and pre-existing chronic diseases in 45.3% (95% CI: 41% - 50%) of participants.

VD occurred in 59.5% (95% CI: 55% - 64%) of participants, planned cesarean section (PCS) in 15.9% (95% CI: 13% - 19%), and emergency cesarean section (ECS) in 24.6% (95% CI: 21% - 28%) of participants. Pregnancy complications were recorded in 70.8% (95% CI: 67% - 75%) of participants, and 50.6% (95% CI: 46% - 55%) developed birth complications.

For the identification and evaluation of sociodemographic, anthropometric, obstetrical, and other health-related factors associated with the mode of delivery, a bivariate analysis was conducted.

Table 1 shows the variations in the rates of VD and CS according to the sociodemographic and anthropometric characteristics of women. The mode of delivery differs significantly depending on the mother's age (p=0.013), with a mean of 38.5±2.8 years, a median of 38.0 (Min=35.0, Max=44.0, IQR=4.0) for PCS, and 37.6±2.4 years, a median of 37.0 (Min=35.0, Max=46.0, IQR=3.0) for ECS, and 37.6±2.5 years, a median of 37.0 (Min=35.0, Max=49.0, IQR=3.0) for VD. Similar differences (p=0.001) are also recorded depending on the age of the father, with a mean of 43.0±3.7 years, a median of 43.0 (Min=35.0, Max=53.0, IQR=4.5) for PCS, and 41.5±3.8 years, a median of 41.0 (Min=35.0, Max=53.0, IQR=7.0) for ECS, compared with the mean of 41.4 ±3.9 years, and the median of 41.0 (Min=34.0, Max=56.0, IQR=6.0) for VD.

Statistically significant variations are also established in the evaluation of the relationship between mode of delivery, specifically PCS and ECS, and the following characteristics: area of residence (p=0.003), education (p=0.001), and nature of work (p=0.028). Additionally, comparative evaluation between mode of delivery and workplace exposure (p=0.6), pre-pregnancy BMI (p>0.9), and recommended weight gain during pregnancy (p=0.6) did not reveal statistically significant differences. (Table 1).

The impact of antenatal care on the mode of delivery was evaluated and presented in Table 2. The study results found that participants who attended antenatal care with a GP had VD in 61.8% (95% CI: 57% - 66%), compared to 44.4% (95% CI: 33% - 56%) among participants who did not attend antenatal care with a GP. Meanwhile, 22.2% (95% CI: 13% - 32%) of participants who did not attend antenatal care with a GP gave birth by PCS, and 33.3% (95% CI: 22% - 44%) by ECS, compared to 14.9% (95% CI: 12% - 18%) of participants who attended antenatal care with a GP and gave birth by PCS, and 23.2% (95% CI: 19% - 27%) by ECS.

Table 1. Relationship between mode of delivery and sociodemographic and anthropometric characteristics

Mode of delivery	VD, N = 314[1]	95% CI[2]	PCS, N = 84[1]	95% CI[2]	ECS, N = 130[1]	95% CI[2]	Statistic Test	p-value[3]
Woman`s age	37.6 (2.5) 37.0 (3.0) 35.0, 49.0	37, 38	38.5 (2.8) 38.0 (4.0) 35.0, 44.0	38, 39	37.6 (2.4) 37.0 (3.0) 35.0, 46.0	37, 38	8,7	0.013
Partner`s age	41.4 (3.9) 41.0 (6.0) 34.0, 56.0	41, 42	43.0 (3.7) 43.0 (4.5) 35.0, 53.0	42, 44	41.5 (3.8) 41.0 (7.0) 35.0, 53.0	41, 42	13	0.001
Area of residence								
rural	150 (47.8%)	42%, 53%	35 (41.7%)	31%, 52%	39 (30.0%)	22%, 38%	12	0.003
urban	164 (52.2%)	47%, 58%	49 (58.3%)	48%, 69%	91 (70.0%)	62%, 78%		
Education								
secondary	154 (49.0%)	44%, 55%	24 (28.6%)	19%, 38%	43 (33.1%)	25%, 41%	18	0.001
vocational	64 (20.4%)	16%, 25%	24 (28.6%)	19%, 38%	30 (23.1%)	16%, 30%		
higher	96 (30.6%)	25%, 36%	36 (42.9%)	32%, 53%	57 (43.8%)	35%, 52%		
Nature of work								
physical	48 (15,3%)	11%, 19%	9 (10.7%)	4.1%, 17%	7 (5.4%)	1.5%, 9.3%		
intellectual	104 (33,1%)	28%, 38%	39 (46.4%)	36%, 57%	59 (45.4%)	37%, 54%	14	0.028
mixed	20 (6,4%)	3.7%, 9.1%	5 (6.0%)	0.89%, 11%	7 (5.4%)	1.5%, 9.3%		
doesn`t work	142 (45,2%)	40%, 51%	31 (36.9%)	27%, 47%	57 (43.8%)	35%, 52%		
Exposure								
yes	34 (10.8%)	7.4%, 14%	11 (13.1%)	5.9%, 20%	11 (8.5%)	3.7%, 13%	2.8	0.6
no	138 (43.9%)	38%, 49%	42 (50.0%)	39%, 61%	62 (47.7%)	39%, 56%		
Pre-pregnancy BMI	25.8 (4.3) 25.8 (6.3) 17.6 47.6	25, 26	25.9 (4.3) 24.7 (4.9) 17.6 39.6	25, 27	25.7 (3.8) 26.0 (5.7) 18.0 35.0	25, 26	0.06	>0.9
Weight gain	12.5 (4.8) 13.0 (7.0) 3.0 51.0	12, 13	12.8 (4.2) 13.0 (7.3) 1.0 21.0	12, 14	12.8 (4.6) 13.0 (7.0) 3.0 29.0	12, 14	0.95	0.6

Note: [1]n (%); Mean (SD); Median (IQR); Minimum Maximum; [2]CI = Confidence Interval; [3]Pearson's Chi-squared test; Kruskal-Wallis rank sum test

The evaluation of the relationship between the average attendance of the GP and the mode of delivery reveals statistically significant deviations (p <0.001). Among participants who had a VD, 40.1% (95% CI: 32% - 49%) had 1-3 GP`s attendances, and 46.5% (95% CI: 41% - 52%) had 4-7 attendances. In comparison, among participants with PCS, 29.8% (95% CI: 11.5% - 48.1%) had 1-3 attendances, and 47.6% (95% CI: 37% - 58%) had 4-7 attendances. For those with ECS, 23.1% (95% CI: 7.7% - 38.4%) had 1-3 attendances, and 55.4% (95% CI: 47% - 64%) had 4-7 attendances.

There is a similar trend observed in the relationship between the average attendances of the obstetrician and the mode of delivery, with statistical deviations yielding p=0.032. The rate of participants with more than 3 attendances of the obstetrician is 70,2% (95% CI: 60% - 80%) for those with PCS and 63.1% (95% CI: 55% - 71%) for those with ECS, compared to participants with up to 3 attendances, representing 29.8% (95% CI: 20% - 40%) for PCS and 36.9% (95% CI: 29% - 45%) for ECS. Simultaneously, the rate of participants with VD is approximately identical for both attendance groups, constituting 55.4% (95% CI: 50% - 61%) for those with > 3 attendances and 44.6% (95% CI: 39% - 50%) for those with 1-3 attendances.

The role of informed decision-making regarding pregnancy and childbirth in women of advanced reproductive age is underscored by statistically significant differences in CS rates based on the timing and content of information about age-related reproductive risks (p=0.005). It is noteworthy that participants who had VD were informed at similar rates either before becoming pregnant or during pregnancy, at 38.9% (95% CI: 33% - 44%) and 38.5% (95% CI: 33% - 44%), respectively. In contrast, for participants who underwent PCS or ECS, the rate of those informed before pregnancy was approximately twice as high compared to those informed during pregnancy, accounting for 59.5% (95% CI: 49% - 70%) and 28.6% (95% CI: 19% - 38%) for PCS, while it was 50.8% (95% CI: 42% - 59%) and 33.8% (95% CI: 26% - 42%) for ECS.

It is noteworthy that in this study, no statistically significant differences were identified for the relationship between the availability and utility of the perinatal book and the mode of delivery in women of advanced reproductive age (p=0.5).

The results of the evaluation of the mode of delivery based on obstetrical characteristics are presented in Table 3. Of the studied group, 59.5% (95% CI: 55% - 64%) of the participants gave birth vaginally, 15.9% (95% CI: 13% - 19%) by PCS, and 24.6% (95% CI: 21% - 28%) by ECS. It is relevant that the evaluation of the mode of delivery based on parity shows statistically significant differences (p<0.001), where, for primiparous, C-section was predominant at 57.9%, including 31.6% ECS, compared to multipara women, where VD was predominant, constituting 65.3%. In the same context, it was found that births among primipa-

Table 2. Relationship between mode of delivery and antenatal care

Mode of delivery	VD, N = 314[1]	95% CI[2]	PCS, N = 84[1]	95% CI[2]	ECS, N = 130[1]	95% CI[2]	Statistic test	p-value[3]
GP attendance								
yes	282 (89.8%)	86%, 93%	68 (81.0%)	73%, 89%	106 (81.5%)	75%, 88%	7.8	0.020
no	32 (10.2%)	6.8%, 14%	16 (19.0%)	11%, 27%	24 (18.5%)	12%, 25%		
Timing of initiation of antenatal care								
first trimester	226 (72.0%)	67%, 77%	55 (65.5%)	55%, 76%	90 (69,2%)	61%, 77%	1.4	0.5
second/third trimester	88 (28.0%)	23%, 33%	29 (34.5%)	24%, 45%	40 (30.8%)	23%, 39%		
GP attendances								
1-3	126 (40.1%)	32%, 49%	25 (29.8%)	11,5%, 48,1%	30 (23.1%)	7.7%, 38.4%		
4-7	146 (46.5%)	41%, 52%	40 (47.6%)	37%, 58%	72 (55.4%)	47%, 64%	34	<0.001
>7	10 (3.2%)	1.2%, 5.1%	3 (3.6%)	-0.40%, 7.5%	3 (2.3%)	-0.27%, 4.9%		
0	32 (10.2%)	6.8%, 14%	16 (19.0%)	11%, 27%	24 (18.5%)	12%, 25%		
Number of USG exams								
<=2	56 (17.8%)	14%, 22%	8 (9.5%)	3.2%, 16%	16 (12.3%)	6.7%, 18%	5.6	0.2
>2	255 (81.2%)	77%, 86%	76 (90.5%)	84%, 97%	113 (86.9%)	81%, 93%		
0	3 (1.0%)	-0.12%, 2.0%	0 (0.0%)	0.0%, 0.0%	1 (0.8%)	-0.73%, 2.3%		
Obstetrician attendances								
1-3	140 (44.6%)	39%, 50%	25 (29.8%)	20%, 40%	48 (36.9%)	29%, 45%	6.9	0.032
> 3	174 (55.4%)	50%, 61%	59 (70.2%)	60%, 80%	82 (63.1%)	55%, 71%		
Risk factors information								
before pregnancy	122 (38.9%)	33%, 44%	50 (59.5%)	49%, 70%	66 (50.8%)	42%, 59%		
after pregnancy	121 (38.5%)	33%, 44%	24 (28.6%)	19%, 38%	44 (33.8%)	26%, 42%	15	0.005
uninformed	71 (22.6%)	18%, 27%	10 (11.9%)	5.0%, 19%	20 (15.4%)	9.2%, 22%		
Pregnancy book								
Useful	262 (83.4%)	79%, 88%	71 (84.5%)	77%, 92%	104 (80.0%)	73%, 87%		
Useless	31 (9.9%)	6.6%, 13%	10 (11.9%)	5.0%, 19%	13 (10.0%)	4.8%, 15%	3.6	0.5
Not available	21 (6.7%)	3.9%, 9.5%	3 (3.6%)	-0.40%, 7.5%	13 (10.0%)	4.8%, 15%		

Note: *[1]n (%); [2]CI - Confidence Interval; [3]Pearson's Chi-squared test; Kruskal-Wallis rank sum test; GP – General practitioner.*

rous constituted 17.8% (95% CI: 14% - 22%) of VD, 41.7% (95% CI: 31% - 52%) of PCS, and 32.3% (95% CI: 24% - 40%) of ECS compared to 82.2% (95% CI: 78% - 86%) of VD, 58.3% (95% CI: 48% - 69%) of PCS, and 67.7% (95% CI: 60% - 76%) of ECS in multipara women, representing statistically significant differences (p=0.001).

In the conducted study, the mean number of previous births among participants who delivered via PCS was 1.2±1.3 births, with a median of 1.0 (Min=0.0, Max=5.0, IQR=2.0), 1.3±1.2 births, median 1.0 (Min=0.0, Max=5.0, IQR=2.0) for those with ECS, and 1.9±1.4 births, median 2.0 (Min=0.0, Max=6.0, IQR=2.0) for those who had VD. These differences are statistically significant (p<0.001). The same trend is observed when comparing the number of pregnancies in medical history (p<0.001). Correlation with other variables such as pre-existing chronic diseases (p=0.2), complicated obstetrical history (p=0.13), history of medical abortion (p=0.9), history of spontaneous abortion (p=0.7), and mode of conception (p=0.4) did not reveal statistically significant differences.

Meanwhile, the proportion of primigravidae who delivered via PCS and ECS is approximately twice as high compared to those who had VD, comprising 29.8% (95% CI: 20% - 40%) and 23.1% (95% CI: 16% - 30%) respectively, compared to 14.3% (95% CI: 10% - 18%). Additionally, the rate of multigravidas who delivered vaginally is about 6 times higher compared to primigravidae, 3.3 times higher for those via ECS, and 2.3 times higher via PCS, constituting 85.7% (95% CI: 82% - 90%) for VD, 70.2% (95% CI: 60% - 80%) for PCS, and 76.9% (95% CI: 70% - 84%) for ECS. These differences reach statistical significance with p=0.002.

According to the results of the present study, among participants who had ECS, 81.5% (95% CI: 75% - 88%) had pregnancy complications, and among those who had PCS, 73.8% (95% CI: 64% - 83%) had pregnancy complications, compared to 65.6% (95% CI: 60% - 71%) among participants with VD (p=0.003).

Of particular interest is the finding that the proportion of women who experienced birth complications is significantly lower among participants who had PCS compared to those who had VD or ECS, comprising 25% (95% CI: 16% - 34%) of OCS, compared to 53.8% (95% CI: 48% - 59%) and 59.2% (95% CI: 51% - 68%) of participants who had VD or ECS, respectively, showing statistically significant differences (p < 0.001).

There are significant variations in the mode of delivery based on the outcomes of the first pregnancy (p=0.0001), which show that participants whose first pregnancy ended in delivery had a VD rate of 66.7% (95% CI: 61.5% - 71.6%)

Table 3. Relationship between the mode of delivery and medical and obstetrical characteristics

Mode of delivery	VD, N = 314[1]	95% CI[2]	PCS, N = 84[1]	95% CI[2]	ECS, N = 130[1]	95% CI[2]	Statistic Test	p-value[3]
Preexisting chronic conditions								
yes	133 (42.4%)	37%, 48%	44 (52.4%)	42%, 63%	62 (47.7%)	39%, 56%	3.1	0.2
no	181 (57.6%)	52%, 63%	40 (47.6%)	37%, 58%	68 (52.3%)	44%, 61%		
Gravidity	3.4 (1.6) 3.0 (2.8) 1.0, 7.0	3.3, 3.6	2.8 (1.6) 3.0 (3.0) 1.0, 7.0	2.4, 3.1	2.9 (1.5) 3.0 (2.0) 1.0, 7.0	2.6, 3.1	20	<0.001
Parity	1.9 (1.4) 2.0 (2.0) 0.0, 6.0	1.8, 2.1	1.2 (1.3) 1.0 (2.0) 0.0, 5.0	0.89, 1.5	1.3 (1.2) 1.0 (2.0) 0.0, 5.0	1.1, 1.5	31	<0.001
Abortion history	0.4 (0.8) 0.0 (0.0) 0.0, 4.0	0.27, 0.43	0.3 (0.7) 0.0 (0.0) 0.0, 3.0	0.15, 0.45	0.3 (0.7) 0.0 (0.0) 0.0, 4.0	0.19, 0.42	0.23	0.9
Spontaneous abortion history	0.2 (0.6) 0.0 (0.0) 0.0, 3.0	0.17, 0.30	0.3 (0.7) 0.0 (0.0) 0.0, 4.0	0.15, 0.47	0.3 (0.7) 0.0 (0.0) 0.0, 4.0	0.18, 0.43	0.78	0.7
Ectopic pregnancy history	0.0 (0.1) 0.0 (0.0) 0.0, 1.0	0.00, 0.03	0.1 (0.3) 0.0 (0.0) 0.0, 2.0	0.01, 0.14	0.0 (0.2) 0.0 (0.0) 0.0, 2.0	0.00, 0.09	6.6	0.037
Parity								
primipara	56 (17.8%)	14%, 22%	35 (41.7%)	31%, 52%	42 (32.3%)	24%, 40%	25	<0.001
multipara	258 (82.2%)	78%, 86%	49 (58.3%)	48%, 69%	88 (67.7%)	60%, 76%		
Mode de conception								
Natural	306 (97.5%)	96%, 99%	80 (95.2%)	91%, 100%	124 (95.4%)	92%, 99%	1.7	0.4
IVF	8 (2.5%)	0.80%, 4.3%	4 (4.8%)	0.21%, 9.3%	6 (4.6%)	1.0%, 8.2%		
Complicated obstetric history								
yes	121 (38.5%)	33%, 44%	41 (48.8%)	38%, 59%	60 (46.2%)	38%, 55%	4.1	0.13
no	193 (61.5%)	56%, 67%	43 (51.2%)	41%, 62%	70 (53.8%)	45%, 62%		
Mode of first pregnancy delivery								
VD	227 (72.3%)	67%, 77%	26 (31.0%)	21%, 41%	56 (43.1%)	35%, 52%	75	<0.001
CS	7 (2.2%)	0.60%, 3.9%	15 (17.9%)	9.7%, 26%	20 (15.4%)	9.2%, 22%		
Nulliparae	80 (25.5%)	21%, 30%	43 (51.2%)	41%, 62%	54 (41.5%)	33%, 50%		
Pregnancy complications								
yes	206 (65.6%)	60%, 71%	62 (73.8%)	64%, 83%	106 (81.5%)	75%, 88%	12	0.003
no	108 (34.4%)	29%, 40%	22 (26.2%)	17%, 36%	24 (18.5%)	12%, 25%		
Delivery complications								
yes	169 (53.8%)	48%, 59%	21 (25.0%)	16%, 34%	77 (59.2%)	51%, 68%	27	<0.001
no	145 (46.2%)	41%, 52%	63 (75.0%)	66%, 84%	53 (40.8%)	32%, 49%		
Gestational age								
22-28 weeks	14 (4.5%)	2.2%, 6.7%	0 (0.0%)	0.00%, 0.00%	2 (1.5%)	-0.58%, 3.7%	12	0.017
29-35 weeks	31 (9.9%)	6.6%, 13%	5 (6.0%)	0.89%, 11%	21 (16.2%)	9.8%, 22%		
36-40 weeks	269 (85.7%)	82%, 90%	79 (94.0%)	89%, 99%	107 (82.3%)	76%, 89%		
Apgar score at 1 min	7.0 (1.1) 7.0 (2.0) 3.0, 9.0	6.9, 7.2	7.6 (0.9) 8.0 (1.0) 5.0, 9.0	7.4, 7.8	7.2 (1.1) 8.0 (1.8) 3.0, 9.0	7.0, 7.4	19	<0.001
Apgar score at 5 min	7.8 (1.0) 8.0 (1.0) 5.0, 9.0	7.7, 7.9	8.3 (0.8) 8.0 (1.0) 6.0, 10.0	8.1, 8.5	7.9 (1.0) 8.0 (2.0) 4.0, 10.0	7.7, 8.1	19	<0.001
Multiple pregnancy								
yes	3 (1.0%)	-0.12%, 2.0%	5 (6.0%)	0.89%, 11%	5 (3.8%)	0.54%, 7.2%	8.3	0.016
no	311 (99.0%)	98%, 100%	79 (94.0%)	89%, 99%	125 (96.2%)	93%, 99%		
Inpatient days	2.6 (1.2) 2.0 (1.0) 1.0, 7.0	2.4, 2.7	3.7 (1.4) 3.0 (1.0) 2.0, 7.0	3.4, 4.0	3.6 (1.4) 3.0 (1.0) 1.0, 7.0	3.4, 3.9	98	<0.001

***Note*:** *[1]n (%); Mean (SD); Median (IQR); Minimum Maximum; [2]CI - Confidence Interval; [3]Pearson's Chi-squared test; Kruskal-Wallis rank sum test; IVF – in vitro fertilization; VD – vaginal delivery; CS – cesarean section.*

and an ECS rate of 21.7% (95% CI: 17.5% - 26.3%), compared to participants whose first pregnancy ended in miscarriage, where 51.5% (95% CI: 33.5% - 69.2%) had a VD and 36.4% (95% CI: 20.4% - 54.9%) had an ECS. This highlights the higher rate of VD among participants whose first birth ended in delivery compared to primipara and primigravidae, emphasizing the role of first pregnancy outcomes on the mode of delivery in subsequent pregnancies (Figure 1).

The same situation is observed in the comparative evaluation of the mode of delivery for the first and present pregnancy delivery, revealing that 73.5% (95% CI: 68.2% - 78.3%) of participants whose first pregnancy ended in VD subsequently had a VD, compared to 16.7% (95% CI: 7.0% - 31.4%) for those whose first pregnancy ended in CS. Conversely, among participants who had a CS, 8.4% (95% CI: 5.6% - 12.1%) had a PCS and 18.1% (95% CI: 14.0% - 22.9%) had an ECS among those whose first pregnancy ended in VD, compared to 35.7% (95% CI: 21.6% - 52.0%) by PCS and 47.6% (95% CI: 32.0% - 63.2%) by ECS among those whose first pregnancy ended in CS. Of interest is that 45.2% (95% CI: 37.7% - 52.8%) of nulliparae had VD, 24.3% (95% CI: 18.2% - 31.3%) by PCS, and 30.5% (95% CI: 23.8% - 37.9%) by ECS (Fig. 2). These results show significant statistical variations (p=0.0000), demonstrating the importance of obstetrical history on the mode of delivery. It is evident that these data could potentially be influenced by elective CS.

The evaluation of the relationship between mode of delivery and a series of parameters revealed significant statistical differences for pregnancy complications (p=0.003), delivery complications (p<0.001), gestational age (p=0.017), Apgar score at 1 minute (p<0.001), Apgar score at 5 minutes (p<0.001), multiple pregnancy (p=0.016), and length of hospital stay (p<0.001) (Table 3).

Further exploration through multivariate analysis based on multiple parameters such as mode of delivery, obstetrical history, and pregnancy complications found significant statistical deviations (p=0.004, Chi^2=11.06049) among par-

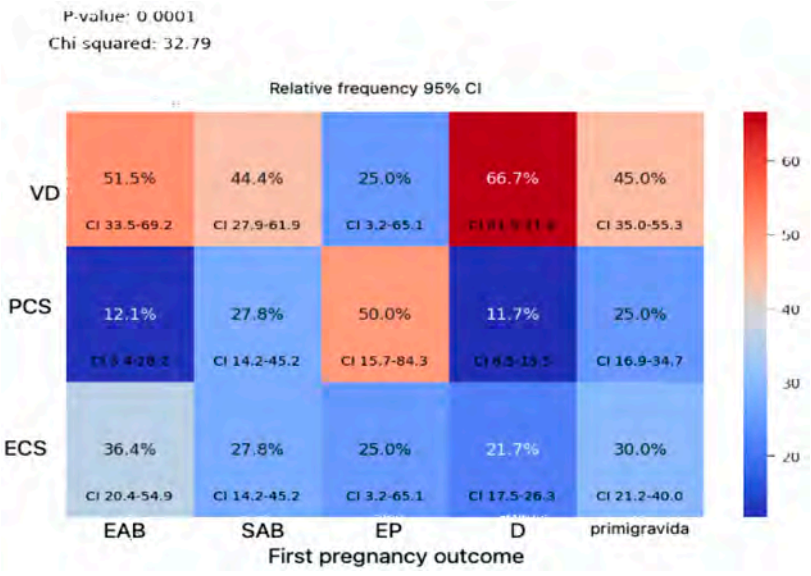


Fig. 1 Relationship between the mode of delivery and the results of the first pregnancy.

Note: *VD – vaginal delivery, PCS – planned cesarean section, ECS – emergency cesarean section, EAB – elective abortion, SAB – spontaneous abortion, EP – ectopic pregnancy*

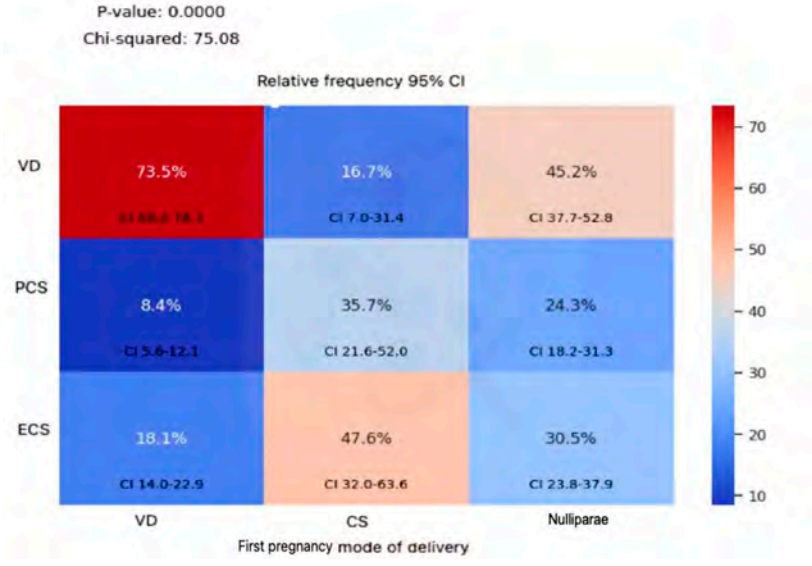


Fig. 2 Relationship between mode of first and present pregnancy delivery

Note: *VD – vaginal delivery, CS – cesarean section, PCS – planned cesarean section, ECS – emergency cesarean section.*

ticipants with complicated obstetric history and pregnancy complications, who had PCS in 85.4% (95% CI: 74.5% - 96.2%) and ECS in 86.7% (95% CI: 78.1% - 95.3%), compared to participants without complicated obstetric history and pregnancy complications, who delivered via PCS in 62.8% (95% CI: 48.3% - 77.2%) and ECS in 77.1% (95% CI: 67.3% - 87%), highlighting the role of complicated obstetric history in the rate of CS (Table 4).

Table 4. Relationship between mode of delivery and obstetrical history and pregnancy complications

Pregnancy complications		%	95% CI[2]	Statistic Test	p-value[3]
Complicated obstetric history	Mode of delivery				
Yes	VD	64.5	55.9%, 73.0%	M^2 = 11.06049, dof = 2	0.004
	PCS	85.4	74.5%, 96.2%		
	ECS	86.7	78.1%, 95.3%		
No	VD	66.3	59.7%, 73.0%		
	PCS	62.8	48.3%, 77.2%		
	ECS	77.1	67.3%, 87.0%		

Note: *[2]CI - Confidence Interval; [3]Pearson's Chi-squared test; Kruskal-Wallis rank sum test; VD – vaginal delivery, PCS – planned cesarean section, ECS – emergency cesarean section.*

Results of the evaluation of the relationship between mode of delivery, pre-existing chronic conditions, and pregnancy complications reveal significant statistical deviations (p=0.0042, Chi^2 test=10.9559). Among participants with pregnancy complications and pre-existing chronic conditions, 72.2% (95% CI: 64.6% - 79.8%) had VD, compared to 60.8% (95% CI: 53.7% - 67.9%) of participants without pre-existing chronic conditions. Additionally, participants with pregnancy complications and pre-existing chronic conditions delivered via PCS in 77.3% (95% CI: 64.9% - 89.7%), compared to 70% (95% CI: 55.8% - 84.2%) of those without pre-existing chronic conditions. Furthermore, participants with pregnancy complications and pre-existing chronic conditions who had ECS constituted 83.9% (95% CI: 74.7% - 93.0%), compared to 79.4% (95% CI: 69.8% - 89.0%) of participants without pre-existing chronic conditions (Fig. 3).

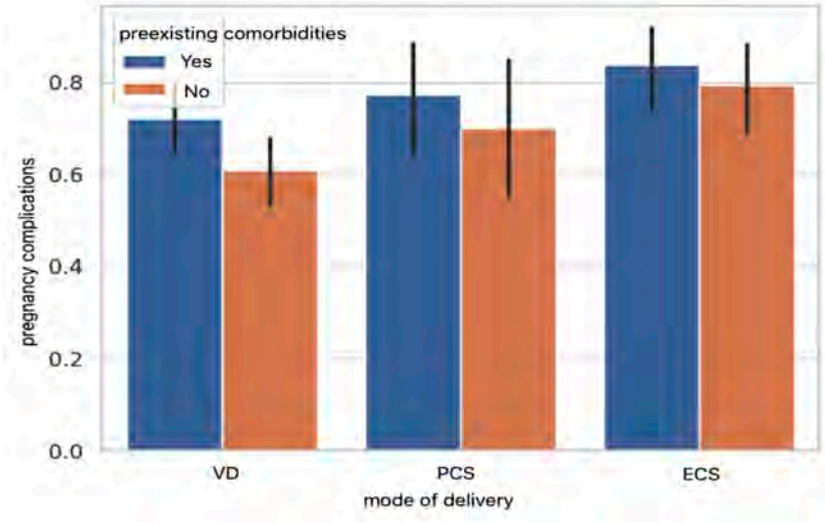


Fig. 3 Relationship between mode of delivery and pre-existing chronic conditions and delivery complications

Note: *VD – vaginal delivery, PCS – planned cesarean section, ECS – emergency cesarean section.*

Discussions

This study aimed to analyze the rates of vaginal and cesarean deliveries among women of advanced reproductive age based on sociodemographic, anthropometric, medical, and obstetrical characteristics and to assess their relationship. The study evaluated the effects of age on the mode of delivery in women of advanced reproductive age, with results showing an increased rate of CS based on several determinant factors. These findings are consistent with recent studies suggesting that advanced reproductive age is a potential risk factor for higher rates of CS and a higher incidence of obstetrical complications. [11, 12].

Results found increased rates of CS, specifically 15,9% (95% CI: 13% - 19%) of participants delivered via PCS and 24.6% (95% CI: 21% - 28%) via ECS. These findings are supported by research indicating that the mean maternal age tends to correlate with higher rates of CS, with older women being more likely to deliver via CS [24]. According to an American study, the incidence of CS increased with maternal age (under 25 years, 11.6%; over 40 years, 43.1%) [24]. Women aged over 25 had a 3.6% chance of CS, while those over 40 had a 21.1% chance. In a German study, 77.1% of women over 22 years old and 53.1% of those over 32 years old delivered spontaneously, whereas

14.5% of women under 22 and 32.3% of those over 32 underwent CS [25].

The evaluation of the relationship between mode of delivery and pregnancy complications (p=0.003) and delivery complications (p<0.001) reveals statistically significant differences. The lowest rate of pregnancy complications is observed in participants who had VD, constituting 65.6% (95% CI: 60% - 71%), compared to the highest rate of 81.5% (95% CI: 75% - 88%) observed in participants who had ECS. Additionally, the association with pre-existing chronic conditions in the multivariate analysis shows the highest rate of ECS at 83.9% (95% CI: 74.7% - 93.0%) in participants with pre-existing chronic conditions, compared to 79,4% (95% CI: 69.8% - 89.0%) in participants without pre-existing chronic conditions, and 77.3% (95% CI: 64.9% - 89.7%) in participants with pre-existing chronic conditions via PCS, compared to 70% (95% CI: 55.8% - 84.2%) in participants without pre-existing chronic conditions.

Complications during pregnancy and pre-existing chronic conditions are potential indicators for cesarean section among women of advanced reproductive age. Recent studies have indicated that pregnant women with medical conditions such as hypertensive disorders, diabetes mellitus, mild renal insufficiency, and multiple sclerosis tend to opt for repeat CS, suggesting that pregnancy complications influence the choice of mode of delivery [26]. All this evidence underscores the importance of managing pre-existing chronic conditions during family planning and antenatal care to reduce the rate of CS among women of advanced reproductive age. It highlights the significance of antenatal care and consultations with obstetricians in determining the appropriate delivery approach, aiming to lower the rate of ECS among participants with pregnancy complications.

Supporting this finding are the results of the evaluation of the mode of delivery based on delivery complications, which indicate that the rate of women who experienced birth complications is twice as low in participants who had PCS compared to those who had VD or ECS. This rate is 25% (95% CI: 16% - 34%) for participants who had PCS, compared to 53.8% (95% CI: 48% - 59%) and 59.2% (95% CI: 51% - 68%) for participants who had VD or ECS, respectively.

Even though there are recognized clinical indicators for opting for CS, non-clinical factors often play a significant role in the decision-making process. It is important to consider the risks associated with subsequent pregnancies and deliveries due to the decision to undergo CS in the absence of medical indications. Pregnant women with a history of CS are at higher risk of developing various complications such as placenta previa, uterine rupture, postpartum hemorrhage, hysterectomy, preterm birth before 37 weeks of gestation, fetal distress, hypertension, and gestational diabetes [27]. The basis of the decision about the mode of delivery often lies in the interaction between the woman and the healthcare provider, and there is a probability that the woman's preferences and beliefs about childbirth, as well as the clinician's subjective assessment of her obstetric risks and perception of the preferred mode of delivery, influence the choice to give birth by CS [28].

Respecting human rights by ensuring each woman's right to complete and accurate information about the risks associated with pregnancy and childbirth at advanced reproductive age empowers women to make informed decisions and actively participate in their health decision-making process. The study's results found that the rate of participants who were informed before becoming pregnant is approximately twice as high as those who were informed during pregnancy, comprising 59.5% (95% CI: 49% - 70%) and 28.6% (95% CI: 19% - 38%) for PCS, and 50.8% (95% CI: 42% - 59%) and 33.8% (95% CI: 26% - 42%) for ECS. In comparison, participants who had VD had similar rates of being informed either before becoming pregnant or during pregnancy, 38.9% (95% CI: 33% - 44%) and 38.5% (95% CI: 33% - 44%). These data demonstrate the impact of information about the risks associated with advanced reproductive age on the decision to give birth in this category of women.

Of course, particular attention is given to understanding and interpreting the information received, as well as the method of information delivery, since risks are often perceived differently by women and healthcare providers. The doubled rate of antenatal information among women who gave birth via CS may result from a high level of responsibility and pregnancy planning among women at increased risk, or an exaggerated interpretation of risk information leading to elective CS. In this regard, an evidence-based tool called the Safe Motherhood Initiative has been implemented by most World Health Organization-associated countries for nearly 30 years [29, 30]. According to WHO recommendations, pregnant women should have at least four antenatal attendances, as the use of antenatal care plays a significant role in the decision-making process regarding the mode of delivery. Women who underwent more than 4 antenatal attendances more often undergo CS, though the exact cause of this phenomenon remains unknown. Additionally, there is a probability that a cautious approach to women with pregnancy difficulties contributed to the preference for CS. The goal of antenatal care is to reduce health risks, identify anomalies early in pregnancy, and, if necessary, take corrective measures to prepare both mother and fetus, ensuring a healthy start in life for every newborn [31]. In 2016, the World Health Organization (WHO) suggested that antenatal care be increased from four to eight consultations with medical professionals during pregnancy. Compared to the previous four attendances, the aim of increasing the number of antenatal attendances is to reduce perinatal deaths by 8 per 1000 live births [32].

The study results also found that women who had regular GP attendances had a significantly higher likelihood – by 50% – of giving birth vaginally compared to those who did not have such attendances (p=0,02). At the same time, there were no statistically significant differences in evaluating the impact of GP attendances in the first trimester or later on the mode of delivery (p=0.5). A different situation was observed in the evaluation of the relationship between

the number of GP attendances (p<0.001) or the number obstetrician's attendances (p=0.032) and the mode of delivery, which showed statistically significant deviations. The ratio between the rate of women who had 4-7 GP attendances compared to 1-3 varied between 1.16 attendances for participants with VD and 2.4 for those with ECS, constituting 1.6 for participants with PCS.

A similar trend was observed in the evaluation of services provided by the obstetrician, which found that the proportion of participants who had more than 3 obstetrician attendances was approximately twice as high among participants with PCS and ECS compared to those who had up to 3 attendances and was approximately identical among participants who gave birth vaginally.

In the absence of other evidence and analyses of associated characteristics, this finding can be interpreted ambiguously. One viable interpretation is that higher attendance at antenatal care services by women with high-risk pregnancies influences the increase in the rate of CS. Additionally, without evaluating the reasons for this high GP and obstetrician attendance, there is a possibility that the increased rate of CS is due to voluntary attendance of participants without medical indications, leading to elective cesareans. Furthermore, consideration must be given to the possibility of overdiagnosis caused by medical staff's desire to prevent pregnancy and delivery complications, given that advanced reproductive age is a risk factor.

The evaluation of the impact of the mode of first delivery on subsequent deliveries identified statistically significant differences (p<0.001), indicating a probability approximately 2 times higher for VD among women whose first delivery ended vaginally, compared to a probability approximately 8 times higher for cesarean delivery among women whose first delivery ended in a CS. This demonstrates the impact of a CS history on subsequent pregnancies.

As reported in several studies, a previous CS has been predictably associated with a subsequent CS. According to a study from Brazil, a previous CS was linked to cesarean delivery in the current pregnancy [33]. Published research also indicates that women who have previously undergone a CS are more likely to experience placenta previa, placental abruption, and uterine rupture in subsequent pregnancies [34].

A significant aspect is the interrelation between the mode of delivery and parity, noting statistically significant differences (p<0.001) and revealing that every 6th woman who delivers vaginally is primipara, compared to every 3rd woman who delivers by ECS, and every 2 out of 5 who deliver by PCS. Supporting these findings, several studies highlight that the risk of CS, including ECS, in women of advanced reproductive age is considerably higher in primipara women, whereas the risk of preeclampsia is significantly higher in multipara women [35]. Like other studies, we found that the effects of increasing age were significantly more pronounced among primipara women than among multipara women [36]. This difference could be influenced by the higher likelihood of older primipara women opting for elective CS [37]. Some studies indicate that the risk of CS increases with age among both nulliparous and multipara women [38]. These findings may result from the higher probability of younger women being healthier and not suffering from preexisting chronic conditions that pose potential risks for pregnancy and delivery. Additionally, the influence of institutional culture and the expertise level of the healthcare provider could potentially affect women's decision-making processes regarding the mode of delivery [39].

Furthermore, in accordance with a previous study, our research demonstrated a positive correlation between maternal age and the likelihood of preterm birth (p=0.007) [40].

Conclusions

Our study identified the influence of biopsychosocial factors on the mode of delivery. Pregnancy at advanced reproductive age is associated with an increased rate of CS. Factors such as area of residence and education were found to have a significant impact on the mode of delivery. Women with higher levels of education are more likely to opt for CS. Previous CS, parity, pregnancy and delivery complications, and preexisting chronic conditions were also identified as contributing factors to CS. Proper information about pregnancy risks and the importance of antenatal care, including managing preexisting chronic conditions, plays a significant role in preventing adverse pregnancy and birth outcomes in this age group. These results highlight that advanced reproductive age can be an individual risk factor, emphasizing that providing detailed information to mothers over 35 about factors affecting pregnancy outcome improves them, particularly for primipara women.

Competing interests

None declared.

Authors' contributions

RS conceptualized the project, drafted the first manuscript and interpreted the data. LS added some conceptual ideas and critically revised the manuscript. Both authors revised and approved the final version of the manuscript.

Acknowledgements and funding

The study had no external funding.

Patient consent

Obtained.

Ethics approval

The study protocol was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy, minutes No.16, from 13th of February 2012.

References

1. Organization for Economic Co-operation and Development Family database. Age of mothers at childbirth and age-specific fertility [Internet]. Paris: OECD; 2022- [cited 2024 Jun 5]. Available from: https://www.oecd.org/content/

dam/oecd/en/data/datasets/family-database/sf_2_3_age_mothers_childbirth.pdf
2. Bréart G, Barros H, Wagener Y, Prati S. Characteristics of the childbearing population in Europe. Eur J Obstet Gynecol Reprod Biol. 2003;111 Suppl 1:S45-S52. doi: 10.1016/j.ejogrb.2003.09.005.
3. Statista.com. Average age of mothers in Europe 2022, by country [Internet]. London: Statista.com; 2022 [cited 2024 Jun 1]. Available from: https://www.statista.com/statistics/612088/mean-age-of-woman-at-childbirth-europe/#statisticContainer
4. Hamilton BE, Martin JA, Osterman MJK. Births: provisional data for 2019. Vital Statistics Rapid Release: Report No 008, May 2020 [Internet]. Hyattsville, Maryland: National Center for Health Statistics; 2020 [cited 2024 Jun 1]. Available from: https://www.cdc.gov/nchs/data/vsrr/vsrr-8-508.pdf?ref=stanfordreview.org
5. Laopaiboon M, Lumbiganon P, Intarut N, et al. Advanced maternal age and pregnancy outcomes: a multicountry assessment. BJOG. 2014;121(Suppl 1):49-56. doi: 10.1111/1471-0528.12659.
6. Sauer MV. Reproduction at an advanced maternal age and maternal health. Fertil Steril. 2015;103(5):1136-43. doi: 10.1016/j.fertnstert.2015.03.004.
7. Kawwass JF, Badell ML. Maternal and fetal risk associated with assisted reproductive technology. Obstet Gynecol. 2018;132(3):763-772. doi: 10.1097/AOG.0000000000002786.
8. Betrán AP, Ye J, Moller AB, Zhang J, Gülmezoglu AM, Torloni MR. The increasing trend in caesarean section rates: global, regional and national estimates: 1990-2014. PLoS One. 2016;11(2):e0148343. doi: 10.1371/journal.pone.0148343.
9. Gibbons L, Belizan JM, Lauer JA, Betran AP, Merialdi M, Althabe F. The global numbers and costs of additionally needed and unnecessary caesarean sections performed per year: overuse as a barrier to universal coverage. World Health Report. 2010;30:1-31.
10. Gerli S, Favilli A, Pericoli S, Di Renzo GC. Re: Moore EK, Irvine LM. The impact of maternal age over forty years on the caesarean section rate: six year experience at a busy district general hospital. J Obstet Gynaecol. 2015;35(4):435. doi: 10.3109/01443615.2014.960825.
11. Frederiksen LE, Ernst A, Brix N, et al. Risk of adverse pregnancy outcomes at advanced maternal age. Obstet Gynecol. 2018;131(3):457-463. doi: 10.1097/AOG.0000000000002504.
12. Marozio L, Picardo E, Filippini C, et al. Maternal age over 40 years and pregnancy outcome: a hospital-based survey. J Matern Fetal Neonatal Med. 2019;32(10):1602-1608. doi: 10.1080/14767058.2017.1410793.
13. Klemetti R, Gissler M, Sainio S, Hemminki E. At what age does the risk for adverse maternal and infant outcomes increase? Nationwide register-based study on first births in Finland in 2005-2014. Acta Obstet Gynecol Scand. 2016;95(12):1368-1375. doi: 10.1111/aogs.13020.
14. Goetzinger KR, Shanks AL, Odibo AO, Macones GA, Cahill AG. Advanced maternal age and the risk of major congenital anomalies. Am J Perinatol. 2017;34(3):217-222. doi: 10.1055/s-0036-1585410.
15. Lean SC, Derricott H, Jones RL, Heazell AEP. Advanced maternal age and adverse pregnancy outcomes: a systematic review and meta-analysis. PLoS One. 2017;12(10):e0186287. doi: 10.1371/journal.pone.0186287.
16. Xie M, Lao TT, Du M, et al. Risk for Cesarean section in women of advanced maternal age under the changed reproductive policy in China: a cohort study in a tertiary hospital in southwestern China. J Obstet Gynaecol Res. 2019;45(9):1866-1875. doi: 10.1111/jog.14048.
17. Nuthalapaty FS, Rouse DJ. The impact of obesity on obstetrical practice and outcome. Clin Obstet Gynecol. 2004;47(4):898-981. doi: 10.1097/01.grf.0000135358.34673.48.
18. Keag OE, Norman JE, Stock SJ. Long-term risks and benefits associated with cesarean delivery for mother, baby, and subsequent pregnancies: systematic review and meta-analysis. PLoS Med. 2018;15(1):e1002494. doi: 10.1371/journal.pmed.1002494.
19. Bowman ZS, Smith KR, Silver RM. Cesarean delivery and risk for subsequent ectopic pregnancy. Am J Perinatol. 2015;32(9):815-820. doi: 10.1055/s-0034-1543952.
20. Saeed KB, Greene RA, Corcoran P, O'Neill SM. Incidence of surgical site infection following caesarean section: a systematic review and meta-analysis protocol. BMJ Open. 2017;7(1):e013037. doi: 10.1136/bmjopen-2016-013037.
21. World Health Organization. WHO statement on Caesarean section rates [Internet]. Geneva: WHO; 2015 [cited 2023 Nov 15]. Available from: https://iris.who.int/bitstream/handle/10665/161442/WHO_RHR_15.02_eng.pdf?sequence=1
22. Green B, Evans J, Subair S, Liao LM. Maternal request for caesarean section: audit of a care pathway. J Obstet Gynaecol. 2014;34(4):317-321. doi: 10.3109/01443615.2013.873776.
23. Mazzoni A, Althabe F, Liu NH, et al. Women's preference for caesarean section: a systematic review and meta-analysis of observational studies. BJOG. 2011;118(4):391-399. doi: 10.1111/j.1471-0528.2010.02793.x.
24. Bayrampour H, Heaman M. Advanced maternal age and the risk of cesarean birth: a systematic review. Birth. 2010;37(3):219-226. doi: 10.1111/j.1523-536X.2010.00409.x.
25. Voigt M, Rochow N, Zygmunt M, Straube S, Schneider KT, Briese V. Risks of pregnancy and birth, birth presentation, and mode of delivery in relation to the age of primiparous women. Z Geburtshilfe Neonatol. 2008;212(6):206-210. doi: 10.1055/s-0028-1098732.
26. Sindiani A, Rawashdeh H, Obeidat N, Zayed F, Alhowary AAA. Factors that influenced pregnant women with one previous caesarean section regarding their mode of delivery. Ann Med Surg (Lond). 2020;55:124-130. doi: 10.1016/j.amsu.2020.05.007.
27. Chen X, Gao J, Liu J, Hu J, Li S, Tang Y, Zhong M, He J, Liao S, Yang J, Liu X, Wang X, Liu X, Liu X, Cao Y, Wang T, Liu C, Sun J. Previous mode of delivery affects subsequent pregnancy outcomes: a Chinese birth register study. Ann Transl Med. 2021;9(14):1135. doi: 10.21037/atm-20-8127.
28. Nguyen MT, McCullough LB, Chervenak FA. The importance of clinically and ethically fine-tuning decision-making about cesarean delivery. J Perinat Med. 2017;45(5):551-557. doi: 10.1515/jpm-2016-0262.
29. World Health Organization. World Health Day Safe Motherhood [Internet]. Geneva: WHO; 1998 [cited 2023 Nov 15].

Available from: https://www.who.int/docstore/world-health-day/en/docum ents1998/whd98.pdf
30. Diniz CSG, Rattner D, d'Oliveira AFPL, Aguiar JM, Niy DY. Disrespect and abuse in childbirth in Brazil: social activism, public policies and providers' training. Reprod Health Matters. 2018;26(53):19-35. doi: 10.1080/09688080.2018.1502019.
31. World Health Organization. Provision of effective antenatal care: integrated management of pregnancy and childbirth. Geneva: WHO; 2002.
32. World Health Organization. Pregnant women must be able to access the right care at the right time, says WHO [Internet]. Geneva: WHO; 2016 [cited 2023 Nov 15]. Available from: https://www.who.int/news-room/detail/07-11-2016-pregnant-women-must-be-able-to-access-the-right-care-at-the-right-time-says-who
33. Osava RH, Silva FM, Tuesta EF, Oliveira SM, Amaral MC. Cesarean sections in a birth center. Rev Saude Publica. 2011;45(6):1036-1043. doi: 10.1590/s0034-89102011000600005. Erratum in: Rev Saude Publica. 2012 Aug;46(4):759.
34. Getahun D, Oyelese Y, Salihu HM, Ananth CV. Previous cesarean delivery and risks of placenta previa and placental abruption. Obstet Gynecol. 2006;107(4):771-778. doi: 10.1097/01.AOG.0000206182.63788.80.
35. Ogawa K, Urayama KY, Tanigaki S, et al. Association between very advanced maternal age and adverse pregnancy outcomes: a cross sectional Japanese study. BMC Pregnancy Childbirth. 2017;17(1):349. doi: 10.1186/s12884-017-1540-0.
36. Kenny LC, Lavender T, McNamee R, O'Neill SM, Mills T, Khashan AS. Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort. PLoS One. 2013;8(2):e56583. doi: 10.1371/journal.pone.0056583.
37. Fitzpatrick KE, Tuffnell D, Kurinczuk JJ, Knight M. Pregnancy at very advanced maternal age: a UK population-based cohort study. BJOG. 2017;124(7):1097-1106. doi: 10.1111/1471-0528.14269.
38. Bergholt T, Skjeldestad FE, Pyykönen A, et al. Maternal age and risk of cesarean section in women with induced labor at term: a Nordic register-based study. Acta Obstet Gynecol Scand. 2020;99(2):283-289. doi: 10.1111/aogs.13743.
39. Kwayke-Ackah G, Burger A, de la Vega G, Kainz G, Rochon M, Quiñones JN. Influence of maternal age in mode of delivery after term induction of labor. J Matern Fetal Neonatal Med. 2022;35(7):1258-1263. doi: 10.1080/14767058.2020.1745180.
40. Koo YJ, Ryu HM, Yang JH, et al. Pregnancy outcomes according to increasing maternal age. Taiwan J Obstet Gynecol. 2012;51(1):60-65. doi: 10.1016/j.tjog.2012.01.012.

https://doi.org/10.52645/MJHS.2024.3.03

UDC: 618.145-007.415:618.177

RESEARCH ARTICLE

Deep endometriosis – impact on infertility, endometriosis fertility index, and reproductive prognosis (comparative study)

Nadejda Codreanu*, Elena Ivanova

Department of Obstetrics and Gynecology, *Nicolae Testemițanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

ABSTRACT

Introduction. Deep infiltrating endometriosis (DIE) is the most severe form of endometriosis, contributes to pelvic pain syndrome, extragenital symptoms, fertility problems, and diminished reproductive prognosis for affected individuals. It is recommended to use the Endometriosis Fertility Index (EFI) to assess reproductive prognosis and conduct clinical research to compare reproductive prognosis in different forms of endometriosis.

Objective. Comparison of the impact of the DIE and others forms of endometriosis on EFI, patients' fertility and on reproductive prognosis to understand the management approach.

Materials and methods. A cohort study included 190 reproductive-age women, divided according to the #Enzian classification: the main group - 85 patients with DIE, the control group - 105 women with other forms of endometriosis. The EFI was utilized for reproductive prognosis. Pain was evaluated with Visual Analog Scale (VAS). Statistical analyses were performed using SPSS, with calculation of the Mann-Whitney U and Pearson's chi-square test (χ^2).

Results. In main group, the frequency of infertility was 83.5% compared to the control group's 71.4% ($p > 0.05$). The EFI in main group was 7.18±0.25 points vs the control group's 7.13±0.28 points ($p = 0.852$). Patients in the main group suffered from intense pelvic pain (>7 points by the VAS, $p < 0.01$), including severe dyspareunia (7.85±0.33 points vs 2.18±0.46 points in control group, $p < 0.01$).

Conclusions. Our results suggest that infertility in women with DIE may be more often associated with sexual abstinence due to significant dyspareunia rather than organic impairments. Thus, EFI in patients with DIE does not reflect all aspects of infertility and has reservations, and consideration of both physical symptoms and sexual health is crucial in managing DIE to optimize fertility outcomes. These findings open the way to the feasibility of surgical treatment of DIE to improve sexual quality of life, which will reduce the need for IVF and increase the chances of spontaneous pregnancy in patients, but this conclusion requires further investigation in randomized clinical trials.

Keywords: endometriosis, deep endometriosis, EFI, reproductive prognosis.

Cite this article: Codreanu N, Ivanova E. Deep endometriosis – impact on infertility, endometriosis fertility index, and reproductive prognosis (comparative study). Mold J Health Sci. 2024;11(3):22-26. https://doi.org/10.52645/MJHS.2024.3.03.

Manuscript received: 14.06.2024

Accepted for publication: 03.09.2024

Published: 20.09.2024

***Corresponding author: Nadejda Codreanu**, PhD, Associate professor, Department of Obstetrics and Gynecology,
Nicolae Testemițanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova
165, Stefan cel Mare și Sfânt blvd., MD-2004
e-mail: nadejda.codreanu@usmf.md

Authors' ORCID IDs
Nadejda Codreanu – https://orcid.org/0009-0008-8740-0379
Elena Ivanova – https://orcid.org/0000-0001-8460-9849

Key messages

What is not yet known on the issue addressed in the submitted manuscript

The connection between deep endometriosis and infertility, the impact of deep endometriosis on the EFI index and the reproductive prognosis of patients – these outstanding questions remain debatable.

The research hypothesis

Deep endometriosis is a form of endometriosis that significantly affects a woman's fertility, reducing the EFI index and dramatically worsening the patient's reproductive prognosis.

The novelty added by the manuscript to the already published scientific literature

The study allowed to clarify the features of the influence of deep endometriosis on infertility, the fertility index, and the reproductive prognosis of patients, and to compare these results with data from patients suffering from other forms of endometriosis.

Introduction

The deep infiltrative endometriosis (DIE) is acknowledged as the most severe manifestation of pelvic endometriosis, comprising a quarter of its various phenotypes [1-3]. DIE is characterized by fibromuscular infiltration of organs and anatomical structures with subperitoneal invasion of endometrial tissues, regardless of the depth of infiltration, and it presents as a systemic, chronic inflammatory disease cyclically dependent on menstruation, with chronic pelvic pain being its common manifestation [1, 4-6].

The occurrence of DIE is on the rise. Despite ongoing research efforts worldwide, understanding its pathogenesis, clinical features, diagnostic methods, and treatment options remains a focus of intensive investigation. Impacting approximately 2% of females in their reproductive years, DIE contributes to pelvic pain syndrome, extragenital symptoms, fertility problems, and diminished reproductive prognosis for affected individuals [1, 5].

At the global consensus in 2021, the following classifications for clinical use in endometriosis were recommended: rASRM (revised American Society for Reproductive Medicine), the EFI scale (Endometriosis Fertility Index), and the #Enzian classification. These classifications not only allow for staging the pathological process but also for evaluating the reproductive prognosis of the patients [7, 8]. Of particular interest for our study are the #Enzian classification, which completely describes all possible forms of DIE, and the EFI, which provides a precise reproductive prognosis and allows for specific recommendations regarding fertility management for patients in the postoperative period [9-11].

As per the literature, clinical manifestations of DIE encompass the 4 "D" symptoms: dysmenorrhea, dyspareunia, dysuria, and dyschezia, frequently accompanied by infertility [12]. The primary cause of infertility associated with endometriosis (DIE) is the distortion of normal pelvic organ anatomy. Additionally, endometriosis impairs fertility through other mechanisms: inflammation and scarring of surrounding tissues lead to dysfunction of the ovaries and uterus, affecting the quality of oocytes and their ability to be fertilized. High levels of inflammatory cytokines and mediators negatively impact embryo implantation [13].

Scientific literature indicates that DIE, being the most aggressive and clinically prominent phenotype of endometriosis, notably diminishes the QoL for patients [14, 15]. This deterioration arises not only due to severe pain and extragenital symptoms but also because of the infertility. These factors collectively exacerbate the challenges faced by affected women, further diminishing their QoL [3].

After analyzing the scientific literature dedicated to the issue of DIE, it was decided to implement a study, the aim of which was to compare the impact of the DIE and others forms of endometriosis on EFI, patients' fertility and on reproductive prognosis to understand the management approach.

Material and methods

A cohort clinical study was carried out over a span of 2 years at the *Gheorghe Paladi* Municipal Clinical Hospital in Chisinau. Approval for the study was obtained from the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (minutes No. 38, from 21.05.2021). The research involved women of reproductive age diagnosed with "Endometriosis," confirmed through intraoperative findings or indications from ultrasound/MRI scans according to the #Enzian classification from 2019, adhering to predefined inclusion and exclusion criteria. Exclusion criteria encompassed patients below the legal age, those who were virgins, retired individuals, cases of endometriosis with malignancy, severe extragenital pathologies (such as hypertension, cardiovascular, or liver disorders), precancerous or cancerous conditions (including cervical, endometrial, or ovarian), and patients who declined participation in the clinical investigation. Each participant provided informed consent prior to enrollment.

Consequently, the cohort comprised 190 women divided into two distinct groups according to the #Enzian classification: the study group comprised 85 patients diagnosed with DIE (compartments A, B, C, F), while the control group consisted of 105 women diagnosed with endometriosis of the ovaries, tubes, and superficial peritoneal endometriosis (corresponding to compartments O, T, P in the #Enzian classification 2019).

To quantify the impact of endometriosis on patient fertility, the EFI was employed. Pain severity was assessed using the Visual Analog Scale (VAS). Data analysis was conducted using an Excel spreadsheet, and statistical analyses were performed using the SPSS software. The Mann-Whitney U test was employed to compare quantitative variables between groups, while the Pearson's Chi-square test (χ^2) was utilized for comparing qualitative variables among groups.

Results

The cohort of women was divided into two groups according to the #Enzian classification. So, in the main group of 85 patients, the lesions were distributed as follows in #Enzian compartments: A - 55.3%; B - 8.2%; C - 1.2%; FA - 17.6%; FB - 17.6%; FI - 9.4%; FO - 12.9%; P - 34.1%; O -

70.6%; T - 51.8%. In the control group of 105 patients, the localization of endometriosis was distributed as follows in compartments by the #Enzian: P - 15.2%; O - 90.5%; T - 50.5%.

Reproductive anamnesis data. An important objective of the study was to determine the frequency of infertility among groups of patients, as well as to calculate the score of the EFI index for patients' reproductive prognosis.

Thus, among patients with DIE, the frequency of infertility was 83.5% (71 patients out of 85). Detailed fertility calculations revealed that primary infertility in main study group is 48.2±5.7%; 95% CI (36.5 – 59.3%), while 35.3±5.4% of women were diagnosed with secondary infertility. Additionally, 14.1±3.8% of women in this group did not suffer from infertility, and 2.4±1.6% utilized contraceptive methods (withdrawal method, condoms, Figure 1).

Among the patients in the control group, the percentage of infertility was 71.4% (75 women out of 105). Fertility calculation in this group revealed that 37.1±4.7% of women experienced primary infertility, while 34.3±4.8% of women reported secondary infertility. However, within this study group, 21.0±4.0% did not suffer from infertility, and 7.6±2.7% utilized contraception (withdrawal method, condoms, Figure 1).

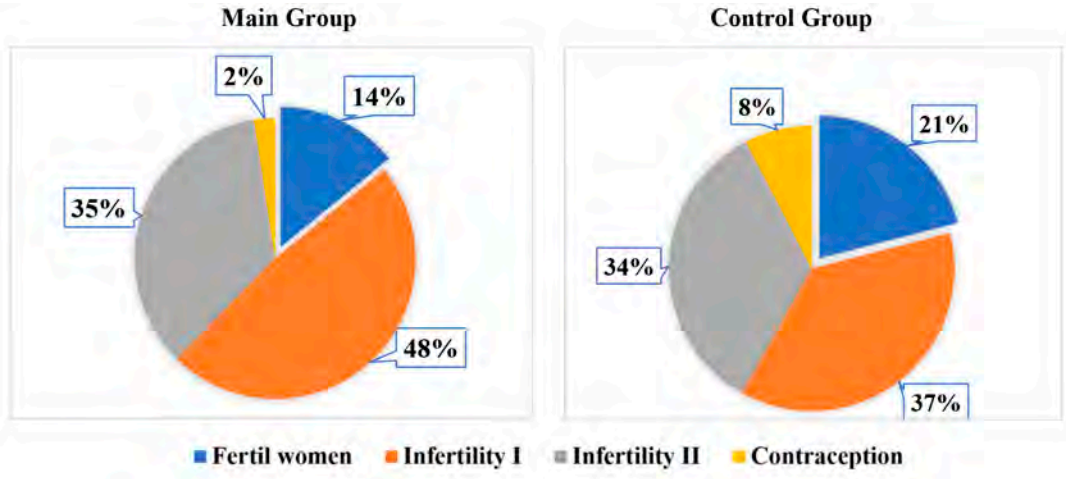


Fig. 1 Frequency of infertility in study groups

Statistical comparison of the infertility parameter did not reveal a statistically significant difference between the study groups ($\chi^2 = 5.088^a$, df = 3, p = 0.165).

Reproductive losses. In addition, comparison between patients in the study groups did not reveal any differences in terms of reproductive losses (U = 4463.000, p = 0.839). In the main group, the frequency of reproductive losses was 13 cases out of 85 - 15.3%, while in the control group it was 11 out of 105 - 10.5% (Figure 2).

Calculations of EFI. For the final fertility prognosis calculation in the study groups, the EFI index was computed (Figure 3). The median EFI among women with DIE was 7.00 points (mean value - 7.18±0.25 points; 95% CI [6.68 – 7.68 points]). Simultaneously, the median EFI in the control group was also 7.00 points (mean value 7.13±0.29 points; 95% CI [6.55 – 7.71 points]).

Comparison of these data did not reveal a statistically significant difference in this parameter between the study groups (U = 3712.000, p = 0.852), despite the fact that the main group included patients with complete obliteration of the Douglas pouch, whose EFI tends towards 0 points.

Pain levels. The distribution of pain levels on the VAS among women of main group in comparison to the control group of patients is reflected in the Table 1. It is worth noting that patients with DIE are characterized by severe

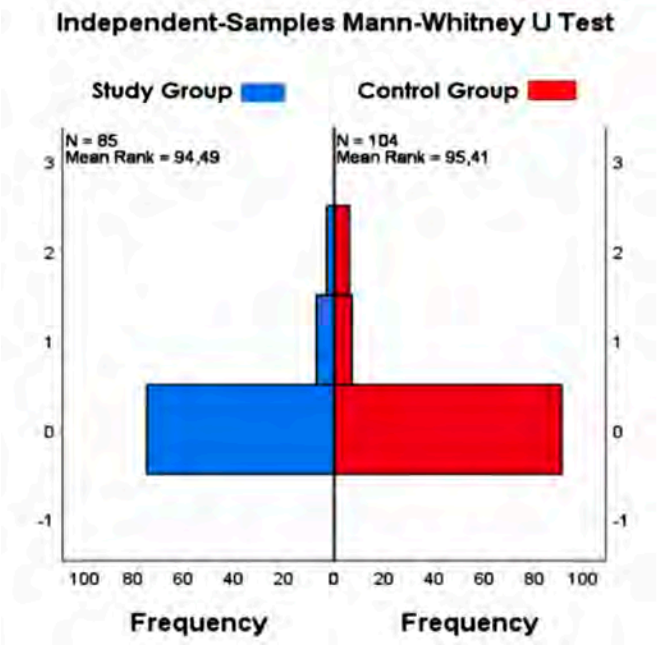


Fig. 2 Comparison of reproductive losses in research groups.

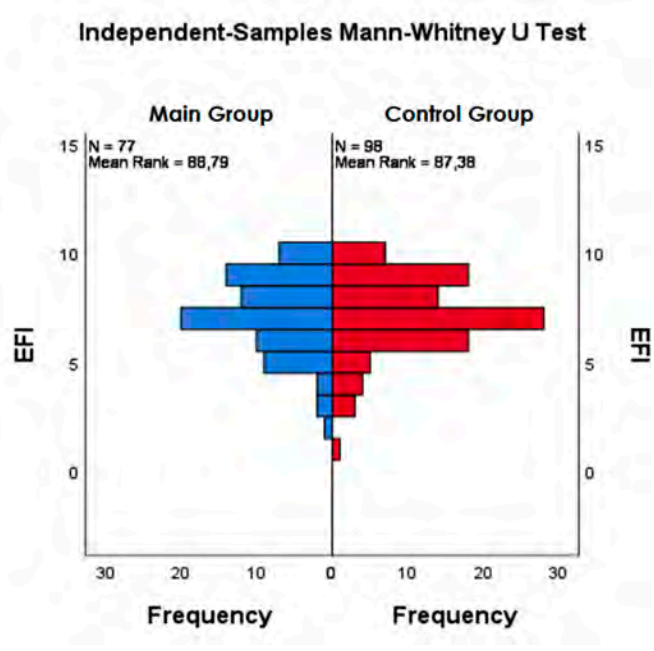


Fig. 3 Comparison of the EFI in the research groups.

dyspareunia (7.85±0.33 points (95% CI; 7.18 – 8.53 points) vs 2.18±0.46 points (95% CI; 1.23 – 3.13 points) in control group, $p < 0.01$), which is the cause of sexual abstinence and, accordingly, infertility.

Table 1. Comparison of pain levels according to the VAS

Pain symptom	Main Group	Control Group	P
CPP	7.90±0.21	2.41±0.45	p < 0.01
Dm	9.02±0.17	5.31±0.52	p < 0.01
Dp	7.85±0.33	2.18±0.47	p < 0.01
Du	1.46±0.47	0	p < 0.01
Dh	3.83±0.56	0	p < 0.01

***Note**: VAS - visual analog scale ; CPP - chronic pelvic pain, Dm - dysmenorrhea, Dp - dyspareunia, Dy - dysuria, Dx – dyschezia*

Discussion

The study found that although bilateral endometriomas ("kissing ovaries") were included in the DIE group, the total EFI score was greater than 7, similar to the control group. If "kissing ovaries", where EFI approaches 0 and pregnancy can only be achieved with ART, are excluded from DIE, other forms of DIE (88%), where the ovaries are not affected, show higher EFI values than the control group. However, infertility I and II frequencies are similar. This suggests that infertility in women with DIE may not be solely due to the organic changes reflected by EFI but also due to sexual disharmony associated with severe dyspareunia, sexual abstinence, or long-term use of pain-relieving medications, which may delay pregnancy but not always inhibit the progression of endometriosis.

Therefore, using EFI in the DIE group has limitations, potentially delaying ART use and wasting time in achieving spontaneous pregnancy. On the other hand, for women with DIE excluding "kissing ovaries", prolonged periods without pregnancy desire may benefit from multidisciplinary surgical treatment, reducing pain syndrome and dyspareunia, achieving spontaneous pregnancy in the future.

The benefits of surgical treatment for DIE were highlighted in a study by the Endometriosis School in Bordeaux (Horace Roman), showing increased rates of spontaneous pregnancies. Recent studies on the failure of progestin treatment due to the lack of progesterone receptors in DIE lesions, and our data, support surgical treatment in patients not opting for immediate pregnancy, especially in distant compartment DIE forms after #Enzian that do not directly involve the genitals.

Therefore, our study demonstrates the limitations of using EFI scores alone, excluding "kissing ovaries", to evaluate reproductive prognosis in DIE patients. Besides EFI, assessing sexual life quality is crucial to support spontaneous pregnancy in women with DIE. Relying solely on EFI for reproductive prognosis in DIE patients could result in wasted time and unfavorable reproductive outcomes, as it fails to consider dyspareunia and high EFI scores that may delay the timely use of IVF or other ART methods.

Conclusions

Our results suggest that infertility in women with DIE may be more often associated with sexual abstinence due to significant dyspareunia rather than organic impairments. Thus, EFI in patients with DIE does not reflect all aspects of infertility and has reservations, and consideration of both physical symptoms and sexual health is crucial in managing DIE to optimize fertility outcomes. These findings open the way to the feasibility of surgical treatment of DIE to improve sexual quality of life, which will reduce the need for IVF and increase the chances of spontaneous pregnancy in patients, but this conclusion requires further investigation in randomized clinical trials.

Competing interests

None declared.

Authors' contributions

NC proposed the study's area, conceived the study design, controlled main points of its realization, reviewed the work critically, and approved the final version of the manuscript. EI participated in the study design, contacted and included subjects in research, analyzed and calculated information from questionnaires, performed the statistical analysis of collected data, drafted the manuscript, reviewed the work critically.

Acknowledgements and funding

We express our gratitude to academician Gheorghe Paladi, who advised us to pursue research in the gynecological field and supported the realization of this study. The study had no external funding.

Patient consent

Obtained.

Ethics approval

The study protocol was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (minutes No. 38, from 21.05.2021).

References

1. Saridogan E, Becker CM, Feki A, Grimbizis GF, Hummelshoj L, Keckstein J, et al. Recommendations for the surgical treatment of endometriosis - part 1: ovarian endometrioma. Gynecol Surg. 2017;14(1):27. doi: 10.1186/s10397-017-1029-x.
2. Imperiale L, Nisolle M, Noël JC, Fastrez M. Three types of endometriosis: pathogenesis, diagnosis and treatment. State of the art. J Clin Med. 2023;12(3):994. doi: 10.3390/jcm12030994.
3. Wild M, Miskry T, Al-Kufaishi A, Rose G, Crofton M. Medical management of deeply infiltrating endometriosis - 7 year experience in a tertiary endometriosis centre in London. Gynecol Surg. 2019;16(1):1-7. https://doi.org/10.1186/s10397-019-1065-9.
4. Bazot M, Daraï E. Diagnosis of deep endometriosis: clinical examination, ultrasonography, magnetic resonance imaging, and other techniques. Fertil Steril. 2017;108(6):886-94. doi: 10.1016/j.fertnstert.2017.10.026.
5. Bazot M, Bharwani N, Huchon C, Kinkel K, Cunha TM, Guerra A, et al. European Society of Urogenital Radiology (ESUR) guidelines: MR imaging of pelvic endometriosis. Eur Radiol. 2017;27(7):2775. doi: 10.1007/s00330-016-4673-z.
6. Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, Kiesel L, et al. ESHRE guideline: endometriosis. Hum Reprod Open. 2022;(2):hoac009. doi: 10.1093/hropen/hoac009.
7. Johnson NP, Hummelshoj L, Adamson GD, Keckstein J, Taylor HS, Abrao MS, et al. World Endometriosis Society consensus on the classification of endometriosis. Hum Reprod. 2017;32(2):315-24. doi: 10.1093/humrep/dew293.
8. Vermeulen N, Abrao MS, Einarsson JI, Horne AW, Johnson NP, Lee TTM, et al. Endometriosis classification, staging and reporting systems: a review on the road to a universally accepted endometriosis classification,. Hum Reprod Open. 2021;2021(4):hoab025. doi: 10.1093/hropen/hoab025.
9. Vermeulen N, Abrao MS, Einarsson JI, Horne AW, Johnson NP, Lee TTM, et al. Endometriosis classification, staging and reporting systems: a review on the road to a universally accepted endometriosis classification. J Minim Invasive Gynecol. 2021;28(11):1822-48. doi: 10.1016/j.jmig.2021.07.023.
10. Fruscalzo A, Dayer A, Londero A Pietro, Guani B, Khomsi F, Ayoubi JM, et al. Endometriosis and infertility: prognostic value of #Enzian Classification compared to rASRM and EFI score. J Pers Med. 2022;12(10):1623. doi: 10.3390/jpm12101623.
11. Vitonis AF, Vincent K, Rahmioglu N, Fassbender A, Buck Louis GM, Hummelshoj L, et al. World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: II. Clinical and covariate phenotype data collection in endometriosis research. Fertil Steril. 2014;102(5):1223-32. doi: 10.1016/j.fertnstert.2014.07.1244.
12. Hernández Cardona MI, Ajewole C, Lewis H, Carrillo JF, Castellanos ME, Barish S, et al. Time to move beyond surgical classification systems for endometriosis. Int J Gynecol Obstet. 2023;163(1):58-62. doi: 10.1002/ijgo.14786.
13. Casals G, Carrera M, Domínguez JA, Abrão MS, Carmona F. Impact of surgery for deep infiltrative endometriosis before in vitro fertilization: a systematic review and meta-analysis. J Minim Invasive Gynecol. 2021;28(7):1303-1312.e5. doi: 10.1016/j.jmig.2021.02.007.
14. Bień A, Rzońca E, Zarajczyk M, Wilkosz K, Wdowiak A, Iwanowicz-Palus G. Quality of life in women with endometriosis: a cross-sectional survey. Qual Life Res. 2020 Oct 1;29(10):2669-77. doi: 10.1007/s11136-020-02515-4.
15. Warzecha D, Szymusik I, Wielgos M, Pietrzak B. The impact of endometriosis on the quality of life and the incidence of depression - a cohort study. Int J Environ Res Public Health. 2020 May 2;17(10):3641. doi: 10.3390/ijerph17103641.

https://doi.org/10.52645/MJHS.2024.3.04

UDC: 616-089.168.1-06:616.62-008.224

RESEARCH ARTICLE

Postoperative urinary retention - prevalence and risk factors: prospective, cohort study

Natalia Belîi[1,2*], Cătălina Lozan[1]

[1]*Valeriu Ghereg* Anesthesiology and Resuscitation Department No.1, *Nicolae Testemițanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova
[2]*Emilian Cotaga* Clinic, Institute of Mother and Child, Chisinau, Republic of Moldova

ABSTRACT

Introduction. Ensuring perioperative urination maintenance can often be challenging, as postoperative urinary retention is frequently overlooked in favor of more clearly defined goals such as successful surgery, comprehensive postoperative pain control, reducing the risk of postoperative cardiorespiratory complications and shortening the patient's overall hospital stay. However, the inability to initiate urination and empty the bladder in the early postoperative period may negatively affect each of the listed success criteria.

Material and methods. A single-center, prospective, observational, cohort study was conducted, enrolling elderly patients without severe comorbidities. A total of 127 complete datasets were analyzed. Anthropometric parameters, type of surgery, duration of anesthesia and surgery; and several parameters previously reported as risk factors for postoperative urinary retention were recorded. The main objective wasto identify the prevalence of postoperative urinary retention in a surgical group in the Republic of Moldova. The secondary objective was to test the predictive value of a series of parameters (modifiable and non-modifiable) related to the patient or surgical treatment received as risk factors for urinary retention in the first 24 hours postoperatively. Statistical software used: Social Science Statistics (https://www.socscistatistics.com).

Results. The studied surgical population was homogeneous in terms of body mass, height, duration of surgery and anesthesia; heterogeneous by gender (62.2% male) and type of anesthesia (64% general anesthesia). Depending on the definition criteria, the prevalence of postoperative urinary retention varied between 5.5% and 7.9%. The preoperative unmodifiable risk factors for postoperative urinary retention: positive history for hypertension OR = 9.0 (X^2 (1, N = 127) = 5.6, p = 0.017), diabetes mellitus OR = 5.1 (X^2 (1, N = 127) = 5.36, p = 0.021) and stroke OR = 4.83 (X^2 (1, N = 127) = 2.098, p = 0.148).

Conclusions. The prevalence of postoperative urinary retention in a single-center surgical population from the Republic of Moldova varies between 5.5% and 7.9%, depending on the criteria for postoperative urinary retention applied. This variation highlights the need for a consensus on diagnostic criteria for postoperative urinary retention is needed. Patients with hypertension and diabetes mellitus were more likely to develop postoperative urinary retention. Patients with pre-existing neurological disorders such as positive history for stroke and diabetic polyneuropathy were more susceptible for postoperative urinary retention.

Keywords: postoperative urinary retention, risk factors, postoperative complications.

Cite this article: Belîi N, Lozan C. Postoperative urinary retention - prevalence and risk factors: prospective, cohort study. Mold J Health Sci. 2024;11(3):27-33. https://doi.org/10.52645/MJHS.2024.3.04.

Manuscript received: 29.05.2024

Accepted for publication: 03.09.2024

Published: 20.09.2024

[*]**Corresponding author: Natalia Belîi**, PhD, associate professor
Valeriu Ghereg Anesthesiology and Resuscitation Department No.1
Nicolae Testemițanu State University of Medicine and Pharmacy
165 Ștefan cel Mare și Sfânt bd., Chisinau, Republic of Moldova, MD-2004
e-mail: natalia.belii@usmf.md

Key messages

What is not yet known on the issue addressed in the submitted manuscript

Currently no national studies would report the prevalence and risk factors for postoperative urinary retention.

Authors' ORCID IDs
Natalia Belîi – https://orcid.org/0000-0002-2351-0279
Cătălina Lozan – https://orcid.org/0009-0004-3554-0514

The research hypothesis
To identify the prevalence of postoperative urinary retention in a surgical population in the Republic of Moldova, with identification of risk factors for this complication.

The novelty added by manuscript to the already published scientific literature
Hypertension is an independent risk factor for postoperative urinary retention. Diabetes mellitus in combination with hypertension predisposes to the development of postoperative urinary retention. Patients with pre-existing neurological disorders such as a history of stroke and diabetic polyneuropathy are more susceptible to postoperative urinary retention.

Introduction

Regardless of the type of surgery, the post-operative period is a critical one, during which many complications can occur, such as acute post-operative pain, respiratory and/or hemodynamic instability, nausea and post-operative vomiting. Postoperative urinary retention (POUR) is one of the complications that can develop in the first 24 hours after surgery and often remains unrecognized and underestimated. Essentially, POUR is the inability to urinate in the presence of a full bladder in the early postoperative period. The prevalence of the complication varies widely, from 5 to 70% which indicates on the one hand a lack of consensus on clear criteria for POUR, and on the other hand confirming the multitude of risk factors related to this complication [1, 2]. Over the years, several risk factors associated with POUR have been studied and reported: unmodifiable (male [2-4], female [4-7], age [1, 2, 4, 8-10], comorbidities (diabetes mellitus (DM) [1, 2, 4], pre-existing neurological disorders [2, 4, 10]) and modifiable, related to the type of surgery (anorectal, colorectal, urogenital surgery [1, 2, 4, 6, 8]) and duration of surgical treatment (consisting of surgery under the protection of a certain type of anesthesia) [2-4, 10], intraoperative fluid volume [1, 2, 4, 6, 10], medication used (opioids [4, 8, 10], anticholinergics and antipsychotics [10]) and high American Society of Anesthesiologists score (ASA) [9], among others .

If left undiagnosed and untreated in a timely manner, POUR can lead to increased morbidity due to urinary tract infections, detrusor muscle dysfunction, arrhythmias and delirium, with prolonged hospital stay [2]. These complications associated with POUR have increased attention on early diagnosis of the phenomenon with the development of prevention strategies. Recently, preventive ultrasound diagnosis of POUR has gained significant importance [11].

The perioperative period may affect micturition with precipitation of POUR. As a spinal reflex controlled by the brainstem, the urination process is a complex one, consisting of 2 phases - the storage phase (mediated by sympathetic innervation) and the emptying phase (provided by parasympathetic fibers). The bladder itself is a container with a flexible muscular wall, which can hold an increasing volume of urine without large variations in pressure until a certain threshold is reached. On average, normal bladder capacity is 400-600 ml [10]. The first impulse to urinate occurs when the bladder volume is about 150 ml, and the sensation of fullness occurs at 300 ml volume, which, once exceeded, transmits the information through the pelvic splanchnic system, e activating emptying process by parasympathetic fibers [4]. For bladder emptying to occur, inhibition of the motor cortex must be absent and the contraction of the detrusor muscle. Motor cortex disinhibition is triggered by pudendal afferents as soon as urine enters the posterior urethra. As a result, relaxation of the pelvic floor muscle, descent of the levator ani muscle and voiding of urine occurs [1, 4, 10].

Surgical and intra-anesthetic stressor factors, acute postoperative pain, medications used, and patient comorbidities can complexly interfere with the physiological pathways of micturition, resulting in POUR [3, 5, 8, 10]. For instance, opioids may alleviate the sensation of bladder fullness through parasympathetic inhibition and increased sphincter tone due to increased sympathetic activity [4, 5, 10]. Beyond smooth muscle relaxation with reduced bladder contractility, multimodal general anesthesia also predisposes to POUR by causing autonomic bladder tone dysregulation [3-5]. Neuraxial techniques interfere with both the afferent and efferent pathways of micturition, with the prevalence of POUR being directly proportional to the duration of action of the local anesthetic molecule introduced intrathecally [2-5, 10]. Neuraxial opioids are associated with an increased prevalence of POUR compared with their intravenous administration [4].

The study aimed to estimate the prevalence of POUR in a medical institution with a surgical profile from Moldova and to identify a series of risk factors.

Material and methods

Study design and parameters

The prospective, observational, monocentric, cohort study, designed to elucidate the prevalence and characteristics of POUR in a medical institution in Moldova, was conducted from June 1, 2022, to December 31, 2022, at *Valeriu Ghereg* Anesthesiology and Resuscitation Department No.1, and the Institute of Emergency Medicine. All included patients signed informed consent to participate in the study.

Participants

A number of surgical patients were evaluated weekly according to eligibility criteria. The inclusion criteria were age > 18 years, signed informed consent; undergoing general, neuroaxial, locoregional or combined type of anesthesia; surgery lasting > 30 minutes, ASA score I - III. Patients were excluded if they expressed their wish to leave the study, positive history of renal failure, benign prostatic hypertrophy with obstruction, required bladder catheterization from the beginning of the surgery or lasting surgery > 3 hours or were scheduled for ambulatory surgery.

The Consort flow chart with the pattern of refusals, enrolment, and follow-up in the first 24 hours postoperatively is shown in Figure 1.

After obtaining informed consent to participate, the study questionnaire, developed based on the literature review, was completed with the patient's personal and clinical data regarding risk factors for POUR. The questionnaire included 3 compartments: general patient data (comorbidities, chronic medication, surgical profile), data related to peri-anesthesic management and a stipulation of study's inclusion and exclusion criteria. The time points of recording the parameters are represented in the study diagram (Figure 2).

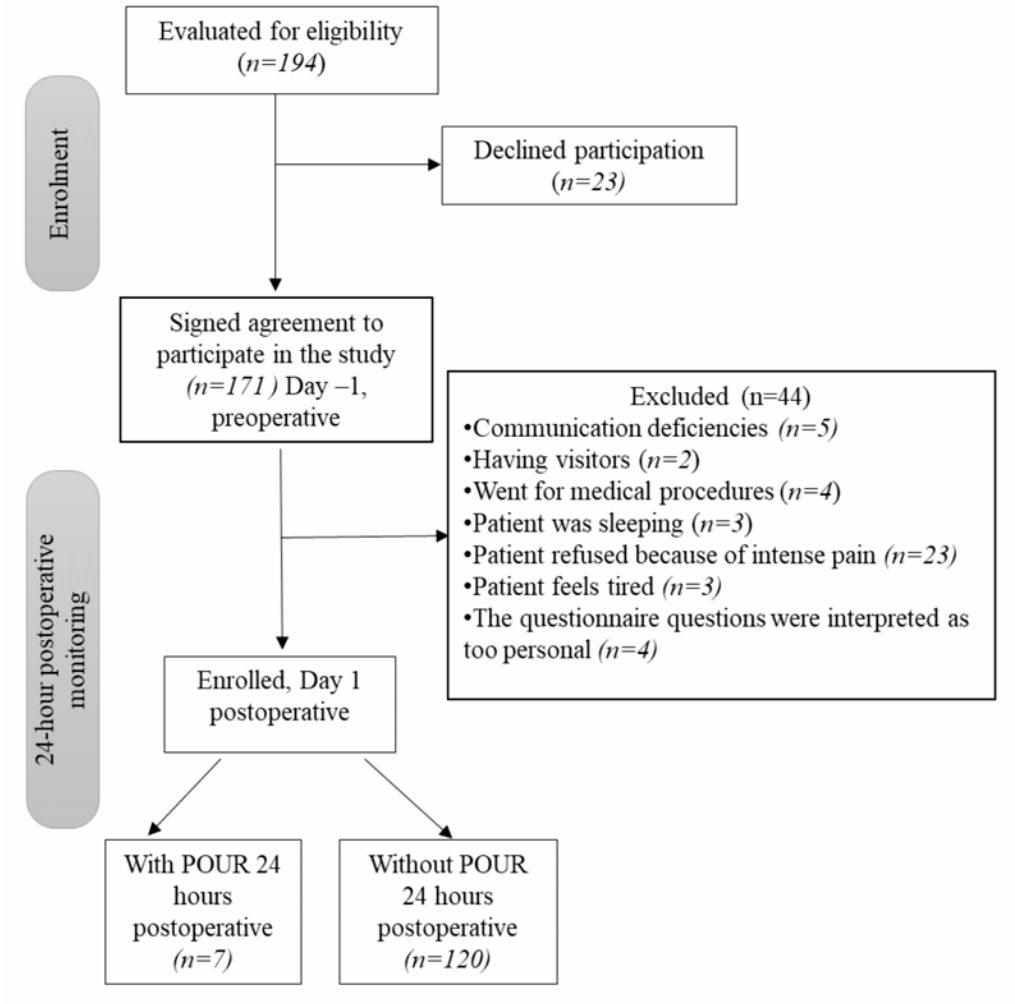


Fig. 1 CONSORT flowchart: refusal scheme, enrolment, postoperative follow-up

***Note*:** *POUR – postoperative urinary retention.*

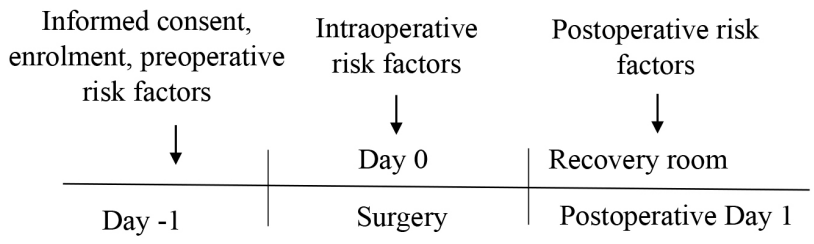


Fig. 2 Study design diagram.

Recorded parameters and statistical analysis

The following general parameters were recorded: age, sex, height, body mass, type of surgery, duration of anesthesia, duration of surgery; and parameters tested as risk factors: preoperative, intraoperative and postoperative factors, directly related to patient or the medical act itself and the medication administered - their nominal detail are presented in the results. The values of the parameters were numerated via de-identification in an Excel table and then imported into the statistical analysis software Social Science Statistics (https://www.socscistatistics.com). Data are presented as absolute and relative values or mean and standard deviation. The Fisher exact test, the hi-squared independence test (X^2) including Yates correction, odds ratio (OR) were calculated, and a $p<0.05$ was considered statistically significant.

All respondents agreed to participate in the research and signed the informed consent for participation in the study, as well as the informed consents for hospitalization, surgery and anesthesia. The present study observes individuals and measures variables of interest but does not attempt to influence the treatment, lacking randomization of exposure. Also, the observational data are reported in grouped format (counts and percentages), ensuring that participants cannot be identified from the results. The nature of the data reported in the manuscript is not of a sensitive nature, and the study is generally considered a low-risk project.

Results

The general characterization of the 127 patients enrolled in the study is presented in Table 1. The mean age of the patients was 47.0±19 years (ranging from 18 to 83 years). The mean age of patients who did not develop POUR versus those who developed POUR was 45.8±18.6 and 60.0±10.9 ($p = 0.951$) years, respectively. The surgical population studied was homogeneous in terms of anthropometric criteria and heterogeneous in terms of gender distribution, with a predominance of males.

Table 1. General characterization of patients enrolled in the study.

Parameter	Enrolled (n = 127)	Non-POUR (n = 120)	POUR* (n = 7)	No difference
Age, years	47.0±19 (18 – 83)	45.8±18.6 (18 – 83)	60.0±10,9 (42 – 70)	
18 – 24	19 (15.0 %)	19(15.8 %)	0 (0 %)	p* = 0.951
25 – 44	41 (32.3 %)	40 (33.4 %)	1 (14.3%)	
45 – 64	35 (27.5 %)	33 (27.5 %)	2 (28.6%)	
>65	32 (25.2 %)	28 (23.3 %)	4 (57.1 %)	
Men/ Women	79 (62.2 %)/ 48/ (37.8 %), 1.6/1	76 (63.3 %)/ 44 (36.7 %), 1.7/1	3 (42.9 %)/ 4 (57.1%), 0.75/1	$X^2 = 1.046$ p* = 0.306
Body mass, kg	77.9 (50 – 108)	77.91 (50 – 108)	76.8 (60 – 101)	t = 0.176 p* = 0.860
BMI<25	47 (37 %)	45 (37.5 %)	2 (28.6 %)	$X^2 = 0.226$ p* = 0.942
BMI>25	80 (63 %)	75 (62.5 %)	5 (71.4 %)	
Height, cm	173.8 (157 – 192.0)	174.0 (157 – 192)	170.3 (160 – 187)	t = 0.331 p* = 0.740

***Note*:** data are presented as absolute and relative values, mean and standard deviation, POUR - acute postoperative urinary retention (POUR* - where POUR was considered the inability to urinate in the presence of bladder globus accompanied by specific clinical signs with the need for bladder catheterization [1]); BMI – body mass index, *p < 0.05 statistically significant, t – T-student test.

The surgical procedures included: abdominal surgery - appendectomy (34/127 [26.8%]), cholecystectomy (6/127 [4.7%]), inguinal/ventral hernioplasty (8/127 [6.3%]), laparotomies for acute abdomen (15/127 [15.8%])); pelvic surgery (3/127 [2.35%]); traumatology surgery - upper/ lower limb (25/127 [40.9%], of which 11 cases of septic trauma); thoracotomies (3,127 [2.35%]; neurosurgery (3/127 [2.35%]); oromaxillofacial surgery (3/127 [2.35%]). The average duration of anesthesia was 122.1±31.4 minutes and the average duration of surgery was 111.3±30.3 minutes. The group comprised 3 types of anesthesia: general anesthesia 64% (81/127), spinal anesthesia 26% (33/127), peripheral nerve block 10% (13/127).

In our study, we identified a POUR prevalence of 5.5%. Patients with ASA IV-V anesthetic risk, who have severe preoperative comorbidities, were not included in the present study. As a result, this limitation will not allow us to generalize the obtained POUR prevalence. In addition, the exclusion of patients with ASA IV-V anesthetic risk also eliminates the risk of overestimating POUR prevalence.

The literature reports a wide range of POUR prevalence, from 5% to 70% [2]. The large discrepancy between the reported prevalence may indicate the complexity and multitude of risk factors contributing to the development of POUR on the one hand, and on the other hand, the heterogeneity of criteria used to diagnose POUR. Thus, in the present study, POUR was defined as the postoperative clinical situation characterized by inability to urinate requiring bladder catheterization. However, Cataldo P. [12] and Paulsen E. [13] establish the diagnosis of POUR even in the absence of micturition for ≥ 8 hours postoperatively. In addition to patients who required the insertion of Foley catheter, we recorded 3 patients who reported their first voiding at ≥ 8 hours after surgery (8, 13 and 9.5 hours), which would contribute to an increased prevalence of POUR in the present study from 5.5% (7/127) to 7.9% (10/127). Dobbs S. defines POUR when patient is unable to urinate for ≥12 hours postoperatively [14]. Applying this criterion in our study, POUR would have a prevalence of 6.3% (8/127) (Table 2).

Table 2. Prevalence of postoperative urinary retention depending on the definition criteria.

Postoperative urinary retention definition criteria	International studies	Moldova (present study)
Bladder catheterization [1]	5 -70%	5,5% (7/127)
Absence of urination ≥ 8 hours postoperatively [1, 12, 13]	52%	7,9% (10/127)
Absence of urination ≥ 12 hours postoperatively [1, 14]	36%	6,3% (8/127)

The first mobilization of patients with POUR was at 13.1±5.0 hours after surgery compared to 9.7±4.4 hours (Student's t = 1.97, p = 0.05) for non-POUR patients.

The secondary outcome parameters of the study involved testing a number of previously reported risk factors to determine whether their presence perioperatively would be associated with POUR. From the preoperative patient-related parameters, none were confirmed as a risk factor for POUR: DM, higher anesthetic risk (ASA III versus ASA I-II), ≥ 3 deliveries in women, female gender, chronic beta-blocker medication, Class II NYHA HF, hypothyroidism, age ≥ 60 years or age ≥ 55 years, previous abdominal surgery, myocardial infarction in patient's history, cerebrovascular accident (CVA) in medical history.

Among the patient-related preoperative risk factors that are unmodifiable, essential hypertension (HTN) was detected as an independent risk factor for POUR (Table 3).

Table 3. Preoperative risk factors for acute postoperative urinary retention

Risk factors	Fisher exact	X^2	p*	Odds ratio	X^2 Yates correction	p*
Diabetes mellitus (DM)	0.114	3.712	0.054	4.93	1.526	0.217
≥ 3 childbirths	0.305	1.731	0.188	0.23	0.623	0.429
Anesthetic risk ASA III	0.680	0.380	0.538	1.62	0.040	0.842
Age ≥ 60 years old	0.205	2.258	0.132	3.11	1.175	0.278
Age ≥ 55 years old	0.111	3.189	0.074	4.17	1.926	0.165
BMI > 25	1.000	0.226	0.634	1.50	0.005	0.942
Female gender	0.425	1.180	0.277	2.30	0.147	0.493
HTN	0.041	5.655	0.017	9.00	3.939	0.047
Beta-blocker medication	0.425	1.180	0.277	2.30	0.470	0.493
NYHA II HF	0.426	0.591	0.441	1.77	0.118	0.730
Hypothyroidism	0.151	2.710	0.996	3.96	1.010	0.315
Association HTN+DM	0.026	10.786	0.001	23.0	5.354	0.020
Previous abdominal surgery	0.248	1.852	0.173	3.06	0.947	0.330
Previous myocardial infarction	0.539	0.132	0.716	1.50	0.077	0.781
Previous CVA	0.250	2.098	0.148	4.83	0.201	0.654

Note: DM - diabetes mellitus, BMI - body mass index, ASA - American Society of Anesthesiology, CVA – cerebrovascular accident/ stroke, HF II NYHA - NYHA heart failure grade II, HTN – arterial hypertension; *p < 0.05 statistically significant.

At the same time, DM, a risk factor often reported in the literature, was parametrically at the limit of statistical significance. This risk factor was further analyzed by applying the extended POUR definition (using the criterion of „lack of micturition in the first 8 hours postoperatively" [12, 13]), proving to be a statistically significant risk factor (OR = 5.1; X^2 (1, N = 127) = 5.36, p = 0.021). Returning to the study group where only the need for bladder catheterization was considered as POUR, we analyzed the association between HTN and DM, in our study they were detected as a combination of risk factors for POUR. Similarly, stroke was tested as a risk factor on the group that included both patients with POUR (7/127) and those who had no voiding in the first 8 hours postoperatively (3/127) with confirmation of risk factor status (OR = 4.83 (X^2 (1, N = 127) = 7.405, p = 0.006).

From the intraoperative and intra-anesthetic parameters tested for the quality of risk factors for POUR none was confirmed (Table 4).

Table 4. Intraoperative and intra-anesthetic risk factors for acute postoperative urinary retention

Risk factors	Fisher exact	X^2	p*	Odds Ratio	X^2 Yates correction	p*
Fasting for fluids ≤ 6 hours	0.706	0.291	0.589	1.52	0.023	0.880
Surgery duration > 90 min.	1.000	0.016	0.899	1.11	0.087	0.767
Spinal anesthesia	1.000	0.026	0.872	1.15	0.080	0.777
Fentanyl ≥ 0,5 mg total	1.000	0.022	0.881	0.87	0.100	0.752
Atropine administration	0.103	3.564	0.059	4.48	2.211	0.137
Fentanyl ≥ 0,5 mg + 0,1 mg p/o	1.000	0.156	0.693	1.78	0.134	0.714
Anesthesia ≥ 95 min.	1.000	0.045	0.832	0.83	0.056	0.813
Abdomen + lower limb	1.000	0.073	0.787	1.35	0.055	0.815
Without NSAIDs	0.129	2.801	0.094	5.88	1.297	0.255
Opioid vs. non-opioid analgesia	0.678	0.070	0.792	0.80	0.036	0.850
Fluids ≥ 1500 ml i/ op	0.707	0.291	0.589	1.520	0.023	0.881
Bleeding volume ≤ 400 ml	0.478	0.296	0.586	0.55	0.0216	0.883
Analgesia (promedol + NSAIDs)	0.330	1.471	0.225	5.17	0.071	0.789
Fentanyl vs. Morphine p/o	1.0	0.037	0.847	1.27	0.173	0.677

Note: *NSAIDs - non-steroidal anti-inflammatory drugs, min - minutes, i/op - intraoperative, p/o - postoperative; *p < 0.05 statistically significant.*

Discussions

The present study aimed to test the risk factor associated with POUR for a number of perioperative parameters.

The surgical population studied inadvertently included predominantly male subjects (79/127 (62.2%)). However, according to our results, the prevalence of POUR was equivalent in both women (4/7) and men (3/7). Thus, sex remains a controversial risk factor. Some studies report that male sex is more frequently associated with POUR [2, 3], particularly due to specific pathologies such as benign prostatic hypertrophy [6]. Other studies report that the female sex is more susceptible to POUR [8]. Regarding patients' chronic medication, in our study patients with benign prostatic hypertrophy were excluded, as they were chronically medicated with alpha-receptor blockers (e.g., tamsulosin), which could have been an important factor of bias.

Advancing age increases the risk of POUR, with reports that patients aged ≥ 50 years develop POUR 2.4 to 2.8 times more frequently, which is attributed to progressive neuronal degeneration with bladder dysfunction [2-4, 6]. In our study, however older age (≥ 60 years/ ≥ 50 years) did not confirm its status as a risk factor for POUR. The explanation could lie in the fact that we excluded from the outset the anesthetic population with ASA score > III and orthopedic surgery.

Among the patient-related preoperative risk factors that are unmodifiable, HTN has been detected as an independent risk factor for POUR, consistent with previous studies.

Thus, in our study, patients with pre-existing neurological disorders such as stroke and diabetic neuropathy more frequently developed POUR. Pathophysiologically, the association of POUR and DM can be explained by impaired bladder sensation, decreased capacity, and contractility [15]. Similarly, Keita H. [3] confirmed that pre-existing neurological disorders (cerebral palsy, multiple sclerosis, alcoholic or diabetic polyneuropathy, poliomyelitis) as a risk factor for POUR. The same study reports a direct correlation between bladder volume ≥ 270 ml after surgery and POUR. In our study, there was no possibility to estimate bladder volume using ultrasound, but among the whole group of patients, only one patient stopped the intake of clear liquids 2 hours preoperatively, 60 patients did not ingest clear liquids 6 hours preoperatively, 67 respondents abstained more than 6 hours from preoperative fluid intake. In addition, an infusion volume ≥ 1500 ml intra-anesthetic or hemorrhage ≤ 400 ml were not identified as risk factors for POUR. No patient with peripheral nerve block developed POUR.

Although opioids are known to cause urinary retention, this concept was not confirmed in our study. At the same time, opioid-associated POUR phenomenon has been described at fentanyl doses above 1 mg [16]. In our study, regarding the total dose of fentanyl used perianesthetically no statistically significant differences were identified between fentanyl ≥ 0.5 mg + 0.1 mg postoperatively (10/127) versus fentanyl < 0.5 mg + 0.1 mg postoperatively (17/127). In addition, all patients had intra-anesthetic summary dose of fentanyl ≤ 0.8 mg.

Although non-steroidal anti-inflammatory drugs (NSAIDs) have often been questioned as contributing factors not only to the induction of acute kidney injury and to the precipitation of POUR, in our study no significant differences in the prevalence of POUR were identified between groups of patients who received NSAIDs intraoperatively and/or postoperatively versus those who were not exposed to these drugs. However, some studies describe the protective role of NSAIDs against the development of POUR, with NSAIDs being used in multimodal analgesia regimens to avoid opioid administration [4].

Patients' postoperative analgesia was also studied. Thus, 24.4% patients received nonopioid analgesia with NSAIDs (31/127) with 2 cases of POUR (2/31), 30.7% patients beneficiated of promedol (39/127) with 2 cases of POUR recorded (2/39), 27.6% fentanyl (35/127) with another 2 cases of POUR (2/35) and 17.3% morphine (22/127) with only 1 case of POUR (1/22). Cases of POUR were observed both in the opioid analgesia group, regardless of the morphine administered, and in the non-opioid analgesia group.

When analyzing risk factors that may be related to surgical treatment per se, it has been reported that the prevalence of POUR varies depending on the type of surgery and the likelihood of autonomic nerve injury (as a result of total mesorectal excision), pelvic nerve injury or reflex increase in internal sphincter tone (caused by pain in patients undergoing anorectal surgery) [17]. In the present study, no statistical differences were detected between the groups of patients who underwent abdominal and lower limb versus thoracic and upper limb surgery.

Previous studies support that increased volumes of intraoperatively administered fluids would be associated with higher prevalence for POUR [2-4]. In the present trial, we did not determine statistically significant differences between study groups in which ≥ 1500 mL infusible fluids versus < 1000 mL was administered intraoperatively. It is noteworthy that none of the patients infused with 500 ml-developed POUR.

Strengths and potential biases of the study

One of the strengths is the prospective methodology of the study. Also, to standardize data collection, patients were assessed postoperatively by the same investigator.

The given study has some limitations that need to be taken into consideration. One factor of bias would reside in the small sample and single-center study. Also, in the institution where the study took place, orthopedic surgery patients undergoing spinal anesthesia are inserted with urinary catheters from the beginning of surgery. Therefore, this large group of patients was excluded from the study. Also, patients who developed complications, with admission to Intensive Care Unit, were excluded from the study.

Conclusions

The prevalence of POUR in a single-center surgical population from the Republic of Moldova varies between 5.5% and 7.9%, depending on which criteria for POUR we apply.

In this regard, a consensus on diagnostic criteria for POUR is needed.

Patients with HTN and DM developed more frequently POUR. Patients with pre-existing neurological disorders such as positive history for stroke and diabetic polyneuropathy are more susceptible to POUR. It was also determined that the first mobilization of patients with POUR was later compared to patients who did not develop this complication.

Competing interests

None declared.

Authors' contribution

NB developed the study concept, literature review and survey questionnaire, analyzed the collected data, wrote, translated into English and approved the final version of the manuscript. CL recruited the eligible patients, completed the study questionnaire, monitored the patients in the first 24 hours postoperatively, numerated the data in Excel, and contributed to the literature review. Both authors approved the final version of the manuscript.

Informed consent for publication

Obtained.

Ethics approval

Not needed for this study.

Funding

The study had no external funding.

References

1. Brouwer TA, Rosier PF, Moons KG, et al. Postoperative bladder catheterization based on individual bladder capacity: a randomized trial. Anesthesiology. 2015;122(1):46-54. doi: 10.1097/ALN.0000000000000507.
2. Baldini G, Bagry H, Aprikian A, et al. Postoperative urinary retention: anesthetic and perioperative considerations. Anesthesiology. 2009;110(5):1139-1157. doi: 10.1097/ALN.0b013e31819f7aea.
3. Keita H, Diouf E, Tubach F, et al. Predictive factors of early postoperative urinary retention in the postanesthesia care unit. Anesth Analg. 2005;101(2):592-596. doi: 10.1213/01.ANE.0000159165.90094.40.
4. Agrawal K, Majhi S, Garg R. Post-operative urinary retention: review of literature. World J Anesthesiol. 2019;8(1):1-12. doi: 10.5313/wja.v8.i1.1.
5. Elsamra SE, Ellsworth P. Effects of analgesic and anesthetic medications on lower urinary tract function. Urol Nurs. 2012;32(6):60-67. doi: 10.7257/1053 816X.2012.32.2.60.
6. Petros JG, Rimm EB, Robillard RJ, Argy O. Factors influencing postoperative urinary retention in patients undergoing elective inguinal herniorrhaphy. Am J Surg. 1991;161(4):431-433. doi: 10.1016/0002-9610(91)91105-R.
7. Myles PS, Hunt JO, Moloney JT. Postoperative 'minor' complications. Comparison between men and women. Anaesthesia. 1997; 52(4):300-306. doi:10.1111/j.1365-2044.1997.89-az0091.x.
8. Toyonaga T, Matsushima M, Sogawa N, Jiang SF, Matsumura N, Shimojima Y, Tanaka Y, Suzuki K, Masuda J, Tanaka M. Postoperative urinary retention after surgery for benign anorectal disease: potential risk factors and strategy for prevention. Int J Colorectal Dis. 2006;21(7):676-682. doi: 10.1007/s00384-005-0077-29.
9. Changchien CR, Yeh CY, Huang ST, Hsieh ML, Chen JS, Tang R. Postoperative urinary retention after primary colorectal cancer resection via laparotomy: a prospective study of 2,355 consecutive patients. Dis Colon Rectum. 2007;50(10):1688-1696. doi: 10.1007/s10350-007-0305-7.
10. Choi S, Awad I. Maintaining micturition in the perioperative period: strategies to avoid urinary retention. Curr Opin Anaesthesiol. 2013;26(3):361-7. doi: 10.1097/ACO.0b013e32835fc8ba.
11. Ozturk NK, Kavakli AS. Use of bladder volume measurement assessed with ultrasound to predict postoperative urinary retention. North Clin Istanb. 2017;3(3):209-216. doi: 10.14744/nci.2016.03164.
12. Cataldo PA, Senagore AJ. Does alpha sympathetic blockade prevent urinary retention following anorectal surgery? Dis Colon Rectum. 1991;34(12):1113-1116. doi: 10.1007/BF02050073.
13. Paulsen EK, Porter MG, Helmer SD, Linhardt PW, Kliewer ML. Thoracic epidural versus patient-controlled analgesia in elective bowel resections. Am J Surg. 2001;182(6):570-577. doi: 10.1016/S0002-9610(01)00792-9.
14. Dobbs SP, Jackson SR, Wilson AM, Maplethorpe RP, Hammond RH. A prospective, randomized trial comparing continuous bladder drainage with catheterization at abdominal hysterectomy. Br J Urol. 1997;80(4):554-556. doi: 10.1046/j.1464-410X.1997.t01-1-00376.x.
15. Kebapci N, Yenilmez A, Efe B, Entok E, Demirustu C. Bladder dysfunction in type 2 diabetic patients. Neurourol Urodyn. 2007;26(6):814-9. doi: 10.1002/nau.20422.
16. Lamonerie L, Marret E, Deleuze A, Lembert N, Dupont M, Bonnet F. Prevalence of postoperative bladder distension and urinary retention detected by ultrasound measurement. Br J Anaesth. 2004;92(4):544-546. doi: 10.1093/bja/aeh099.
17. Jang HJ, Kang S, Lee S, Park JS, Kim D, Ahn S. Randomized controlled trial of tamsulosin for prevention of acute voiding difficulty after rectal cancer surgery. World J Surg. 2012;36(11):2730-7. doi: 10.1007/s00268-012-1712-z.

https://doi.org/10.52645/MJHS.2024.3.05

UDC: [616.98:578.834.1]-085.835:546.214

RESEARCH ARTICLE

The impact of ozone therapy on the progression of COVID-19 patients

Natalia Cernei[1*], Serghei Şandru[1], Serghei Cobîleţchi[1], Ivan Cîvîrjîc[1], Ion Chesov[1,2], Ruslan Baltaga[1,3]

[1]*Valeriu Ghereg* Anesthesiology and Resuscitation Department No. 1, *Nicolae Testemiţanu* State University of Medicine and Pharmacy, Chişinău, Republic of Moldova
[2]Department of Anesthesiology and Intensive Care, *Gheorghe Paladi* Municipal Clinical Hospital, Chişinău, Republic of Moldova
[3]Department of Anesthesiology and Intensive Care, Oncology Institute, Chişinău, Republic of Moldova

ABSTRACT

Introduction. Ozone therapy can be used as a monotherapy or as an adjunctive treatment to standard COVID-19 treatment protocols. Current evidence indicates that this approach may improve clinical outcomes, paraclinical markers, and reduce radiological signs of inflammation, with no side effects.

Material and methods. The study included 100 consecutive patients aged 18 and older with COVID-19, admitted to the Intensive Care Unit at the Institute of Emergency Medicine. Patients were randomly divided into two groups: 50 patients underwent treatment according to the National Clinical Protocol along with major ozonated autohemotherapy (the study group), while the other 50 patients were treated only according to the National Clinical Protocol (the control group).

Results. Although the initial oxygenation index (PaO2/FiO2) values were similar in both study groups, a dynamic analysis revealed a clear efficacy of ozone therapy. By the end of the first-week treatment, the mean oxygenation index in the ozone-treated group was significantly higher than in the standard treatment group: 296.8±105.1 mm Hg versus 232.8±110.6 mm Hg ($p<0.01$). The use of oxygen therapy (70.0% vs. 78.0%), non-invasive ventilation (70.0% vs. 76.0%), and invasive mechanical ventilation (22.0% vs. 38.0%) tended to be lower in the ozone group, though this difference was not statistically significant ($p>0.05$). Both treatment groups showed a significant clinical improvement, with 54.0% of COVID-19 patients in the ozone group and 50.0% in the conventional treatment group achieving a two-point reduction in clinical severity score ($p>0.05$).

Conclusions. The mean oxygenation index significantly increased in the study patient group (246.86±30.3 mm Hg on day 1 and 296.75±105.1 mm Hg on day 7 of treatment; $p<0.01$) and remained unchanged in the control group (235.86±33.4 mm Hg on day 1 and 232.82±110.6 mm Hg on day 7 of treatment; $p>0.05$). Although the mortality rate was lower among COVID-19 patients treated with ozone therapy (24.0%) compared to those receiving standard treatment (34.0%), this difference did not achieve any statistical significance.

Keywords: ozone therapy, major ozonated autohemotherapy, COVID-19, SARS-CoV-2, Brixia score, oxygenation index, D-dimers.

Cite this article: Cernei N, Şandru S, Cobîleţchi S, Cîvîrjîc I, Chesov I, Baltaga R. The impact of ozone therapy on the progression of COVID-19 patients. Mold J Health Sci. 2024;11(3):34-41. https://doi.org/10.52645/MJHS.2024.3.05.

Manuscript received: 14.08.2024

Accepted for publication: 03.09.2024

Published: 20.09.2024

***Corresponding author:**
Natalia Cernei, PhD fellow, assistant professor,
Valeriu Ghereg Anesthesiology and Resuscitation Department No. 1,
Nicolae Testemiţanu State University of Medicine and Pharmacy,
Ştefan cel Mare şi Sfânt Blvd. 165, Chişinău, Republic of Moldova, MD-2004,
e-mail: nataliacernei1@gmail.com

Key messages

What is not known yet about the issue addressed in the submitted manuscript

A therapeutic approach based on symptomatic support remains a *sine qua non* condition to prevent the SARS-CoV-2 pandemic and its complications. Despite the slow emergence of an ideal antiviral treatment, various other effective therapeutic options have gained substantial scientific and practical interest, showing promising potential to reduce the damage caused by SARS-CoV-2. In this con-

Author's ORCID IDs
Cernei Natalia – https://orcid.org/0000-0002-2031-5881
Serghei Şandru – https://orcid.org/0000-0002-2973-9154
Ivan Cîvîrjîc – https://orcid.org/0000-0002-1360-5485
Ion Chesov – https://orcid.org/0000-0001-5083-4757
Ruslan Baltaga – https://orcid.org/0000-0003-0659-4877

text, oxygen-ozone therapy has been recognized as a highly effective adjunctive treatment that can effectively counteract the effects of COVID-19, leading to improvements in clinical symptoms, paraclinical markers, and radiological parameters in patients.

The research hypothesis

This study aims to evaluate the clinical and paraclinical effectiveness of combining conventional ozone therapy treatment (major ozone autohemotherapy) in SARS-CoV-2 infected patients, in comparison to a conventional treatment alone.

The novelty added to the scientific literature in the field

This study is scientifically significant as it evaluates the impact of ozone therapy on inflammation and respiratory parameters in COVID-19 patients. These factors are critical for clinical outcomes and survival rates, offering potential ways to improve patient recovery.

Introduction

Today, the COVID-19 pandemic continues to have a significant impact worldwide, as the global scientific community remains focused on discovering new therapeutic approaches, identifying mortality predictors, and implementing these findings into clinical practice. The goal is to achieve better clinical outcomes, manage symptoms effectively, and reduce both critical complications and overall mortality rates [1].

Ozone therapy is a promising complementary treatment with a wide range of therapeutic applications [2]. A systematic review of the literature indicates that ozone therapy can be used as a monotherapy or as a complementary treatment to standard protocols for COVID-19 patients. The scientific evidence suggests that this therapy has contributed to improvements in clinical symptoms, paraclinical markers, and radiological signs of inflammation, all without significant side effects [3].

Oxygen-ozone therapy, due to its antioxidant, anti-inflammatory, and antithrombotic properties, may play a crucial role in combating hyperinflammation, immunodeficiency, hypercoagulability, and poor response to conventional therapies induced by COVID-19. Based on the studies published so far, researchers suggest that oxygen-ozone treatment might be a promising adjunctive therapy for mild to severe cases of SARS-CoV-2 infection [4, 5].

Despite encouraging preliminary results from clinical studies and expert opinions, there is still not enough evidence to prove that ozone therapy is a viable treatment for COVID-19 [1, 5]. Therefore, to confirm ozone therapy as a feasible complementary treatment for COVID-19, to guide further clinical applications, and to assess its effect on the progression of SARS-CoV-2 infection, randomized controlled trials are needed [6].

In this context, the purpose of the study is to assess the clinical efficacy of ozone treatment (major ozonated autohemotherapy) in patients with SARS-CoV-2.

Material and methods

The present study was carried out at the *Valeriu Ghereg* Anesthesiology and Resuscitation Department No.1 of *Nicolae Testemiţanu* State University of Medicine and Pharmacy, Republic of Moldova.

To assess the efficacy of ozone therapy (major ozonized autohemotherapy – MAH) in patients with SARS-CoV-2, a prospective, randomized clinical study was conducted. This research evaluated the clinical features of COVID-19 patients based on their treatment regimen (either conventional treatment alone or conventional treatment combined with ozone therapy).

The study included patients aged 18 and older with COVID-19 who were admitted to the Intensive Care Unit (ICU) of the Emergency Medicine Institute (IMU) from July 2020 to February 2021. The author identified the patients for the study at the time of their admission to IMU. All patients admitted during the reference period who met the inclusion criteria were enrolled in the study.

To improve the accuracy of sample size calculation and increase precision, the Chi-squared power test was used. The data analysis focused on testing the hypothesis that ozone therapy is related to survival, using the following parameters:

$$Effect\ size\ (w)\ =\ 0.3$$

$$Significance\ level\ =\ 0.05$$

$$Power\ =\ 0.8$$

$$Df\ =\ 1$$

$$Total\ sample\ size\ =\ 87\ [682].$$

For a 95.0% confidence interval, the required sample size was calculated to include at least 87 patients. The representative study sample involved 100 patients for a 5% margin of error, thus, exceeding the minimum threshold of 88 patients. The patients were randomly divided into two groups with a 1:1 ratio: 50 COVID-19 patients were treat-

ed based on the National Clinical Protocol combined with ozone therapy (major ozonated autohemotherapy) in the COVID-19 ICU of IMU (main study group), and 50 COVID-19 patients received only the conventional treatment as outlined in the National Clinical Protocol in the COVID-19 ICU of IMU (control group).

The study was conducted in several stages:

Stage 1: Patients included in the study underwent clinical and paraclinical assessments (including laboratory and instrumental diagnostic methods).

Stage 2: Statistical processing of the results obtained.

Stage 3: Evaluation of the main indicators characterizing the study groups. Comparative assessment of clinical features, biochemical and imaging indicators depending on the treatment method. Improving the treatment algorithm for COVID-19 patients.

Stage 4: Data presentation.

Inclusion in the study required written informed consent from each patient for the investigations, treatment, collection of relevant clinical data, and outcome assessment.[9]

To provide greater research accuracy, a set of inclusion and exclusion criteria was used to define the study parameters and thus focusing on a specific representative group.

Inclusion criteria for the study were as following:

- Patients diagnosed with COVID-19 based on WHO guidelines and confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 RNA from nasopharyngeal swabs (a molecular biology technique).
- Patients with COVID-19 aged ≥18 years.
- Patients with COVID-19 who have a mildly reduced oxygenation index (PaO_2/FiO_2 >200-≤300 mmHg) and SpO_2 levels between 88-96%.
- Patients with COVID-19 with radiologically confirmed pneumonia and a Brixia score within 6-10 points.
- Patients without contraindications for systemic ozone therapy.
- Patients who have read and signed the informed consent for participation in the study.

Exclusion criteria for the study included:

- Patients under 18 years old.
- Patients with multiple organ failure syndrome.
- Pregnant women, postpartum women, and breastfeeding women.
- Patients on immunosuppressive therapy.
- Individuals undergoing mechanical ventilation at the time of study enrollment.
- Patients with contraindications for systemic ozone therapy.
- Patients who refused to participate in the study.

The cases were randomized using block randomization procedures. According to the estimated sample size, 100 consecutive patients (who were not excluded) were selected for analysis and allocated to one of two groups: (a) the experimental group or (b) the control group. The study is based on the hypothesis that early systemic oxygen-ozone therapy may be effective in improving disease progression and/or partially improving the onset of "cytokine storm" syndrome, at least partially, having a significant impact on patient prognosis.

Upon confirming eligibility, patients with COVID-19 were fully informed about the study's purpose, objectives, the benefits and risks associated with the research and the treatment, the expected outcomes, as well as the practical applications of the study.

Standard medical care and monitoring for all COVID-19 patients were administered in accordance with national and institutional protocols for inpatient and outpatient management of this patient population.

The study protocol was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (Minutes No. 1 dated 20.07.2020).

All patients included in the study were examined using the following research methods:

Clinical methods. Clinical, biochemical, and imaging indicators were assessed, as well as rates of invasive and non-invasive mechanical ventilation, mortality rates, and length of hospital stay. Data were collected from medical records, including initial and follow-up visits, as well as clinical, instrumental, and laboratory investigations conducted both during and after treatment. The data were then analyzed comparatively, assessing changes over time between the two study groups.

Treatment methods. The standard treatment for patients infected with SARS-CoV-2 in ICU followed the guidelines set forth in the National Clinical Protocol, Provisional Editions III and IV [7, 8], and the Practical Guide for Managing Severe Complications from COVID-19 [9].

Ozone therapy included:

- Conventional or standard treatment.
- MAH – the intravenous infusion of ozonated autologous whole blood under strict aseptic and antiseptic conditions. Specifically, 80-120 ml of venous blood mixed with 10 ml of 3.13% sodium citrate solution (as an anticoagulant) was enriched with a gas mixture of oxygen and ozone at a 1:1 ratio, with an ozone concentration of 40 μgN/mL. The mixture was thoroughly agitated for 5 minutes. Following ozonation, the blood was reinfused into the same vein over approximately 10-15 minutes. This procedure was repeated 7 times, with one session every 24 hours for 7 consequent days [10]. The ozone was generated by the Medozon Herrman medical device.

All ozone therapy methods used in patients with COVID-19 comply with the recommendations of the World Federation of Oxygen and Ozone Therapy (WFOT Review of Evidence-Based Ozone Therapy) and international guidelines (The International Scientific Committee of Ozone Therapy "Madrid Declaration on Ozone Therapy") and are included into the ozone generator software [5].

Clinical assessment. Fever was defined as an armpit temperature of ≥37.5°C [2]. Clinical improvement was characterized by a two-point reduction on a 6-point severity scale [11] (while comparing the patient's condition on the

first day in the ICU), either upon transfer from the ICU to the COVID-19 ward, at discharge, or at the time of death:

6 points = death

5 points = hospitalization for invasive mechanical ventilation

4 points = hospitalization for non-invasive ventilation or high-flow oxygen therapy

3 points = hospitalization for oxygen therapy (excluding high-flow oxygen therapy or non-invasive ventilation)

2 points = hospitalization with no need for oxygen therapy

1 point = while the patient being transferred to the COVID-19 ward, met the discharge criteria, or discharged from the hospital alive.

Table 1. Standard Treatments for SARS-CoV-2 Infected Patients in the ICU

1. Oxygen therapy	• Facial mask • High-Flow Nasal Cannula (HFNC) • Non-Invasive Ventilation (NIV) • Mechanical Ventilation (MV)
2. Glucocorticoids	Methylprednisolone: Administer 0.75 to 2 mg/kg/day (based on the CRP level at admission, divided into two doses as determined by the attending physician).
3. Anticoagulants	Enoxaparin: Administer 4000 IU (40 mg) subcutaneously twice daily.
4. Antibiotic Therapy: • Initiation criteria: * suspected bacterial superinfection in the second week of disease; * prior glucocorticoid therapy before ICU admission; * elevated procalcitonin levels >0.5 ng/ml; * sensitivity results from bacterial cultures.	Antibiotic options included macrolides, second- and third-generation cephalosporins, and carbapenems. Doses and treatment length were customized based on the attending physician's decision.
5. Complementary therapy	• H2 Receptor antagonists: * Famotidine 20 mg, twice/day • Vitamin therapy: * Ascorbic acid 500 mg x 3 times/day * Vitamin D3 8-10 drops daily • Pentoxifylline 400 mg, once daily
6. Infusion therapy:	Fluid intake restriction, by maintaining a mean arterial pressure above 60 mmHg, the urinary output greater than 0.5 ml/kg/h, with no increase in nitrogen retention by-products, as well as the hematocrit level at 30%.

Note: ICU- intensive care unit; HFNC- High-Flow Nasal Cannula; NIV- Non-Invasive Ventilation; MV- Mechanical Ventilation; CRP- C-reactive protein; Enoxaparin 4000IU- Anti Xa IU/0,4 ml.

The discharge criteria showed a clinical recovery, including fever management, respiratory rate of <24 breaths per minute, oxygen saturation >94% on FiO_2 of 0.21%, and no cough for at least 72 hours [11].

One study objective was to measure the time to clinical improvement within 28 days, defined as the time (in days) from study randomization to the day of a 2-point decline on a 6-point ordinal scale (from 1 = discharge to 6 = death) or discharge from hospital alive, whichever occurred first [11].

Decisions regarding invasive mechanical ventilation and non-invasive ventilation were made based on clinical standards and the medical consultant's assessment.

Biochemical methods. Hematological tests were conducted, including a complete blood count (CBC), counts of lymphocytes and neutrophils, the neutrophil-to-lymphocyte ratio (NLR), and platelet count. Biochemical assessments included procalcitonin (PCT), C-reactive protein (CRP), creatinine, urea, electrolytes (sodium and potassium), total bilirubin, aspartate aminotransferase (AST), creatine kinase (CK), fibrinogen, and D-dimers. These tests were performed using the HumaStar 300SR Mindray BS-240Pro automatic biochemical analyzer in the Biochemistry Laboratory at IMU [12].

D-dimer levels were measured using an immunofluorescence assay and reported in fibrinogen-equivalent units (μg/ml) [12].

The following biochemical test values were used for normal reference: D-dimers – <0.5 mg/mL, CRP – 0.8-3.0 mg/L, PCT – <0.5 ng/mL, and leukocytes – 4-10^9/L. Lymphocytopenia was characterized by a lymphocyte count <1500 cells per cubic millimeter of blood. Thrombocytopenia was identified as a platelet count <150,000 cells per cubic millimeter of blood.

X-ray imaging test. A chest X-ray was conducted using the SHIMADZU Mobile Art Evolution portable radiography unit. To assess the severity of COVID-19 pneumonia and guide the selection of appropriate ventilation support, the Brixia score was employed. This score offers a feasible and efficient semi-quantitative evaluation of COVID-19 severity, using an 18-point scale to classify lung involvement based on the type and extent of pulmonary abnormalities [13].

Statistical data processing methods. The primary study data were introduced into an electronic database and processed using functions and modules from SPSS version 16.0 for Windows (SPSS Inc., Belmont, CA, USA, 2008) and *Microsoft Office Excel 2019* on a personal computer. Both descriptive and inferential statistical procedures were applied. Pearson's χ^2 test, Yates' correction, or Fisher's exact test were used to compare categorical variables. The t-test or non-parametric tests were applied to assess the statistical significance of mean differences between the study groups: one-way analysis of variance (ANOVA) was conducted, followed by post-hoc tests to explore multiple mean differences among the study groups; the correlation analysis was performed to determine the strength and direction of statistical associations. A bilateral p-value <0.05 was considered statistically significant.

Results and discussions

Additionally, to conventional treatment, ozone therapy has been proposed as an adjunctive treatment for SARS-CoV-2 infection, due to its therapeutic effects, including antioxidant, anti-inflammatory, antithrombotic, antiviral, and immunomodulatory properties. Oxygen-ozone therapy could play a crucial role in fighting off hyperinflammation, immunodeficiency, hypercoagulability, and inadequate response to treatments caused by COVID-19. Research find-

ings suggest that ozone therapy could be a promising complementary treatment for SARS-CoV-2 infection, including both mild and severe cases [4, 11].

The study compared 50 ICU patients with COVID-19 who received both conventional treatment and ozone therapy (SG) with another 50 ICU patients treated exclusively with conventional methods (CG). The gender distribution was similar across both groups: the study group consisted of 22 men (44.0%) and 28 women (56.0%), while the control group had 23 men (46.0%) and 27 women (54.0%).

The mean age of patients was similar in both study groups: 58.08±9.9 years (ranging 28-73 years old) in SG and 62.36±11.6 years (ranging 34-84 years old) in CG.

The mean time from symptoms onset to ICU admission was also similar between the study groups: 6.86±4.3 days in COVID- 19 patients who underwent ozone therapy and 7.94±3.8 days in those receiving standard treatment (p>0.05).

The mean values for clinical assessments, PaO_2/FiO_2 ratio, blood parameters, NLR, CRP, PCT, urea (mmol/L), and the Brixia score were similar in both study groups. Several studies found that the mean overall hospital stay length was also similar between patients treated with ozone and those receiving standard treatment (p>0.05): 8 days vs. 28 days [11], 9.37±3.84 days vs. 9.37±5.38 days [14], and 8 days vs. 9 days [15]. The average hospital stay (17.80±8.9 days in the SG and 17.06±10.6 days in the CG, p>0.05) was not significantly different between the study groups. Similarly, the average ICU stay (8.56±5.3 days in the SG and 10.22±9.0 days in the CG, p>0.05) showed only a slight shorter-term trend in the SG.

Mortality rates among COVID-19 patients have varied significantly, from 3.6% to 26.0%, depending on the study sample and disease severity. Previous research has reported a range of mortality rates for patients requiring ICU admission, including 16%, 38%, 62%, 67%, and 78% [16, 17].

In the current study, the mortality rate for COVID-19 patients treated with ozone therapy in the ICU was notably lower, ranging from 12% to 24.0%, compared to 17% to 34.0% for those receiving conventional treatment. However, this difference did not reach a statistical significance (p>0.05). Similar findings have been reported in other prospective cohort and case-control studies: one study reported 11.0% mortality for patients treated with conventional therapy and ozone therapy vs. 22% for those receiving conventional therapy alone (p>0.05) [11, 18], while another study registered 0% mortality for those treated with both approaches compared to 7% for those treated conventionally alone (p>0.05) [14].

The use of oxygen therapy (35 - 70.0% of COVID-19 patients treated with ozone vs. 39 - 78.0% of patients treated conventionally, p>0.05), non-invasive ventilation (35 - 70.0% of patients treated with ozone vs. 38 - 76.0% treated conventionally, p>0.05), and invasive mechanical ventilation (11 - 22.0% of patients treated with ozone vs. 19 - 38.0% treated conventionally, p>0.05) indicated a decreasing trend in patients from the primary group, though it did not reach statistical significance.

The mean durations for oxygen therapy (8.20±5.4 days for ozone-treated patients vs. 9.77±8.7 days for conventionally treated patients, p>0.05), non-invasive ventilation (6.06±3.9 days for ozone-treated patients vs. 6.29±6.8 days for conventionally treated patients, p>0.05), and invasive mechanical ventilation (6.82±5.5 days for ozone-treated patients vs. 7.47±6.8 days for conventionally treated patients, p>0.05) also showed a non-significant decreasing trend in the ozone-treated group.

The treatment led to significant clinical improvements in both study groups. The average clinical improvement score decreased notably, from 3.66±0.5 points on day 1 to 2.52±1.6 points on day 7 (p<0.001) in the ozone therapy group (SG), and from 3.70±0.5 points on day 1 to 2.84±1.8 points on day 7 (p<0.001) in the conventional therapy group (CG). Clinical improvement, characterized by a decrease of two or more points in the score, was seen in 27 (54.0%) of COVID-19 patients treated with ozone and in 25 (50.0%) of those treated with conventional methods (p>0.05) (Table 1).

A research study revealed that, within 10 days of ozone treatment, there was a significant reduction in inflammatory and thromboembolic markers (PCR and D-dimers) with p-values ranging from <0.05 to <0.001, and a significant improvement in major respiratory indices (SpO_2/FiO_2 ratio). By day 10, all patients showed significant resolution of bilateral interstitial infiltrates [18].

In this study, the average oxygenation index – PaO_2/FiO_2 – increased significantly in the ozone therapy group (from 246.86±30.3 mm Hg on day 1 to 296.75±105.1 mm Hg on day 7 of treatment; p<0.01), whereas no change was observed in the control group (from 235.86±33.4 mm Hg on day 1 to 232.82±110.6 mm Hg on day 7; p>0.05). Despite similar initial values of the oxygenation index in both groups, the dynamic analysis demonstrated a clear efficacy of ozone treatment. At the end of the first week, the mean oxygenation index was significantly higher in the ozone therapy group compared to the standard treatment group: 296.8±105.1 mm Hg vs. 232.8±110.6 mm Hg (p<0.01). Additionally, the median absolute difference between the oxygenation index on the 7th day of ozone treatment and its initial value was positive – 53.5 (IQR -19.7 to 106) mm Hg, while the control group showed a negative difference of -19 (IQR -85.2 to 56.5) mm Hg (p<0.05). Thus, combined ozone therapy treatment showed a more positive trend in the oxygenation index compared to standard treatment.

On the 7th day of treatment, COVID-19 patients from the SG showed a trend towards increased frequencies of normal PaO_2/FiO_2 ratios (21 - 43.8% and 14 - 28.0% of cases, respectively; p>0.05) and milder ARDS (PaO_2/FiO_2 >200-≤300 mmHg) (18 - 37.5% and 15 - 30.0% of cases, respectively; p>0.05). In contrast, patients with COVID-19 from the CG experienced a statistically significant increase in worsening ARDS (≤200 mmHg) (21 - 42.0% and 9 - 18.8% of cases, respectively; p<0.05). There was also an increasing trend in oxygenation impairment from moderate (15 - 30.0% and 7 - 14.6% of cases, respectively; p>0.05) to severe (6 - 12.0% and 2 - 4.2% of cases, respectively; p>0.05) in patients from CG.

Table 1. Clinical, laboratory, and imaging parameters (X±SD) for COVID-19 patients on day 1 and day 7 of treatment, within both study groups

Parameters	Study Group		p	Control Group		p	p (Day 1)	p (Day 7)
	Day 1	Day 7		Day 1	Day 7			
PaO_2/FiO_2 (mm Hg)	246,86±30,3	296,75±105,1	<0,01	235,86±33,4	232,82±110,6	NS	NS	<0,01
PCR (mg/L)	75,17±53,9	44,88±53,2	<0,01	82,52±59,9	44,85±57,9	<0,001	NS	NS
PCT (ng/mL)	0,18±0,3	0,17±0,3	NS	0,13±0,1	0,14±0,2	NS	NS	NS
Brixia Score (points)	8,30±1,6	7,48±4,0	NS	8,38±1,3	9,44±4,1	NS	NS	<0,05
D-Dimers (μg/mL)	0,98±0,8	2,58±2,9	<0,01	1,98±2,5	2,97±2,9	<0,05	<0,01	NS
Fibrinogen (g/L)	4,36±0,8	3,60±1,2	<0,01	4,36±1,1	4,57±2,9	NS	NS	<0,05
Leucocytes ($x10^9$/L)	10,09±5,2	9,80±4,1	NS	9,25±4,5	11,79±7,9	<0,01	NS	NS
Neutrophiles (%)	71,68±13,3	72,08±12,8	NS	71,84±10,6	74,04±11,5	NS	NS	NS
Lymphocytes (%)	10,42±6,5	11,77±7,3	NS	11,88±7,1	11,30±6,9	NS	NS	NS
RNL	11,78±13,2	9,85±7,4	NS	9,02±5,9	10,74±9,0	NS	NS	NS
Monocyte s ($x10^9$/L)	5,48±3,3	6,6±3,9	NS	5,66±3,0	5,58±3,7	NS	NS	NS
ESR (mm/h)	26,22±15,9	28,65±16,6	NS	26,14±15,4	32,58±16,2	<0,05	NS	NS
Platelets ($x10^9$/L)	241,58±91,1	284,21±101,0	<0,01	219,84±80,0	276,48±112,3	<0,001	NS	NS
Hemoglobin (g/L)	128,78±14,6	119,85±17,1	<0,001	127,24±16,5	119,94±18,2	<0,01	NS	NS
Albumin (g/L)	36,52±4,1	31,77±4,1	<0,001	34,80±5,7	30,68±4,3	<0,001	NS	NS
Urea (mmol/L)	7,41±3,4	7,32±2,9	NS	8,06±5,6	9,34±7,7	<0,05	NS	NS
Creatinine (mmol/l)	100,92±53,9	92,42±28,3	NS	107,66±63,1	99,88±75,5	NS	NS	NS
ALAT (U/l)	52,34±61,8	68,58±53,2	<0,05	48,04±33,2	67,64±58,8	<0,01	NS	NS
ASAT (U/l)	46,52±35,3	42,50±40,3	NS	51,82±39,6	42,84±33,1	NS	NS	NS
Clinical assessment (points)	3,66±0,5	2,52±1,6	<0,001	3,70±0,5	2,84±1,8	<0,001	NS	NS

Note: SD – standard deviation; PaO_2/FiO_2 – partial pressure of oxygen/fraction of inspired oxygen; CRP – C-reactive protein; PCT – procalcitonin; N/L ratio – neutrophil-to-lymphocyte ratio; VSH – erythrocyte sedimentation rate; ALT – alanine aminotransferase; AST – aspartate aminotransferase; NS – not significant. Data are presented as mean values and standard deviation. Differences in mean values were assessed using the paired t-test or Wilcoxon test.

The average Brixia score was similar between the two groups on day 1 (8.30±1.6 points in SG and 8.38±1.3 points in CG; p>0.05). By day 7, a decreasing trend in the Brixia score was reported towards in SG (7.48±4.0 points; p>0.05), while the CG showed an increasing trend (9.44±4.1 points; p>0.05). However, these changes did not achieve any statistical significance.

A reduced Brixia score in the main cohort was recorded in 50% of cases compared to 42% in the control group (p>0.05). Notably, patients treated with ozone showed a statistically significant improvement in radiological pulmonary findings by the 7th day compared to the control group. On the 7th day of treatment, the average Brixia score was significantly higher in the ozone treatment group (p<0.05). The median absolute change in the Brixia score was 0.5 (IQR – 2.0-3.0) points, compared to 0 (IQR – 4.0-2.0) points in the control group (p<0.05).

Increased levels of D-dimers, C-reactive protein (CRP), ferritin, and interleukin-6 (IL-6) serve as prognostic indicators for patients with COVID-19. These parameters have been associated to an unfavorable prognosis in several studies [10, 19].

In both study groups, there was a statistically significant decrease in the mean hemoglobin levels (128.78±14.6 g/L on day 1 and 119.85±17.1 g/L on day 7, p<0.001 in the study group; 127.24±16.5 g/L on day 1 and 119.94±18.2 g/L on day 7, p<0.01 in the CG) as well as in PCR values (75.17±53.9 mg/L on day 1 and 44.88±53.2 mg/L on day 7, p<0.01 in the SG; 82.52±59.9 mg/L on day 1 and 44.85±57.9 mg/L on day 7, p<0.001 in the CG).

In the SG group, there was a decreasing trend in the mean leukocyte count (10.09±5.2x10^9/L on day 1 and 9.80±4.1x10^9/L on day 7, p>0.05), whereas in the CG, a statistically significant increase was reported (9.25±4.5x10^9/L on day 1 and 11.79±7.9x10^9/L on day 7, p<0.01). A similar pattern was seen in the mean urea levels: a tendency to decrease in the SG (7.41±3.4 mmol/L on day 1 and 7.32±2.9 mmol/L on day 7, p>0.05) and a statistically significant rise in the CG (8.06±5.6 mmol/L on day 1 and 9.34±7.7 mmol/L on day 7, p<0.05).

Mean platelet values increased significantly in patients in SG (241.58±91.1x10^9/L on day 1 and 284.21±101.0x10^9/L on day 7, p<0.01) and in patients in CG (219.84±80.0x10^9/L on day 1 and 276.48±112.3x10^9/L on day 7, p<0.001). D-dimer levels also showed a statistically significant increase in both groups: in the MG (0.98±0.8 μg/mL on day 1 and 2.58±2.9 μg/mL on day 7, p<0.01) and in the CG (1.98±2.5 μg/mL on day 1 and 2.97±2.9 μg/mL on day 7, p<0.05).

Fibrinogen plays a crucial role in blood coagulation and is also considered an indicator of the severity of inflammation. Data analysis showed that in ozone -treated patients, fibrinogen levels decreased significantly by day 7, with values of 3.6 (IQR 2.7-4.2) g/L compared to 4.3 (IQR 3.9-4.8) g/L at the time of enrollment (p<0.001). In contrast, no significant change in plasma fibrinogen concentration was observed in the control group, with levels of 4.6 (IQR 3.6-4.7) g/L on day 7 and 4.4 (IQR 3.9-4.6) g/L on day 1 (p>0.05). On day 7, the mean fibrinogen value was significantly lower in the ozone treatment group: 3.8 (IQR 2.7-4.2) g/L compared to 4.0

(IQR 3.6-4.7) g/L in the control group (p<0.05). Additionally, the median absolute difference between initial and final fibrinogen concentrations was significantly greater in the ozone-treated group: 0.55 (IQR 0.07-1.52) g/L compared to 0.25 (IQR -0.7-0.7) g/L in the control group (p<0.05).

These findings are consistent with a case-control study showing a significant reduction in fibrinogen levels in patients with COVID-19 and severe bilateral pneumonia (n=14) who received both conventional treatment and ozone therapy (713±112 mg/dL and 572±163 mg/dL, respectively; p<0.05). In contrast, patients treated with only conventional methods had fibrinogen levels of 602±160 mg/dL and 528±149 mg/dL, respectively (p>0.05) [20].

The study's strengths include its prospective and randomized design. Nevertheless, several limitations should be mentioned: a) the small sample size, b) the relatively short follow-up duration, c) inclusion of only patients not requiring mechanical ventilation, d) the study was conducted at a single healthcare center, e) it was not a blinded study in terms of treatment provided, f) a slightly younger age of the main study group undergoing ozone autohemotherapy, and g) the inability to calculate patients' BMI due to pandemic conditions.

Thus, the evidence from specialized literature and the current study results indicate that ozone therapy has clinical benefits for COVID-19 patients. Ozone therapy shows promise as an adjunctive treatment for those infected with SARS-CoV-2. The mechanisms of action of ozone therapy support its combined use with other treatments. Additionally, multiple clinical studies have also reported positive outcomes. Systemic oxygen-ozone therapy is particularly important at the disease's onset and before the condition worsens to the point of requiring mechanical ventilation. It also helps modulate laboratory biomarkers, which are crucial for assessing risk and prognosis in COVID-19 patients.

The lack of statistically significant differences in the current study parameters may be due to the small sample size and the study's unicentric design.

Conclusions

Ozone therapy restrains the progression of the SARS-CoV-2 infection and its complications, promotes the recovery of the clinical condition due to its several beneficial properties such as immunomodulatory, antioxidant, anti-inflammatory, and cytoprotective effects. Our study demonstrated that the mortality rate among COVID-19 patients treated with ozone in the ICU was lower compared to those receiving conventional treatment. The impact of ozone therapy on oxygen metabolism resulted in a statistically significant increase in the mean oxygenation index by reactivating the intracellular and extracellular antioxidant systems, effectively countering long-term oxidative stress in various inflammatory and degenerative processes. If administered early in the course of the disease, ozone therapy can prevent the progression to ARDS and help alleviate the severe effects of COVID-19 on lung tissues. Ozone therapy improves blood flow, facilitates oxygen transport in hypoxemic tissues, and reduces blood clotting phenomena in COVID-19 patients. So, under this therapy, COVID-19 patients showed improved blood circulation and oxygen delivery to ischemic tissue and optimized overall metabolism leading to a trend toward milder ARDS.

Our research study showed a decreasing trend in use of oxygen therapy, non-invasive ventilation, and invasive mechanical ventilation with ozone therapy, specifically major ozonized autohemotherapy in COVID-19 patients. Despite encouraging preliminary data from ongoing clinical trials, as well as expert opinion, there is still insufficient evidence to confirm that ozone therapy is a viable treatment option for patients with COVID-19

Competing interests

None declared.

Authors' contributions

NC and RB conceived the study, participated in the study design and assisted in drafting the manuscript. NC data interpretation. IC drafted the manuscript. ICh and SȘ conceived the significant revision of the manuscript and provided significant intellectual involvement. The authors have read and approved the final version of the manuscript.

Acknowledgements and funding

The study had no external funding.

Patient consent

Obtained.

Ethics approval

The study protocol was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (minutes No.1, from 20.07.2020).

References

1. Arias-Vázquez P, Arcila-Novelo R, Ramírez-Wakamatzu M. Is Ozone therapy an adjunct treatment for SARS-CoV-2 / COVID-19 infection? Braz J Pharm Sci. 2022;58:e20775. http://dx.doi.org/10.1590/s2175-97902022e20775.
2. Viebahn-Hänsler R, Fernández O, Fahmy Z. Ozone in medicine: clinical evaluation and evidence classification of the systemic Ozone applications, major autohemotherapy and rectal insufflation, according to the requirements for evidence-based medicine. Ozone Sci Eng. 2016;38(5):322-345. https://doi.org/10.1080/01919512.2016.1191992.
3. Barbosa R, Santo R, Navegante Z, Santos S, Rivera J, Gomes A. Ozone therapy as a treatment option against COVID-19: a literature review. Res Soc Devel. 2021;10(13):e469101321228. https://doi.org/10.33448/rsd-v10i13.21228.
4. Hernández A, Viñals M, Isidoro T, Vilás F. Potential role of Oxygen-Ozone therapy in treatment of COVID-19 pneumonia. Am J Case Rep. 2020;21:e925849. doi: 10.12659/AJCR.925849.
5. International Scientific Committee of Ozone Therapy (ISCO3); Schwartz A, Martínez-Sánchez G. Potential use of ozone in SARS-CoV-2 / COVID-19 [Internet]. Madrid:

ISCO3; 2020 [cited 2022 Sep 23]. Available from: https://docs.bvsalud.org/biblioref/2020/04/1095104/potential-use-of-ozone-in-sars-cov-2-covid-19.pdf.
6. Harapan B, Harapan T. The role of ozone therapy in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19): a review. Med Gas Res. 2023;13(4):165-171. doi: 10.4103/2045-9912.369237.
7. Ministerul Sănătăţii al Republicii Moldova [Ministry of Health of the Republic of Moldova]. Infecţia cu coronavirus de tip nou (COVID-19): Protocol clinic naţional provizoriu (PCN-371) [Novel coronavirus infection (COVID-19): National clinical protocol]. 3rd ed. Chisinau: The Ministry; 2020. 65 p. Romanian.
8. Ministerul Sănătăţii al Republicii Moldova [Ministry of Health of the Republic of Moldova]. Infecţia cu coronavirus de tip nou (COVID-19): Protocol clinic naţional provizoriu (PCN-371) [Novel coronavirus infection (COVID-19): National clinical protocol]. 4th ed. Chisinau: The Ministry; 2020. 78 p. Romanian.
9. Ministerul Sănătăţii al Republicii Moldova [Ministry of Health of the Republic of Moldova]; Cojocaru V, Holban T, Cusnir O, et al. Managementul complicaţiilor severe cauzate de infecţia provocată de coronavirus (COVID-19): Ghid practic [Management of severe complications caused by the coronavirus infection (COVID-19): Practical guide]. Chişinău; The Ministry; 2020. 67 p. Romanian.
10. Çolak Ş, Genç Yavuz B, Yavuz M, Özçelik B, Öner M, Özgültekin A, et al. Effectiveness of ozone therapy in addition to conventional treatment on mortality in patients with COVID-19. Int J Clin Pract. 2021;75(8):e14321. doi: 10.1111/ijcp.14321.
11. Hernández A, Viñals M, Pablos A, Vilás F, Papadakos P, Wijeysundera D, et al. Ozone therapy for patients with COVID-19 pneumonia: preliminary report of a prospective case-control study. Int Immunopharmacol. 2021;90:107261. doi: 10.1016/j.intimp.2020.107261.
12. Gudumac V, Tagadiuc O, Rîvneac V, Sardari V, PanteaV, Andronache L, et al. Investigaţii biochimice. Vol. 2: Micrometode [Biochemical investigations. Vol. 2: Micromethods]. Chişinău: Elena VI; 2010. 97 p. ISBN 978-9975-106-06-1. Romanian.
13. Fogante M, Cavagna E, Rinaldi G. Chest X-ray scoring system in COVID-19 pneumonia: an added value in the evaluation of the disease severity. Eurasian J Med Oncol. 2021;5(4):305-310. doi: 10.14744/ejmo.2021.70171.
14. Tascini C, Sermann G, Pagotto A, Sozio E, De Carlo C, Giacinta A, et al. Blood ozonization in patients with mild to moderate COVID-19 pneumonia: a single centre experience. Intern Emerg Med. 2021;16(3):669-675. doi: 10.1007/s11739-020-02542-6.
15. Shah M, Captain J, Vaidya V, Kulkarni A, Valsangkar K, Nair P, et al. Safety and efficacy of ozone therapy in mild to moderate COVID-19 patients: a phase 1/11 randomized control trial (SEOT study). Int Immunopharmacol. 2021;91:107301. doi: 10.1016/j.intimp.2020.107301.
16. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323(16):1574-1581. doi: 10.1001/jama.2020.5394.
17. Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. J Infect. 2020;80(6):656-665. doi: 10.1016/j.jinf.2020.03.041.
18. Hernandez A, Viñals M, Pablos A, Vilás F, Papadakos P, Wijeysundera D, et al. Ozone therapy for patients with SARS-COV-2 pneumonia: a single-center prospective cohort study. Insights Biomed. 2020;5(4):13. doi: 10.36648/2572-5610.4.4.75.
19. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020;18(6):1324-1329. doi: 10.1111/jth.14859.
20. Fernández-Cuadros M, Albaladejo-Florín M, Álava-Rabasa S, Gallego-Galiana J, Pérez-Cruz G, Usandizaga-Elio I, et al. Compassionate use of rectal Ozone (O3) in severe COVID-19 pneumonia: a case-control study. SN Compr Clin Med. 2021;3(5):1185-1199. doi: 10.1007/s42399-021-00849-9.

https://doi.org/10.52645/MJHS.2024.3.06

UDC: 616.8-009.1:[616.711.6/.7+616.721.1]-073.75

RESEARCH ARTICLE

Comparative analysis of imaging data in sensory and motor disorders in lumbar neurocompressive syndrome

Victoria Seu*, Oxana Malîga

Department of Radiology and Imaging, *Nicolae Testemițanu* State University of Medicine and Pharmacy, Chișinău, Republic of Moldova

ABSTRACT

Introduction. Lumbar neurocompressive syndrome is a condition characterized by radicular pain, motor, sensory and reflex changes, as well as paresthesia or numbness in the lower limb. These symptoms can be triggered by positions and/or movements of the spine. In lumbar radiculopathy, both mechanical and inflammatory factors play significant roles.

Material and methods. The study included 102 patients with signs of lumbar neurocompressive syndrome. Of these, 51 (group I) patients were examined using MRI and the other 51 patients (group II) were examined using conventional radiographic investigation of the lumbosacral region of the spine.

Results. By analyzing the magnetic resonance imaging data of the lumbar spine, a threshold of statistical significance was determined (of 10%, $p < 0.10$) for patients with sensory disturbances in the lower limb in cases of stenosis of the lumbar spinal canal, and in patients with motor disorders in the lower limb, in the case of disc protrusions. The analysis of the magnetic resonance imaging data determined a significance threshold (of 5%, $p < 0.05$) in patients with sensory disorders (in the case of disc sequestrations and in the case of disc extrusions) as well as for motor disorders (in the case of disc extrusions, disc sequestrations and static disorders of the spine). The analysis of standard radiographs of the lumbar spine allowed the determination of the threshold of statistical significance (of 5%, $p < 0.05$) in patients with sensory disorders in the lower limb in cases of coxofemoral osteoarthritis and Schmorl's hernias. For patients with motor disorders at the level of the lower limb, conventional radiography was informative in the presence of calcification of the intervertebral discs and in coxofemoral osteoarthritis.

Conclusion. MRI can be considered the first-choice imaging technique for diagnosis of the lumbar spine pathologies characterized by sensory and motor changes in the lower limbs.

Keywords: motor disorders, sensory disorders, MRI, radiological examination.

Cite this article: Seu V, Malîga O. Comparative analysis of imaging data in sensory and motor disorders in lumbar neurocompressive syndrome. Mold J Health Sci. 2024;11(3):42-47. https://doi.org/10.52645/MJHS.2024.3.06.

Manuscript received: 14.06.2024

Accepted for publication: 03.09.2024

Published: 20.09.2024

***Corresponding author: Victoria Seu,** MD, assistant professor, Department of Radiology and Imaging, *Nicolae Testemițanu* State University of Medicine and Pharmacy, 165, Stefan cel Mare și Sfânt Blvd., MD-2004, Chișinău, Republic of Moldova
e-mail: victoria.seu@usmf.md

Authors' ORCID IDs
Victoria Seu – https://orcid.org/0009-0007-0394-9368
Oxana Malîga – https://orcid.org/0000-0001-9848-5525

Key messages

What is not known yet about the issue addressed in the submitted manuscript

Assessing the value of imaging methods (Magnetic Resonance Imaging and Conventional Radiography of the lumbo-sacral region of the spine) in determining motor and sensory changes in lumbar radiculopathy.

The research hypothesis

Identifying the preferred method for radiological diagnosis of lumbar neurocompressive syndrome to eliminate the need for additional radiological studies.".

The novelty added to the scientific literature in the field

The study aims to achieve a comprehensive and rapid diagnosis of patients with lumbar neurocompressive syndrome to determine appropriate treatment. It compares two imaging methods and evaluates their contribution in identifying characteristic signs of lumbar radiculopathy.

Introduction

Lumbar neurocompressive syndrome is a condition characterized by radicular pain, motor, sensory and reflex disorders, paresthesia or numbness in the lower limb, which can be caused by positions and/or movements of the spine [1]. In lumbar radiculopathy, the association of the mechanical and inflammatory factors play an important role. Often large hernias are asymptomatic, indicating that the size of the hernia is not responsible for neurological symptoms and signs [2].

Sensory and motor changes are produced by pure compression of an uninflamed nerve, but without pain. The pain is caused by excitation of an inflamed nerve [3]. It has been established that neurophysiological dysfunctions, degenerative changes, and reduced blood flow in nerve roots are induced by spinal nerve root compression [4]. The forms of pain are different and depend on the degree of compression of the nerve roots and its duration [5]. Pain occurs in the case of cellular damage by producing cellular degeneration, while in moderate ischemia with cellular demyelination pain does not occur [6]. The changes produced by the contact of the nucleus pulposus with the epidural elements have been established in observational studies with the appreciation of convincing evidence of tissue-level changes. After such contact, alterations in nerve electrical activity and intraneural blood flow are observed [7]. During an inflammatory process, nociceptive neurons become sensitized and begin to respond to stimuli that were previously unable to elicit a response. This phenomenon, called hyperalgesia, is common to all inflammatory processes and is characterized by a decrease in the nociceptive threshold and increased activity in response to thermal and mechanical stimulation [8].

Standard radiography in a supine position constitutes the initial stage of the patient's assessment [9]. Lumbar spine radiography cannot determine disc herniation, but indirect signs can be visualized that suggest their presence. These are the so-called classic Barr triad which includes: scoliosis, flattening of the physiological lordosis, and narrowing of the intervertebral space [10, 11]. Spondylosis and subchondral sclerosis of the upper and lower endplates are known as degenerative-dystrophic signs [12]. Lumbar spine radiography in frontal, lateral and oblique incidences is often necessary to exclude other more serious pathologies and to detect degenerative changes in the lumbar spine, for example: osteochondrosis, osteoporosis and changes in the facet joints. Plain radiographic examination is not recommended for patients with low back pain who do not present important or "alarm" signs [13, 14].

Studies by different authors show that the role of MRI in the diagnosis of radiculopathy is limited to visualizing of disc herniation and spinal canal stenosis. In addition, the studies have not provided conclusive information about the accuracy of MRI diagnosis [15]. This is largely explained by the absence of a "gold" standard for the identification of serious vertebral pathology in radiculopathy [16]. MR imaging reflects disc degeneration in the area of low T2 signal intensity, but it is uncertain whether this is a reliable indicator of degenerative structural changes [17]. Disc degeneration and an area of high signal intensity on MRI were not helpful in identifying a symptomatic disc, and when the endplates became abnormal, all discs caused pain consistent with the imaging picture [18].

Imaging signs of degenerative-dystrophic process in the lumbar region of the spine include a decrease in the height of the intervertebral disc, the presence of fissure, edema, vacuum, or calcifications at the level of the intervertebral disc. Changes in the signal at the level of the ligament apparatus and the spinal cord, as well as the presence of marginal osteophytes, disc herniation, listhesis and stenosis, and Modic-type changes in the vertebral bodies can be also determined [19].

Material and methods

The study included 102 patients with signs of lumbar neurocompressive syndrome, of which 51 patients (group I) were examined by MRI and another 51 patients (group II) were examined using standard radiography of the lumbosacral region of the spine. All patients clinically and - neurological examination in the Department of Neurosurgery of the *Timofei Moșneaga* Republican Clinical Hospital between November 2015 and April 2017. The research protocol obtained a favorable opinion from the Research Ethics Committee (minute no. 74 of 17.06.2016), *Nicolae Testemițanu* State University of Medicine and Pharmacy, Chișinău, Republic of Moldova.

The reason for the patients to see the doctor was lumbar and leg pain.

Criteria for inclusion in the study:

(1) Adult patients (> 18 years), who signed the informed consent for participation in the study.

(2) Patients with radiculopathy.

(3) People who have no absolute contraindications for standard radiography and/or MRI.

Exclusion criteria:

(1) Patients with acute abdominal syndrome.

(2) Patients with tumors, arterio-venous malformations and spinal infections.

(3) Patients with spinal trauma.

(4) Patients with all forms of intervertebral disc instability.

(5) Patients with systemic diseases, with or without intestinal manifestations (clinically and laboratory confirmed).

(6) People who have absolute contraindications to exploration by radiological methods and MRI.

The following formula was used to determine the required number of patients for the research:

$$n = \frac{1}{(1-f)} \times \frac{2(Z_\alpha + Z_\beta)^2 x P(1-P)}{(P_o - P_1)^2}$$ where:

P_o = According to the bibliographic data, the success rate of detecting the diagnosis by applying the traditional (radiological) method is on average 40.0% (P0=0.40).

P_1 = In the research group, patients will be investigated by the modified method (MRI) with the success rate of detecting 80.0% of cases (P_1 = 0.80)

$P = (P_0 + P_1)/2 = 0.60$

Z_α – tabular value. When the statistical significance is 95.0%, then the coefficient Z_α =1.96

Z_β – tabular value. When the statistical power of the comparison is 99.0%, then the coefficient Z_β = 1.96

f = Proportion of subjects expected to drop out of the study for reasons other than the investigated effect q = 1/(1-f), f = 10.0% (0.1).

Entering the data into the formula, we obtained:

$$n = \frac{1}{(1-0.1)} \times \frac{2\,(1.96+1.96)^2 \times 0.60 \times 0.40}{(0.40-0.80)^2} = 51$$

Thus, the patients were divided into two groups.

• Group I – patients with lumbar neurocompressive syndrome patients in whom the diagnosis was established by applying the MRI examination of the lumbar region of the spine (n = 51).

• Group II – patients with lumbar neurocompressive syndrome patients in whom the diagnosis was established by applying standard radiographic examination to the lumbar region of the spine (n = 51).

Both MRI and radiological examination of the lumbar spine were performed at the Euromed Diagnostic Medical Center. The clinical examination included: medical history, including evaluating the followings parameters: pain, using visual analogue scale of pain; psychological changes, using assessment scale of psychological changes (HADS scale); social and professional adjustment disorders (ODI scale); patient satisfaction; quality of life (EQ-5D – Euro Quality of Life 5 Dimension). Specific tests and neurological examinations were also performed. Spine radiography was performed in the frontal and lateral views on a Siemens Axiom Luminos dRF machine. Functional radiological investigations were performed at the same facilities. Magnetic resonance imaging was performed on a closed-type Siemens Magnetom Skyra machine with a magnetic field strength of 3 Tesla. The examination was performed with the patient lying on his back. Patient positioning was achieved using a laser to ensure a more homogeneous magnetic field. A localizer-type protocol was used to obtain a 3-plane image positioning and preview. The 3 planes were taken with a step of 4 mm using the sequences T1 and T2 weighted, T2 FS (fat saturation), PD FS. The obtained results were recorded in Excel tables. To compare the sensitivity, specificity, as well as the positive and negative predictive values of the imaging data of the pathologies recorded in the study groups, the 95% confidence interval (95CI) was calculated. Fisher's exact test was used to estimate significant differences in imaging signs between the means of the two groups. The significance threshold was considered p<0.10.

Results

The imaging data obtained in the 2 groups of patients are presented in table 1.

Table 1. Imaging data about the pathologies recorded in the study groups.

	Group I	Group II	p[1]
Disc herniations	51 (100%)	0 (0%)	0.0000
disc extrusions	43 (84.3%)	0 (0%)	0.0000
disc protrusions	39 (76.5%)	0 (0%)	0.0000
polysegmental damage	43 (84.3%)	0 (0%)	0.0000
Marginal osteophytes without signs of root conflict	51 (100%)	48 (94.1%)	0.0813
Narrowing of the intervertebral space	49 (96.1%)	48 (94.1%)	0.6409
Schmorl's hernias	48 (94.1%)	31 (60.8%)	0.0001
Static disorders	38 (74.5%)	46 (90.2%)	0.0401
Modic-type edematous changes	16 (31.4%)	0 (0%)	0.0000
Vertebral hemangiomas	14 (27.5%)	0 (0%)	0.0001
Stenosis of the lumbar spinal canal	12 (23.5%)	0 (0%)	0.0004
Disc sequestration	8 (15.7%)	0 (0%)	0.0040
Marginal osteophytes with root conflict	5 (9.8%)	0 (0%)	0.0240
Disruption of the flow of cerebrospinal fluid	4 (7.8%)	0 (0%)	0.0445
Spondylodiscitis	3 (5.9%)	0 (0%)	0.0813
Sacroiliitis	2 (3.9%)	21 (41.2%)	0.0000
Coxofemoral osteoarthritis	1 (2.0%)	14 (27.5%)	0.0004
Subchondral sclerosis	0 (0%)	48 (94.1%)	0.0000
Intervertebral discs calcification	0 (0%)	3 (5.9%)	0.0813

Note: p[1] applied statistical test – Fisher's exact

The analysis data of the magnetic resonance imaging investigation of the lumbo-sacral region obtained in the 2 groups of patients are presented in table 2 and 3.

Table 2. Multivariate analysis of magnetic resonance imaging data obtained in patients with sensory disorders (loss of sensation in the lower limb)

The dependent variable	F statistic	p[1]
Disc sequestration	12.321	0.001
Disc extrusions	6.085	0.017
Lumbar spinal canal stenosis	2.895	0.095
Static disorders of the spine	1.485	0.229
Narrowing of the intervertebral space	1.217	0.275
Sacroiliitis	1.217	0.275
Schmorl's hernias	1.160	0.287
Polysegmental disc herniation	0.642	0.427
Coxofemoral osteoarthritis	0.589	0.447
Modic-type edematous changes	0.408	0.526
Disruption of the flow of cerebrospinal fluid	0.269	0.606
Disc protrusions	0.126	0.724
Spondylodiscitis	0.020	0.888
Vertebral hemangiomas	0.019	0.891
Marginal osteophytes with root conflict	0.017	0.896

Note: p[1] applied statistical test – Fisher's exact

By analyzing the data of the magnetic resonance imaging investigation of the lumbar spine, a threshold of statistical significance (of 10%, p < 0.10) was determined in patients with sensory disturbances in the lower limb in the case of stenosis of the lumbar spinal canal, and in patients with

motor disorders in the lower limb in the case of disc protrusions. In addition, by analyzing the magnetic resonance imaging data, a significance threshold (of 5%, $p < 0.05$) was determined in patients with sensory disorders (in the case of disc sequestrations and in the case of disc extrusions), and with motor disorders in the case of disc extrusions, disc sequestrations and static disorders of the spine.

Table 3. Multivariate analysis of magnetic resonance imaging data obtained in patients with lower limb motor disorders (gait disorders)

The dependent variable	F statistic	p[1]
Disc extrusions	8.839	0.005
Disc sequestration	7.654	0.008
Static disorders of the spine	6.808	0.012
Disc protrusions	3.007	0.089
Narrowing of the intervertebral space	1.700	0.198
Coxofemoral osteoarthritis	0.818	0.370
Spondylodiscitis	0.582	0.449
Schmorl's hernias	0.172	0.680
Lumbar spinal canal stenosis	0.147	0.703
Polysegmental disc herniation	0.089	0.767
Marginal osteophytes with root conflict	0.056	0.814
Disruption of the flow of cerebrospinal fluid	0.041	0.841
Vertebral hemangiomas	0.038	0.847
Sacroiliitis	0.019	0.890
Modic-type edematous changes	0.016	0.898
Note: p[1] applied statistical test – Fisher's exact		

The analysis of the results of conventional radiographic investigation of the lumbosacral region obtained in the 2 groups of patients is presented in tables 4 and 5.

Table 4. Multivariate analysis of radiographic data obtained in patients with sensory disturbances (loss of sensation in the lower limb)

The dependent variable	F statistic	p[1]
Coxofemoral osteoarthritis	25.039	0.000
Schmorl's hernias	4.689	0.035
Static disorders of the spine	1.334	0.254
Marginal osteophytes without root conflict	0.759	0.388
Narrowing of the intervertebral space	0.759	0.388
Subchondral sclerosis	0.759	0.388
Sacroiliitis	0.624	0.433
Intervertebral discs calcification	0.369	0.546
Note: p[1] applied statistical test – Fisher's exact		

Table 5. Multivariate analysis of radiographic data obtained in patients with motor disorders in the lower limb (gait disorders)

The dependent variable	F statistic	p[1]
Intervertebral discs calcification	20.176	0.000
Coxofemoral osteoarthritis	18.356	0.000
Sacroiliitis	1.609	0.211
Schmorl's hernias	1.306	0.259
Static disorders of the spine	1.169	0.285
Narrowing of the intervertebral space	0.665	0.419
Subchondral sclerosis	0.665	0.419
Marginal osteophytes without root conflict	0.524	0.473
Note: p[1] applied statistical test – Fisher's exact		

The analysis of standard radiography of the lumbar spine allowed the determination of the threshold of statistical significance (of 5%, $p < 0.05$) in patients with sensory disorders in the lower limb in the case of coxofemoral osteoarthritis and Schmorl's hernias. In patients with motor disorders at the level of the lower limb, standard radiography of the lumbar spine was informative in case of calcification of the intervertebral discs and in coxofemoral osteoarthritis.

Discussions

Imaging investigations have important clinical significance for the diagnosis and treatment of disc herniation. They can provide not only basic information for diagnosis but also help in making a choice between conservative treatments or surgery and in selecting surgical tactics as well to improve the quality of treatment [20]. Currently, commonly used imaging examinations include MRI, CT, myelography, and radiography. MRI has the advantage of using non-ionizing radiation and offers good visualization capabilities, especially for soft tissues [21]. MRI can also comprehensively observe whether each lumbar intervertebral disc has lesions, identify the degree and location of nucleus pulposus herniation in the sagittal plane, and distinguish whether there are other lesions involving the space in the spinal canal. Lumbar intervertebral disc extrusion is a frequent cause of low back pain that not only manifests as local pain but also is frequently accompanied by radicular pain, sensory deficits, and/or muscle weakness due to nerve root involvement [22, 23]. The results of some studies showed that the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio was 0.89 (95% CI: 0.87-0.91), 0.83 (95% CI: 0.78-0.87), 4.57 (95% CI: 2.95-7.08), 0.14 (95% CI: 0.09-0.22) respectively, for magnetic resonance imaging. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio was 0.82 (95% CI: 0.79–0.85), 0.78 (95% CI: 0.73–0.82), 3.54 (CI 95%: 2.86–4.39), 0.19 (CI 95%: 0.12–0.30) respectively calculated for tomography. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio was 0.79 (95% CI: 0.75–0.82), 0.75 (95% CI: 0.70–0.80), 2.94 (CI 95%: 2.43–3.56), 0.29 (CI 95%: 0.21–0.42), respectively for myelography [24]. In our study, significant correlations were observed in MRI images in patients with signs of radiculopathy (manifested by lumbar pain, motor and sensory deficit) or found in the presence of extrusion, sequestration of the intervertebral disc as well as in spinal canal stenosis (significance threshold from 5% to 10%). This corresponds to the literature data. The sensitivity, specificity, positive predictive value, negative predictive value of the method in the case of disc extrusion were 60.78% (CI 95%: 7.02%–33.12%), 100% (CI 95%: 93.02%– 100%), 100% (CI 95%: 93.02%–100%), 55.43% (CI 95%: 52.07%–58.75%), respectively. In case of intervertebral disc sequestration: 9.80% (CI 95%: 3.26%–21.41%), 100% (95% CI: 93.02%–100%), 100% (95% CI: 93.02%–100%), 52.58% (95% CI: 50.32%–54.83%) and in spinal canal stenosis: 5.88% (95% CI: 1.23%–16.24%),

100% (95% CI: 93, 02%–100%), 100% (95% CI: 93.02%–100%), 51.52% (95% CI: 49.80%–53.23%), respectively. In determining the cause of lumbar pain accompanied by motor and sensory deficit due to disc extrusion, MRI sensitivity, specificity, as well as positive and negative predictive values are high. In case of intervertebral disc sequestration as well as the narrowing of the vertebral canal the sensitivity of the method will have low values, but the specificity, the positive and negative predictive values will have high values.

Conventional radiography cannot directly identify the existence of intervertebral disc herniation. Scoliosis, marginal vertebral hyperplasia, and narrowing of the intervertebral space detected radiographically all suggest degenerative changes. If the lumbosacral structure is altered (for example, the presence of transitional vertebrae, spondylolisthesis and spondylolysis), it indicates that the adjacent intervertebral discs present degenerative changes with an increased risk of intervertebral disc prolapse due to increased overloads. With the development of technology today, a radiographic examination is rarely used [25]. In our study, significant correlations following radiological analyses of patients with lumbar radiculopathy are found in case of coxofemoral osteoarthritis, intervertebral disc calcifications and Schmorl's hernias (significance threshold of 5%). The sensitivity, specificity, positive predictive value and negative predictive value of the method in the presence of coxofemoral osteoarthritis is 3.92% (CI 95%: 0.48%–13.46%), 74.51% (CI 95%: 60.37 %–85.67%), 13.33% (CI 95%: 3.53%–39.30%), 43.68% (CI 95%: 39.55%–47.89%), respectively. In the case of intervertebral disc calcification, they are 0.00% (95% CI: 0.00%–6.98%), 94.12% (95% CI: 83.76%–98.77%), 0% (95% CI: 0 %), 48.48% (95% CI: 46.77%–50.20%) and for Schmorl's hernias 70.59% (95% CI: 56.17%–82.51%), 39.22% (95% CI: 25.84%–53.89%), 53.73% (95% CI: 46.67%–60.64%), 57.14% (95% CI: 43 .59%–69.70%), respectively. For conventional radiography of the lumbosacral region of the spine, sensitivity, specificity, as well as high positive and negative predictive values are found in the case of Schmorl's hernias; in the case of intervertebral disc calcifications, the method's sensitivity and positive predictive value are practically zero, with high specificity and negative predictive value. In the case of coxofemoral osteoarthritis, the sensitivity of the method and the positive predictive value of the indices are lower compared to the indices for the specificity of the method and the negative predictive value.

Conclusion

MRI can be considered the imaging technique of first choice in the diagnosis of pathologies of the lumbar spine characterized by sensory and motor changes in the lower limbs.

Competing interests

None declared.

Authors' contributions

Study design (VS, OM), clinical material acquisition (VS), data interpretation and statistical analysis (VS, OM), manuscript preparation (VS, OM). The final version of the manuscript was read and approved by both authors.

Acknowledgements and funding

The study had no external funding.

Patient consent

Obtained.

Ethics approval

The study protocol was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (minutes No. 74, from 17.06.2016).

References

1. Ropper AH, Zafonte RD. Sciatica. N Engl J Med. 2015;372(13):1240-1248. doi: 10.1056/NEJMra1410151.
2. Goupille P, Mulleman D, Valat JP. Radiculopathy associated with disc herniation. Ann Rheum Dis. 2006;65(2):141-143. doi: 10.1136/ard.2005.039669.
3. Lurie JD. What diagnostic tests are useful for low back pain? Best Pract Res Clin Rheumatol. 2005;19(4):557-575. doi: 10.1016/j.berh.2005.03.004.
4. Verhaar JAN, van Mourik JBA. Orthopedie [Orthopedics]. 2nd ed. Houten: Bohn Stafleu van Loghum; 2008. 455 p. Dutch.
5. van Rijn RM, Wassenaar M, Verhagen AP, et al. Computed tomography for the diagnosis of lumbar spinal pathology in adult patients with low back pain or sciatica: a diagnostic systematic review. Eur Spine J. 2012 Feb;21(2):228-239. doi: 10.1007/s00586-011-2012-2.
6. Patrick DL, Deyo RA, Atlas SJ, Singer DE, Chapin A, Keller RB. Assessing health-related quality of life in patients with sciatica. Spine. 1995;20(17):1899-1908. doi: 10.1097/00007632-199509000-00011.
7. International Association for the Study of Pain; Boyd D, Butler M, Carr D, Cohen M, Devor M, Dworkin R, Greenspan J, et al. IASP Pain Terminology. Washington: IASP; 2011 [cited 2023 Oct 12]. Available from: https://www.iasp-pain.org/resources/terminology/#pain
8. Hestbaek L, Korsholm L, Leboeuf-Yde C, Kyvik KO. Does socioeconomic status in adolescence predict low back pain in adulthood? A repeated cross-sectional study of 4,771 Danish adolescents. Eur Spine J. 2008;17(12):1727-1734. doi: 10.1007/s00586-008-0796-5.
9. Powell HC, Myers RR. Pathology of experimental nerve compression. Lab Invest. 1986;55(1):91-100.
10. Imhof H, Breitenseher M, Kainberger F, Rand T, Trattnig S. Spine disease. European Radiol. 2000;10(Suppl 2):313-319.
11. Milette PC. Classification, diagnostic imaging, and imaging characterization of a lumbar herniated disc. Radiol Clin North Am 2000; 38: 1267-1292.
12. Bodiu A. Fiziopatologia durerii radiculare în hernia discală lombară [Pathophysiology of nerve root pain in lumbar disc

herniation]. Curierul Medical (Chişinău). 2008;(3):149-152. Romanian.
13. Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it? Spine. 2006;31(18):2151-2161.
14. Şavga N. Principii de alegere a tacticii curative a proceselor displazice din segmentul lombosacral [The principes of choice of optimal medical tactics of displastical processes in lumbar-sacral vertebral part]. Arta Medica (Chişinău). 2009;(6):38-41.
15. Pedachenko IuE, Krasienko EP, Bodiu AP. [Assessment of the results of surgical treatment of lumbar spinal stenosis in different age groups]. Curierul Medical (Chişinău). 2013;56(3):20-28. Russian.
16. Moraru I, Sangheli M. Spondilodiscita infecţioasă: diagnostic şi tratament [Infectious spondylodiscitis: diagnosis and management]. Bull Acad Sci Mold. Med Sci. 2011;1(29):113-117. Romanian.
17. Sampiev MT, Zagorodnii NV, Dotsenko VV. [Minimally invasive retroperitoneal approach in surgery of degenerative lumbar stenosis]. RUDN J Med (Moscow). 2003;(2):113-116. Russian.
18. Kushniruk PI, Drevali ON. [Morphological rationale for medial facetectomy during microsurgical removal of herniated lumbar intervertebral discs]. Burdenko J Neurosurg. 2006;(1):13-18. Russian.
19. Carragee EJ, Tanner CM, Khurana S, et al. The rates of false-positive lumbar discography in select patients without low back symptoms. Spine. 2000;25(11):1373-80. doi: 10.1097/00007632-200006010-00009.
20. Tsai MD, Jou SB, Hsieh MS. A new method for lumbar herniated inter-vertebral disc diagnosis based on image analysis of transverse sections. Comput Med Imaging Graph. 2002;26(6):369-80. doi: 10.1016/s0895-6111(02)00033-2.
21. Wassenaar M, van Rijn RM, van Tulder MW, Verhagen AP, van der Windt DA, Koes BW, et al. Magnetic resonance imaging for the diagnosis of lumbar spine pathology in adult patients with low back pain or sciatica: a systematic review of the diagnosis. Eur Spine J. 2012;21(2):220-7. doi: 10.1007/s00586-011-2019-8.
22. Amin RM, Andrade NS, Neuman BJ. Lumbar disc herniation. Curr Rev Musculoskelet Med. 2017;10(4):507-516. doi: 10.1007/s12178-017-9441-4.
23. Vialle LR, Vialle EN, Suárez Henao JE, Giraldo G. Lumbar disc herniation. Rev Bras Ortop. 2015;45(1):17-22. doi: 10.1016/S2255-4971(15)30211-1.
24. Huang Z, Zhao P, Zhang C, Wu J, Liu R. Value of imaging examinations in diagnosing lumbar disc herniation: a systematic review and meta-analysis. Front Surg. 2023;9:1020766. doi: 10.3389/fsurg.2022.1020766.
25. Yu X, Niu G, Yang J, Ni L, Zhang W, Guo Y. Quantitative evaluation for the diagnostic efficacy of computed tomography and magnetic resonance imaging in patients with lumbar disc herniation. Natl Med J China. 2011;91(1):23-7. doi: 10.3760/cma.j.issn.0376-2491.2011.01.007.

https://doi.org/10.52645/MJHS.2024.3.07

UDC: 616.314.17-008.1-08

RESEARCH ARTICLE

Temporary splinting in periodontally mobile teeth: review before application

Mariana Ceban, Victor Ceban, Vitalie Pântea*

Ilarion Postolachi Department of Orthopedic Stomatology, *Nicolae Testemițanu* State University of Medicine and Pharmacy, Chișinău, Republic of Moldova

ABSTRACT

Introduction. Temporary splinting of mobile, periodontally compromised teeth is an important stage in the complex treatment of periodontitis, used to improve mastication, aesthetics, and the prognosis for teeth with pathological mobility. It helps prevent this phenomenon and consolidate the success of conservative and surgical treatment, which also has a positive effect on the patient's psycho-emotional state.

Materials and methods. 12 patients (6 female and 6 male), aged 26–60 years, with pathological teeth mobility due to chronic generalized periodontitis, were included in the study. Temporary splinting was performed using *fiberglass threads braided with polyester microfibers*, *polyethylene fibers*, and *aramid fibers,* and in all clinical cases, it was secured with photo-composite material designed for teeth splinting.

Results. Temporary splinting is a very important step in periodontitis treatment, and dynamic monitoring is necessary throughout the entire period of splinting. The interval between visits is determined based on the type of splinting, the risk of complications, the severity of periodontitis, systemic and local factors, the level of individual oral hygiene, and the patient's motivation. The interval can be 6 months, 4 months, or, in aggressive forms of periodontitis, 2 months.

Conclusions. Temporary splinting contributes to the effectiveness of pathogenetic and symptomatic therapy.

Keywords: periodontal disease, temporary splinting, adhesion, splinting, composite materials.

Cite this article: Ceban M, Ceban V, Pântea V. Temporal splinting in periodontaly mobile teeth: review before application. Mold J Health Sci. 2024;11(3):48-53. https://doi.org/10.52645/MJHS.2024.3.07.

Manuscript received: 17.07.2024

Accepted for publication: 05.09.2024

Published: 20.09.2024

Corresponding author: Vitalie Pântea, MD, assistant professor, *Ilarion Postolachi* Department of Orthopedic Stomatology, *Nicolae Testemițanu* State University of Medicine and Pharmacy, 42, Toma Ciorbă str., Chișinău, Republic of Moldova, MD-2004
e-mail: vitalie.pantea@usmf.md

Author's ORCID IDs
Mariana Ceban – https://orcid.org/0000-0001-7203-358X
Victor Ceban – https://orcid.org/0009-0000-4039-0478
Vitalie Pântea – https://orcid.org/0000-0002-3489-030X

Key messages

What is not yet known on the issue addressed in the submitted manuscript?
Analysis of changes in periodontal parameters in patients with periodontal disease before and after applying temporary splinting with three different materials.
The research hypothesis.
Temporary splinting decreases the mobility of periodontally compromised teeth and improves periodontal tissue healing.
The novelty added by the manuscript to the already published scientific literature.
Assessing the change in periodontal parameters in patients with periodontal disease before and after applying temporary splinting with three different materials, following clinical and paraclinical patient examination analysis.

Introduction

With the increase in life expectancy and the improvement of social conditions, natural dentition has to be preserved for a long time to ensure quality of life. However, the prevalence of some dental and jaw diseases remains significant, with dental caries and periodontal disease being the most common. The destruction of periodontal ligaments and the alveolar process that occurs in periodontitis gradually reduces the stability of the tooth in the alveolar socket and increases its mobility [1, 2]. Once tooth mobility appears, the rate of bone tissue destruction accelerates very quickly, leading to even greater tooth mobility and resulting in one of the complications of periodontitis - loss of one or more teeth [3]. The unrestored edentulous space and alveolar ridges may lead to impairment of biomechanics in the dental-facial system, continued deterioration of periodontal tissues, and negative effects on general health. In advanced periodontal disease, teeth loss is often accompanied by severe bone loss, leading to tooth migration, which seriously affects aesthetics and the patient's social behavior. However, it is known that functionally and aesthetically adequate dentition is important for psychological well-being and quality of life, and prosthodontic rehabilitation is often necessary to restore lost aesthetics and function in periodontally compromised dentition. It is proven that remission of the pathological process in periodontal tissues cannot be achieved without stabilizing mobile, periodontally compromised teeth [4]. The clinical management of mobile teeth is a complex issue that improves the prognosis of teeth and provides stability in periodontal treatment. There are several methods for stabilizing and preserving mobile teeth in periodontitis using various designs of permanent and temporary splinting systems, represented by fixed and movable constructions, each with its own goals, indications, contraindications, advantages, and disadvantages [5-7]. The goal of both removable and non-removable splint-prostheses is to control oral disease while restoring aesthetics and function with durable, biocompatible designs. When choosing the design of a splint-prosthesis, it is important to remember that the preparation of the margin, contour, and profile of protrusion of the prosthesis elements can affect the gum tissue's response [8-10]. An improperly made denture can damage even healthy oral tissues or aggravate existing periodontal disease [11-13]. Temporary splinting of mobile, periodontally compromised teeth is an important stage in the complex treatment of periodontitis, used to improve mastication, aesthetics, and the prognosis for teeth with pathological mobility. Depending on the purpose of splinting, temporary splints can be used for several days to several months. However, with the development of modern adhesive fixation methods, the duration of temporary splinting can be extended. After the removal of dental deposits, curettage of periodontal pockets, gingivectomy and other therapeutic measures, pathological tooth mobility may increase. Temporary splints help prevent this phenomenon and consolidate the success of conservative and surgical treatments, which also has a positive effect on the patient's psycho-emotional state.

To develop treatment plans with a predictable prognosis for temporary splinting, as well as permanent splinting, it is necessary to consider the proportions of the teeth, the ratio of the weight and length of the elements that make up the splint, the zenith of the gums, and the aesthetics of the periodontium. Bio-functionality and harmony between the temporary splint and periodontal tissues are important for restoring the biomechanics of chewing, aesthetics, and the durability of the remaining teeth and their periodontium. In this regard, its design, occlusion, and biomaterials are of great importance and must be considered in planning.

Visible lengthening of the teeth (which increases the degree of trauma to periodontal tissues) creates some difficulties in choosing the type of temporary splinting system, especially in planning the design of the system and choosing materials to reduce functional overloading of support teeth, which can increase when using fixed splinting system composed of artificial crowns or fixed partial dentures due to their weight. In prosthetic dentistry, temporary splints made from acrylic resin, directly in the patient's mouth, have often been used. However, these splints are unaesthetic, have limited geometric mechanical strength, and poor adhesion to hard tissues of the teeth, which can lead to demineralization of the enamel. That is why temporary splinting using adhesive fibrous splints, for which flexible reinforcing elements and light-curing composite materials are used, has been recognized as one of the most promising methods. This approach allows the creation of aesthetic and fracture-resistant temporary splinting structures. Currently, many manufacturers produce special materials for reinforced splinting of teeth based on an inorganic matrix (ceramics, fiberglass) and materials based on an organic matrix (polyethylene, aramid fibers). The fittings of the elements are made of a variety of the finest fibers with a diameter of 3-5 microns, woven together. Reinforcement fibers gain special strength through their impregnation with resin and flowable composites.

But at the same time, it is necessary to mention that the restorative materials used in such types of splinting can influence biofilm formation because their rough and uneven surfaces create a favorable environment for bacterial colonization. Gingival phenotype, the depth of the gingival sulcus, as well as the location of the alveolar ridge vary from one patient to another and should also be considered in treatment planning. However, contraindications to the procedure are minimal, with increased tooth sensitivity and an allergy to the materials used being among them.

That is why the analysis of the properties of adhesive splints indicates the need for further detailed study of the properties of composite materials used for splinting mobile teeth and the selection of design or structural peculiarities of future constructions. These studies are necessary to develop tactics and criteria for choosing splinting structures for mobile teeth based on the specifics of clinical situations.

The aim *of the study is* to assess the change in periodontal parameters in patients with periodontal disease before and after the application of temporary splinting with

different materials, aimed at restoring periodontal function and occlusal stability.

Material and methods

12 patients (6 female and 6 male), aged 26–60 years, with pathological teeth mobility due to chronic generalized periodontitis were included in the study (Table 1).

Table 1. Features of the lots of patients

Features	Study lot I	Study lot II	Study lot III
Men	2	2	2
Women	2	2	2
Average age	46	48	51
Number of examined teeth	22	26	28

All patients were clinically (subjective, objective) and para-clinically examined (OPG, diagnostic models, microbiological examination, parodonto-screen).

Inclusion criteria:

- age of the participants 26–60 years old
- both males and females
- gingival bleeding
- gingival recessions
- periodontal pockets of varying depth
- tooth mobility
- partial edentulism of one tooth
- no burdened history of general health (according to the patient's own account, without any complaints)
- obtained ethical clearance to include the patient in the study.

The examination of the patient with chronic marginal periodontitis was carried out according to the classic scheme: 1 – anamnesis gathering; 2 - objective clinical examination; 3 - complementary or additional examination. Anamnesis is a valuable component in supporting the data from the objective examination and forming an accurate understanding of the location and nature of the pathological process. The anamnesis included two basic components: the anamnesis of the disease (determining the patient's complaints such as gingival bleeding, changes in color, size, and volume, gum swelling, gingival pain, gingival retraction, tooth mobility, tooth sensitivity, the presence of dental deposits, purulent discharges, and foul odor) and the life anamnesis (providing extensive information about the condition and particularities of the body, living and working conditions, harmful habits, etc.), guiding us toward a correct and comprehensive diagnosis and treatment plan. The objective clinical examination of the patients was recorded in the periodontograms, including clinical-instrumental examination data in graphic form. This allows us to systematize the data from the basic methods used in the examination of the marginal periodontium.

The objective clinical examination was carried out through inspection, palpation, percussion, and auscultation, allowing the confirmation or refutation of the anamnestic data and their objective completion for establishing a preliminary diagnosis. The exo-buccal examination provided information about the facial structure, the condition of the skin, and the presence of changes characteristic of various general ailments or jaw anomalies, occlusion, the condition of the labio-chin and nasolabial areas, chin, lips, facial profile type, latero-mandibular deviations, and the condition of the nervous, lymphatic, salivary, and TMJ systems, among others. The detailed intraoral examination was carried out according to a consistent scheme, determining the condition and depth of the oral vestibule, lip frenulum, the degree of mouth opening, the transition zone of the mucosa, the condition of the teeth and periodontal tissues, interdental contacts, dental migrations, dental arches, and the type of occlusion. During the clinical examination of the gums, attention was focused on their position, color, texture, shape (retractions or inflammations), contour, gingival insertion at the tooth level, the degree of bacterial plaque accumulation, dental tartar, root exposure, the depth of periodontal pockets, etc.

The objective clinical examination of the patients was recorded in the periodontal charts, including clinical-instrumental examination data in graphic form.

The determination of tooth mobility was performed in the usual way, using dental forceps with slight pressure in the vestibulo-oral and axial directions. It was assessed according to the three degrees of mobility based on Miller's classification, modified by P. Fleszar (1980), and recognized in scientific-practical dentistry as:

- grade 1 - tooth movement in the transverse plane does not exceed 1 mm;

- grade 2- in the same plane, tooth movement exceeds 1 mm;

- grade 3- very pronounced mobility, in both transverse and axial directions.

All patients received etiotropic treatment (scaling, root planning, professional brushing). Before completing other treatments (endodontic, surgical, and prosthetic), depending on clinical conditions, temporal splinting using a minimally invasive method with different adhesive fibers for stabilizing mobile teeth was performed. The 12 patients included in our study were divided into three groups: in the I-st group (4 patients), temporary splinting was performed using *fiberglass threads braided with polyester microfibers*; in the II-nd group (4 patients), temporary splinting was performed using *polyethylene fibers*; and in the III-rd group (4 patients), temporary splinting was performed using *aramid fibers*. In all clinical cases, splint fibers were covered with photo-composite material designed for teeth splinting. Restoration of the dental arch integrity (one tooth missing gap) was achieved with an artificial acrylic tooth fixed onto the splint system using the same photo-composite material. Clinical assessment parameters, including the depth of periodontal pockets, the degree of attachment loss, the bleeding index, and the plaque accumulation index, were determined at the beginning of treatment, as well as 1, 3, and 6 months after etiotropic treatment and the installation of splinting devices.

Results and discussions

Periodontitis is one of the most common and serious diseases in dentistry. Timely treatment of periodontitis is necessary to prevent irreversible changes in periodontal tissues, dentition, and overall health. The most effective approach to treating periodontal diseases is considered to be an integrated one, including diagnostics, professional oral hygiene, and a combination of therapeutic, surgical, orthopedic, and orthodontic methods. Splinting mobile teeth occupies a special place in tooth-preserving methods of periodontal treatment and can be used either as a primary therapeutic measure or as an adjunct to stabilize the teeth. A periodontal splint is a device used to maintain and stabilize (immobilize) mobile teeth in their functional and physiological position. Among the various types of splinting, temporary splinting (stabilizing) holds a special and very important role, offering characteristic advantages and indications based on the patient's overall and dental status.

Assessing the change in periodontal parameters in patients with periodontal disease before and after applying temporary splinting with different materials is possible after a detailed clinical and paraclinical patient examination. The clinical symptoms and their frequency observed in our study groups are described in Table 2.

Table 2. Clinical features of periodontal symptoms in patients groups

Periodontal disease symptoms	% out of the number of patients
- Redness, swelling and gingival bleeding	56%
- Gingival overgrowth	5%
- Bad breath	60%
- Gingival recessions	42%
- Enamel hypersensitivity	72%
- Teeth displacement, tilts and rotations, the appearance of gaps between them	50%
- Periodontal pockets of varying depths	92%
- Tooth mobility	100%
- One tooth partial edentulism in frontal area	62%
- One tooth partial edentulism in lateral area	38%

Radiological examination results confirmed the presence of signs of periodontitis: atrophy of the alveolar bone to varying degrees, signs of functional overload of the teeth indicated by widening of the periodontal space, and evidence of resorption of alveolar bone tissue, as well as varying degrees of inclination of the remaining teeth. Diagnostic models allowed for the determination of the degree of tooth migration, the presence, location, and extent of furcation invasions, the number and topography of absent teeth, occlusal and interdental relationships, and signs of parafunctional habits.

Temporary splinting of periodontal teeth was performed during conservative treatment, as well as before periodontal surgery and full oral rehabilitation.

For splinting periodontally compromised teeth in the *Ist group of patients,* fiberglass *Cord* ***Armosplint*** was used. This cord is made of special high-modulus weaving, with fiberglass threads braided with polyester microfibers, having a diameter of 1.5 mm. The cord is silanized (treated) to improve bonding with the composite. It is a moisture-resistant material, well impregnated with a special wetting liquid, which ensures a strong connection between the fiberglass and composite. It can be used with any flowable composite and has similar transparency qualities, which avoids color imitation issues during restoration, especially important for splinting anterior teeth. For convenience, the set with fiberglass "Armosplint" includes a liquid for wetting the fiberglass, a flowable composite, and an adhesive system that provides a strong bond and a reliable marginal fit based on chemical adhesion to tooth tissues. Working with this material, we observed that its flexibility allows good adaptation to uneven tooth surfaces, it can be cut with ordinary sharp scissors and does not unravel. Intra-dental application of the material was done after preparing square-shaped grooves with a depth of 1,5 mm and a width of 1,8-2,0 mm. However, we can mention that the cord thickness plus the covering composite material layer often requires endodontic preparation of the teeth. For fixing an artificial acrylic tooth to restore dental arch integrity, it will be prepared with the same grooves as in the splinted natural teeth.

For splinting periodontally compromised teeth in the *IInd group of patients,* ***Construct*** Kerr was used. This reinforcing tape is made of heavy-duty polyethylene fibers treated with cold gas discharge plasma and impregnated with unfilled resin Construct Resin. After application, the tape does not interfere with brushing and oral hygiene and provides sufficient aesthetics and durability. It can be used in combination with various composite materials. Intra-dental application of the material was performed after preparing square-shaped grooves with a depth of 1,5-2,0 mm and a width of 1,8-2,0 mm, or square-shaped grooves with a depth of 1,5 mm and a width of 1,8-2,0 mm with additional platforms of different shapes (square or dovetail) with the same depth. For fixing an artificial tooth in the reconstruction of dental arch integrity, the same grooves as those in splinted teeth will be prepared

For splinting periodontally compromised teeth in the *IIIrd group of patients,* aramid fiber ***Splintkord*** was used. This material is characterized by its strength, safety, resistance to saliva and food influence, and long service life. When using this material and technique, the teeth are first separated with a thin diamond disk, or the proximal surfaces are cleaned with strips. Wheel-shaped diamond burs are used to create a circular groove of 0.5-0.8 mm depth on the vestibular and oral sides of the tooth, and a deepening with a thin fissure bur to 1.2 mm on the vestibular surface. For fixing artificial acrylic teeth in the restoration of dental arch integrity, the same circular grooves as those in splinted natural teeth will be prepared.

Table 3. Types of applied splinting devices

Type of device	Number of dental arches
Splinting type – palatal	4
Splinting type – lingual	4
Splinting type – circular	4

The temporal splint may be unilateral or bilateral, depending on the number of mobile teeth involved, and requires at least 6 months for monitoring abutment teeth. Temporal splinting in all our three groups of patients necessarily concluded with the control and thorough correction of static and functional occlusal contacts to prevent occlusal trauma. In the cases of frontal edentulism with the absence of one tooth on the lower jaw (6 clinical cases) and on the upper jaw (2 clinical cases), as well as lateral edentulism with the absence of one tooth (first premolar) on the lower jaw (2 clinical cases) and on the upper jaw (2 clinical cases with first premolar absence), the integrity of the dentition was restored using a factory-made artificial acrylic tooth attached to the splint system with fibers used for splinting teeth and closed with the photopolymer composite material **Flowrest set**. Light-cure composite restorative material Flowrest set with a flowable consistency (low modulus) is used in therapeutic and of orthopedic dentistry for filling cavities of classes III, IV, and V; filling undercuts and making lower layers of classes I and II during restoration; sealing fissures; restoring small defects in indirect porcelain and composite veneers; and *splinting movable teeth*. It has high thixotropy and medium flowability, allowing it to fill well-prepared grooves in the teeth. We observed that the use of temporary splinting systems in patients included in the study positively affected the condition of periodontal tissue.

One of the essential diagnostic criteria for determining the degree of periodontitis is the depth of periodontal pockets This was assessed in our study across different groups before and after temporal splinting, demonstrating the effectiveness of the treatment method, as shown in Table 4.

Table 4. Average depth of periodontal pockets before and after etiotropic therapy and the application of splinting devices in all three patient groups

	Group I	Group II	Group III
Pre-treatment ($\bar{x}$)	4,7	3,9	4,2
Post-treatment ($\bar{x}$)	3.1	2,2	2,7
difference	1,6	1,7	1,5

Note: *Periodontal pockets were measured using a periodontal probe - a blunt-tipped instrument with millimeter markings. The depth of periodontal pockets was measured in millimeters. It was noted that the response to treatment was better in the second group of patients.*

The plaque index according to Silness-Löe was significantly reduced in each group compared to the initial values, though the reduction was less significant in the third group (Table 5).

Table 5. Difference in average plaque index before and after etiotropic therapy and the application of splinting devices

	Lot I	Lot II	Lot III
Pre-treatment ($\bar{x}$)	1,56	1,9	2,2
Post-treatment ($\bar{x}$)	0.65	1,2	1,7
difference	0,91	0,7	0,5

Note: *The measurement of oral hygiene status using the Silness-Löe plaque index is based on recording both soft debris and mineralized deposits on the teeth. Group I – average difference consisted of 0,91; in group II – 0,7; and in group III – 0,5.*

Violations of the qualitative and quantitative balance between normal forms of microflora and opportunistic microorganisms (micro biocenosis of the oral cavity), characteristic of dysbiosis, involve an increase in the number of potentially pathogenic microorganisms and/or an increase in the pathogenic strength of some microorganisms. In our study, such changes were determined through laboratory diagnostic methods in the diagnostic of periodontitis. The microbiocenosis of the oral cavity includes various types of microorganisms (bacteria, viruses, fungi, and protozoa). Qualitative and quantitative balance disruptions between normal microflora forms and opportunistic microorganisms are specific to dysbiosis. In this state, there is an increase in the number of potentially pathogenic microorganisms and/or an enhancement in the pathogenic power of some microorganisms. An effective solution for diagnosing dysbiotic disorders in the oral cavity is ParodontoScreen, a technology for quantitative real-time PCR analysis. Some examples of clinical cases, presented as photos from the investigation results, (that is why they are in Romanian), are shown in Fig.1.

Paradontoscreen (Cantitatea microorganismelor în depunerile dentare moi și lichidul gingival)

Denumirea	Rezultat cantitativ	Norma
Masa bacteriana totala	10^8.1	< 10^6,5
Actinobacillus actinomycetemcomitans	Nu sunt decelați	< 10^4,0
Porphyromorans gingivalis	10^7.6	< 10^5,0
Prevotella intermedia	10^6.4	< 10^4,5
Tannerella forsythensis	10^6.6	< 10^5,0
Treponema denticola	10^6.6	< 10^3,5
Candida albicans	Nu sunt decelați	< 10^4,5

Paradontoscreen (Cantitatea microorganismelor în depunerile dentare moi și lichidul gingival)

Denumirea	Rezultat cantitativ	Norma
Masa bacteriana totala	10^8.1	< 10^6,5
Actinobacillus actinomycetemcomitans	10^6.0	< 10^4,0
Porphyromorans gingivalis	10^6.6	< 10^5,0
Prevotella intermedia	10^5.8	< 10^4,5
Tannerella forsythensis	10^5.9	< 10^5,0
Treponema denticola	10^5.1	< 10^3,5
Candida albicans	Nu sunt decelați	< 10^4,5

Fig. 1 Results of Parodontoscreen for some study clinical cases before treatment.

ParodontoScreen, for detecting opportunistic microorganisms living in the human oral cavity, enabled us to objectively assess the qualitative and quantitative composition of anaerobic microorganisms in different biotopes of the oral cavity. This optimization of diagnosis and determination of treatment effectiveness is demonstrated in Table 6.

In the treatment of patients with periodontal disease, dynamic monitoring is necessary throughout the entire period of temporary splinting. The interval between visits is determined based on the type of splinting, the degree of risk for complications, and factors such as the severity of periodontitis, systemic and local conditions, the level of individual oral hygiene, and the patient's motivation. In cases

of gingivitis, mild chronic generalized periodontitis, or mild to moderate periodontal disease, an interval of 6 months between visits is recommended. In cases of moderate to severe chronic generalized periodontitis, or severe periodontitis, the interval is 4 months, while for aggressive forms of periodontitis, it is 2 months.

Table 6. Average data of Microbiological and Parodontoscreen results before and after conservative treatment and temporal splinting

	Actinobacillus actinomycetemcomitans	Porphyromonas gingivalis	Prevotella intermedia	Tannerella forsythensis	Treponema denticola	Candida albicans
Pre-treatment	10^4.1	10^7.6	10^6.6	10^6.8	10^6.6	10^5.1
Post-treatment	-	10^5.7	10^4.7	10^5.1	10^4.1	10^3.1
Normal quantity	< 10^4,0	< 10^5,0	< 10^4,5	< 10^5,0	< 10^3,5	< 10^4,5

Note: *Normal data on the quantity of opportunistic microorganisms in the human oral cavity, according to Parodontoscreen exam, were taken from the data of the MedExpert laboratory.*

Conclusions

1. Temporary splinting helps to decrease tooth mobility, allowing for the restoration of periodontal balance, decreased inflammation, and improved tissue healing and attachment gain, contributing to the effectiveness of pathogenetic and symptomatic therapy.

2. An analysis of the properties of adhesive splints indicates the need for further detailed study of composite materials used for tooth splinting. These studies are necessary for developing strategies and criteria for choosing splinting structures based on the specific details of clinical situations.

Competing interests

None declared.

Authors' contributions

All authors participated in the study design and contributed to drafting the manuscript. The authors critically reviewed the work and approved the final version of the manuscript.

Acknowledgment

We would like to express our special gratitude to University Professor Valeriu Fala, who assisted us in conducting this research.

Patient consent

Obtained.

Ethics approval

No approval was required for this study.

References

1. Könönen E, Gursoy M, Gursoy UK. Periodontitis: a multifaceted disease of tooth-supporting tissues. J Clin Med. 2019;8(8):1135. doi: 10.3390/jcm8081135.
2. Genco RJ, Borgnakke WS. Risk factors for periodontal disease. Periodontol 2000. 2013;62(1):59-94. doi: 10.1111/j.1600-0757.2012.00457.x.
3. Newman MG, Takei HH, Klokkevold P, Carranza FA, editors. Carranza's clinical periodontology. 12th ed. St. Louis: Elsevier/Saunders; 2015. 875 p.
4. Durrani F, Galohda A, Rai SK, Singh NK, Verma R, Yadav DS, Karthickraj SM. Evaluation and comparison of stress distribution around periodontally compromised mobile teeth splinted with different materials: three-dimensional finite element analysis. Indian J Dent Res. 2019 Jan-Feb;30 (1):97-101. doi: 10.4103/ijdr.IJDR_250_17.
5. Al-Sinaidi A, Preethanath RS. The effect of fixed partial dentures on periodontal status of abutment teeth. Saudi J Dent Res. 2014;5(2):104-108. doi: 10.1016/j.ksujds.2013.11.001.
6. Avetisyan A, Markaryan M, Rokaya D, Tovani-Palone MR, Zafar MS, Khurshid Z, Vardanyan A, Heboyan A. Characteristics of periodontal tissues in prosthetic treatment with fixed dental prostheses. Molecules. 2021;26(5):1331. doi: 10.3390/molecules26051331.
7. Bluma E, Vidzis A, Zigurs G. The influence of fixed prostheses on periodontal health. Stomatologija. 2016;18(4):112-121.
8. Hao Y, Huang X, Zhou X, Li M, Ren B, Peng X, Cheng L. Influence of dental prosthesis and restorative materials interface on oral biofilms. Int J Mol Sci. 2018;19(10):3157. doi: 10.3390/ijms19103157.
9. Heboyan A. Marginal and internal fit of fixed prosthodontic constructions: a literature review. Int J Dent Res Rev. 2019;2(19):21-28. doi: 10.28933/ijdrr-2019-06-1105.
10. Mangoush E, Säilynoja E, Prinssi R, Lassila L, Vallittu PK, Garoushi S. Comparative evaluation between glass and polyethylene fiber reinforced composites: a review of the current literature. J Clin Exp Dent. 2017 Dec;9(12):e1408. doi: 10.4317/jced.54205.
11. Nagaraj KR, Savadi RC, Savadi AR, Prashanth Reddy GT, Srilakshmi J, Dayalan M, John J. Gingival biotype – Prosthodontic perspective. J Indian Prosthodont Soc. 2010;10(1):27-30. doi: 10.1007/s13191-010-0011-3.
12. Knoernschild KL, Campbell SD. Periodontal tissue responses after insertion of artificial crowns and fixed partial dentures. J Prosthet Dent. 2000;84(5):492-498. doi: 10.1067/mpr.2000.110262.
13. Srimaneepong V, Heboyan A, Zafar MS, Khurshid Z, Marya A, Fernandes GVO, Rokaya D. Fixed prosthetic restorations and periodontal health: a narrative review. J Funct Biomater. 2022 Feb 1;13(1):15. doi: 10.3390/jfb13010015.

https://doi.org/10.52645/MJHS.2024.3.08

UDC: 617.735-002-02:616.379-008.64:618.2

REVIEW ARTICLE

Management of diabetic retinopathy in pregnancy

Cristina Şcerbatiuc

Department of Ophthalmology, *Nicolae Testemiţanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

ABSTRACT

Introduction. The onset and development of diabetic retinopathy are more common during pregnancy. Pregnancy has no long-term effect on diabetic retinopathy; however, in 50-70% of cases, changes in retinopathy continues. The probability of worsening is highest in the second trimester and up to one year postpartum. Additional factors that have been associated with disease progression include duration of diabetes, the degree of retinopathy at the time of conception, management of hyperglycemia, anemia, and development of associated hypertension. In cases of severe non-proliferative retinopathy, it is recommended to promptly initiate laser photocoagulation rather than wait for early proliferative changes. Maintaining good diabetic control before and during pregnancy can help prevent disease progression and serious vision loss.

Material and methods. Diabetic retinopathy management in pregnancy was the subject of a comprehensive review of the scientific and medical literature. A structured search was performed in the PubMed, Scopus and HINARI databases, considering relevant articles published in the last 10 years. The search terms used (in English) were: „Diabetic retinopathy"; „pregnancy"; „laser photocoagulation"; „intravitreal steroids"; „anti-vascular endothelial growth factor".

Results. It is suggested that women with diabetes receive pre-conception and post-pregnancy counselling from a multidisciplinary team including an ophthalmologist, endocrinologist, and perinatologist, as diabetic retinopathy may worsen during pregnancy. The risk of progression of the disease and the importance of appropriate metabolic control before and during pregnancy should be clearly explained to the patient. Careful monitoring is required in patients with advanced gestation, significant retinopathy, concomitant hypertension, and nephropathy.

Conclusion. The risk of retinopathy development may increase during pregnancy. Serious effects can arise for both the mother and the fetus, even though retinopathy is not common during pregnancy. It is possible to avoid significant retinopathy by carefully planning a young diabetic woman's pregnancy and proceeding promptly to laser photocoagulate in cases of severe non-proliferative retinopathy. A tendency for regress is frequently seen in diabetic retinopathy during the post-natal period. Subsequent pregnancies do not significantly increase the risk of progression if the retinopathy is stable before pregnancy.

Keywords: Pregnancy; diabetic retinopathy; laser photocoagulation; anti-vascular endothelial growth factor; intravitreal steroids.

Cite this article: Şcerbatiuc C. Management of diabetic retinopathy in pregnancy. Mold J Health Sci. 2024;11(3):54-58. https://doi.org/10.52645/MJHS.2024.3.08.

Manuscript received: 18.04.2024

Accepted for publication: 03.09.2024

Published: 20.09.2024

Corresponding author: Cristina Şcerbatiuc, PhD, assistant professor
Department of Ophthalmology,
Nicolae Testemiţanu State University of Medicine and Pharmacy,
165 Ştefan cel Mare şi Sfânt bd., Chişinău, Republic of Moldova, MD-2004
e-mail: cristina.scerbatiuc@usmf.md

Author's ORCID ID:
Cristina Şcerbatiuc – https://orcid.org/0000-0002-4512-0626

Key messages

What is not yet known on the issue addressed in the submitted manuscript

The control of diabetic retinopathy is becoming more difficult due to the lack of information regarding the safety and effectiveness of existing therapy options during pregnancy.

The research hypothesis

When treating patients who already have diabetic macular edema, caution must be exercised in determining the necessity, timing, and level of therapy, as panretinal photocoagulation increases the risk of exacerbating the condition.

The novelty added by manuscript to the already published scientific literature

The recommended treatments for diabetic macular edema during pregnancy are intravitreal steroids or focal laser, if the condition responds to these measures. When treated with anti-VEGF medications, ranibizumab remains the preferred agent due to its shortened half-life and faster plasma clearance.

Introduction

Women with diabetes - regardless of the type of diabetes - must plan a pregnancy to ensure optimal conditions for the child's development and their own health and to reduce the risk of perinatal complications. The main problem with pre-existing diabetes is the development of diabetic embryopathy [1].

Pregnancy in women with manifest forms of diabetes primarily affects women with type 1 diabetes mellitus. However, recent surveys also show a continuous increase in type 2 diabetes mellitus, which, in addition to hyperglycemia, is complicated by obesity-related risks and often by older maternal age [2]. Even among pregnant women with diabetes type 1, a significant increase in BMI has been observed over the last decade. In both T1DM and T2DM, higher maternal BMI and higher blood pressure, in addition to metabolic control and diabetes duration at the start of pregnancy, were associated with poorer pregnancy outcomes. Migrant women and women from low socioeconomic backgrounds account for a significant proportion of women with diabetes type 2, particularly those who were inadequately treated and prepared for pregnancy or whose pre-existing diabetes was only newly discovered during pregnancy. Persistently poor pregnancy outcomes in women with pre-conceptional diabetes are also confirmed in recent population-based surveys [3].

Maternal obesity and inadequate metabolic control are the main modifiable risk factors, while maternal age, duration of diabetes and maternal deprivation are the main non-modifiable risk factors. No differences were found in congenital malformations and stillbirths between women with type 1 and type 2 diabetes, while premature births were more common in type 1 diabetes [4]. However, women with type 2 diabetes had a higher neonatal mortality rate. An HbA1C ≥ 6.5 % in the 3rd trimester, type 2 diabetes, and social disadvantage of the mothers were independent risk factors for perinatal death. Increased attention should be paid to achieve optimal glycaemia in women with type 2 diabetes before and during pregnancy, as these patients often already have additional cardiovascular risk factors, comorbidities, and the risk of complications is often underestimated [4].

According to The Diabetes Control and Complications Trial (DCCT), pregnancy increases the risk of retinal damage by 1.63 times compared to the state of the retina before pregnancy and by 2.48 times compared to similar indicators in non-pregnant women [5].

Potin *et al.* note that 61.2% of patients with type 1 diabetes mellitus and microvascular changes during pregnancy have DR. However, the occurrence or progression of DR is observed in 9.7% of pregnant women [6].

The worsening of DR during pregnancy is due to a number of factors: pregnancy itself, changes in retinal blood flow, inadequate glycemic control before and during pregnancy, the rapid normalization of blood sugar, the presence and severity of diabetic retinopathy before pregnancy, the duration of diabetes, the presence of hypertension, diabetic neuropathy, and pre-eclampsia [7].

The progression of DR depends considerably on the severity of glucose metabolism decompensation before conception and in the first 6-14 weeks of pregnancy, as well as the rate at which normoglycemia is achieved. The Diabetes in Early Pregnancy (DIEP) study revealed that 10.3% of women with DM1 who had an initial absence of ocular changes and progression of DR during pregnancy had baseline HbA1c level 4 standard deviations above normal. The DCCT study proved that the risk of DR progression in pregnant women with DM1 is directly related to baseline DM compensation [5].

B. Rosenn *et al.* note that patients with chronic hypertension or pregnancy-related hypertension have a higher frequency of diabetic retinopathy progression. Increased retinal blood flow, corresponding to the hyperdynamic circulatory state in pregnancy, can stimulate endothelial damage and become a significant factor in the progression of the condition [8].

There is a common belief that DR regresses in the postpartum period. The DCCT study indicated the transient nature of the changes occurring during pregnancy [5].

S. Arun and R. Taylor studied women with DM1 for 5 years after childbirth and found that pregnancy does not lead to long-term worsening of DR [9].

However, W. Chan *et al.* observed pregnant women with an aggressive course of DR and found that in this group of patients, in 81% of cases, the condition progressed to the proliferative stage in the postpartum period. Moreover, the most unfavorable outcomes in the form of traction and rhegmatogenous retinal detachment and neovascular glaucoma were observed when spontaneous regression of the disease was expected after delivery and timely retinal laser coagulation was not performed [10].

The progression of DR may depend on whether retinal laser photocoagulation was performed in the pregestational period. A study of patients with proliferative DR detected in early pregnancy who subsequently underwent laser photocoagulation showed progression and significant visual impairment in 58% of cases. In contrast, among patients in whom retinopathy was detected and treated before pregnancy, only 26% of cases showed progression of DR during the gestational period [11]. The indications for treatment and response to retinal laser photocoagulation in preg-

nant women are the same as in all patients with diabetes. Pre-conceptional stabilization of glycemia and blood pressure levels is of paramount importance to prevent the manifestation and progression of DR during pregnancy in diabetes. Glycated hemoglobin concentration should be maintained below 6.1% if possible and safe. It is important to monitor the ocular fundus throughout pregnancy - at least twice in different trimesters, as well as in the postpartum period until the process is completely stabilized. If progression of DR is detected, timely treatment, primarily retinal laser photocoagulation, improves visual prognosis [12].

Laser Treatment

It makes sense to advise close supervision in cases where a pregnant woman first develops moderate to severe diabetic macular edema, with a priority on achieving and maintaining adequate glucose control. Two diabetic individuals in the first trimester of their pregnancies were included in a Danish article. They had retinal edema 500–1500 μm in the fovea area. Good glucose management helped both patients improve, and as a result, they did not require any furhter care [13].

Although observation is a good choice for pregnant patients with mild to moderate diabetic macular edema (DME), it is important to observe these women more carefully than non-pregnant adults. If DME does not resolve after a period of follow-up, the first-line treatment option is laser treatment. The ETDRS reported that grid or focused laser treatment of clinically significant macular edema was successful in preventing continued visual disability [13, 14]. According to a study conducted in Copenhagen, two pregnant women diagnosed with type 1 DM and macular edema received targeted laser treatment and did not require any additional medical intervention during their pregnancy. When foveal involvement makes traditional laser therapy unsafe, subthreshold MicroPulse or endpoint management are two further options that could be taken into consideration. Following treatment using a MicroPulse laser, Italian researchers found a substantial short-term improvement in DME and visual acuity [15]. These non-invasive techniques might be useful in situations when traditional laser treatments are inappropriate or potentially dangerous, especially when a woman is newly pregnant [13, 15].

For pregnant patients with DR, panretinal photocoagulation is regarded as a reliable and effective therapy option. It has been shown to be an effective treatment for diabetic retinopathy during pregnancy and remains a vital treatment for stopping disease's progression. When administering PRP to pregnant people, proper scheduling is essential. According to recommendations, PRP therapy may be necessary for pregnant women at earlier stages, especially if their degree of DR approaches severe nonproliferative DR or higher [16].

Intravitreal Steroids in DME

There is little data in the literature on the use of intravitreal steroids during pregnancy, and much of the material available comes from modest research. A collection of research supporting intravitreal steroid usage and evaluation of its safety profiles at different phases of pregnancy may exist, although it is not as extensive as the research supporting certain other therapies. It is critical to recognize the moral difficulties that arise when conducting extensive research on expectant mothers, as these challenges may limit the amount of high-caliber, widely available material. Because of the potential consequences for the developing baby as well as the mother, the safety of any medical intervention during pregnancy is a serious concern.

The use of intravitreal steroids during pregnancy should be decided on a case-by-case basis, carefully balancing the possibility of benefits versus any existing or prospective hazards, given the lack of information [13, 17].

Intravitreal Anti-VEGF Substances

Due to the lack of long-term efficacy evidence for anti-VEGF medication in pregnant patients, it is often used only as an emergency measure during gestation. Anti-VEGF medications, such as bevacizumab, ranibizumab and aflibercept are frequently used to treat a range of eye disorders, particularly retinal illnesses. Because the possible effects on the developing baby are a serious concern, pregnant women are frequently cautious about using drugs that have not been thoroughly investigated for their safety during pregnancy [18].

Consequently, anti-VEGF medication is usually considered only when alternative medical options are not possible or effective for a pregnant woman, and if it is determined that she needs it. Moreover, it is usually preferable to start anti-VEGF medication afterwards in pregnancy, especially in the third trimester. This period was chosen based on the idea of reducing possible hazards to fetal development during the critical early stages of pregnancy. In a patient with foveal-involving diabetic macular edema and a contraindication to steroids, the use of anti-VEGF therapy could be considered. The Diabetic Retinopathy Clinical Research Network study has shown that anti-VEGF therapies are highly effective in the treatment of DME. This study compared the outcomes of anti-VEGF therapy combined with laser treatment versus laser treatment alone. The drug's half-life in the plasma plays a role in deciding which anti-VEGF therapy to choose. Bevacizumab is known to have a longer half-life and to remain in the plasma for a longer period of time. Bevacizumab administered intravitreal has been demonstrated to lower plasma VEGF levels for a minimum of one month. Ranibizumab, on the other hand, has a shorter half-life and is cleared from the plasma quickly. Given that ranibizumab has a shorter half-life, it is considered a viable treatment option for expectant mothers and those who plan to become pregnant soon after receiving an anti-VEGF injection [13, 18, 19].

Women diagnosed with preproliferative DR during pregnancy should be counseled to attend regular eye examinations for at least 6 months postpartum and typically up to 1 year postpartum. This monitoring is important to track the progression of diabetic retinopathy and to ensure timely intervention if necessary. The DCCT study demonstrated that the higher risk of progression of DR during pregnancy per-

sisted for one year after delivery. Several of these women required laser photocoagulation for up to 12 months after delivery [20, 21]. Another study found that DR was more likely to progress 4 months after delivery than during pregnancy. This phenomenon may be related to the successful control of glycaemia during pregnancy, which then decreases in the postpartum period. Dilated fundoscopy should be performed 1-2 months after delivery in those who had treated or untreated DME during pregnancy and in patients with mild, moderate or severe nonproliferative DR. This follow-up examination is recommended to assess the retinal status postpartum and should be continued until 12 months after delivery [22, 23].

Conclusions

Numerous factors affect how DR progresses throughout pregnancy, including the level of retinopathy at conception, the efficacy of medication, the duration of diabetes, the state of glucose regulation prior to pregnancy, and the existence of other vascular complications, such as associated or pre-existing hypertensive conditions. Retinopathy progression is less likely when risk factors are precisely identified, and diabetes is well managed. To protect the wellness of both the fetus and mother's eyes by improving early diagnosis and management of potential ophthalmic disorders, an ophthalmologist consultation is advised for women who have recently been diagnosed with diabetes during pregnancy.

The probability of vision loss is low for those who have mild retinopathy at the beginning of pregnancy; a fundus exam every three months is usually sufficient. Further regular evaluation is advised for patients with mild baseline retinopathy, with ophthalmoscopy carried out at each obstetrician visit. Investigations should be performed every two weeks if there are signs of progression. In situations where high-risk retinal modifications are suspected, laser photocoagulation should be performed immediately, with ophthalmoscopy used to monitor the process. Laser photocoagulation is recommended to be carried out before pregnancy or as soon as significant retinal alterations manifest in women with severe diabetic retinopathy [15, 23].

Competing interests

None declared.

Acknowledgements and funding

No external funding.

Ethics approval

Not needed for this study.

References

1. Widyaputri F, Rogers SL, Kandasamy R, Shub A, Symons RCA, Lim LL. Global estimates of diabetic retinopathy prevalence and progression in pregnant women with preexisting diabetes. JAMA Ophthalmol. 2022;140(5):486-494. https://doi.org/10.1001/jamaophthalmol.2022.0050.
2. Sarvepalli SM, Bailey BA, D'Alessio D, Lemaitre M, Vambergue A, Rathinavelu J, Hadziahmetovic M. Risk factors for the development or progression of diabetic retinopathy in pregnancy: meta-analysis and systematic review. Clin Exp Ophthalmol. 2022;51(3):195-204. https://doi.org/10.1111/ceo.14168.
3. Bourry J, Courteville H, Ramdane N, Drumez E, Duhamel A, Subtil D, Deruelle P, Vambergue A. Progression of diabetic retinopathy and predictors of its development and progression during pregnancy in patients with type 1 diabetes: a report of 499 pregnancies. Diabetes Care. 2020;44(1):181-187. https://doi.org/10.2337/dc20-0904.
4. Scanlon PH. The English National Screening Programme for diabetic retinopathy 2003–2016. Acta Diabetologica. 2017;54(6):515-525. https://doi.org/10.1007/s00592-017-0974-1.
5. Nathan DM. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care. 2013;37(1):9-16. https://doi.org/10.2337/dc13-2112.
6. Potin VV, Borovik NV, Tisel'ko AV. Insulinoterapiia bol'nyh sakharnym diabetom 1 tipa vo vremia beremennosti [Insulin therapy for patients with type 1 diabetes during pregnancy]. Diabetes Mellit. 2009;12(1):39-41. https://doi.org/10.14341/2072-0351-5420. Russian.
7. Amoaku WM, Ghanchi F, Bailey C, Banerjee S, Banerjee S, Downey L, et al. Diabetic retinopathy and diabetic macular oedema pathways and management: UK Consensus Working Group. Eye. 2020;34(Suppl 1):1-51. https://doi.org/10.1038/s41433-020-0961-6.
8. Rosen RB, Andrade Romo JS, Krawitz BD, Mo S, Fawzi AA, Linderman RE, Carroll J, Pinhas A, Chui TY. Earliest evidence of preclinical diabetic retinopathy revealed using optical coherence tomography angiography perfused capillary density. Am J Ophthalmol. 2019;203:103-115. https://doi.org/10.1016/j.ajo.2019.01.012
9. Arun CS, Taylor R. Influence of pregnancy on long-term progression of retinopathy in patients with type 1 diabetes. Diabetologia. 2008;51(6):1041-1045. https://doi.org/10.1007/s00125-008-0994-z.
10. Chan WC, Lim LT, Quinn MJ, Knox FA, McCance D, Best RM. Management and outcome of sight-threatening diabetic retinopathy in pregnancy. Eye. 2004;18(8):826-832. https://doi.org/10.1038/sj.eye.6701340.
11. Rafferty J, Owens DR, Luzio SD, Watts P, Akbari A, Thomas RL. Risk factors for having diabetic retinopathy at first screening in persons with type 1 diabetes diagnosed under 18 years of age. Eye. 2020;35(10):2840-2847. https://doi.org/10.1038/s41433-020-01326-8.
12. Zhang B, Zhang B, Zhou Z, Guo Y, Wang D. The value of glycosylated hemoglobin in the diagnosis of diabetic retinopathy: a systematic review and meta-analysis. BMC Endocr Disord. 2021;21(1):82. https://doi.org/10.1186/s12902-021-00737-2.
13. Rosu LM, Prodan-Bărbulescu C, Maghiari AL, Bernad ES, Bernad RL, Iacob R, Stoicescu ER, Borozan F, Ghenciu LA. Current trends in diagnosis and treatment approach of diabetic retinopathy during pregnancy: a narrative review.

Diagnostics. 2024;14(4):369. https://doi.org/10.3390/diagnostics14040369.
14. Bakri S, Dedania V. Novel pharmacotherapies in diabetic retinopathy. Middle East Afr J Ophthalmol. 2015;22(2):164-173. https://doi.org/10.4103/0974-9233.154389.
15. Değirmenci MFK, Demirel S, Batıoğlu F, Özmert E. Short-term efficacy of micropulse yellow laser in non-center-involving diabetic macular edema: preliminary results. Turk J Ophthalmol. 2018;48(5):245-249. https://doi.org/10.4274/tjo.04657.
16. Gomułka K, Ruta M. The role of inflammation and therapeutic concepts in diabetic retinopathy - a short review. Int J Mol Sci. 2023;24(2):1024. https://doi.org/10.3390/ijms24021024.
17. Chauhan MZ, Rather PA, Samarah SM, Elhusseiny AM, Sallam AB. Current and novel therapeutic approaches for treatment of diabetic macular edema. Cells. 2022;11(12):1950. https://doi.org/10.3390/cells11121950.
18. Kohly RP, Muni RH, Kertes PJ. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Evidence-Based Ophthalmol. 2010;11(4):199-201. https://doi.org/10.1097/ieb.0b013e3181f4ce75.
19. Chandrasekaran P, Madanagopalan V, Narayanan R. Diabetic retinopathy in pregnancy - a review. Indian J Ophthalmol. 2021;69(11):3015-3025. https://doi.org/10.4103/ijo.ijo_1377_21.
20. Ghanchi F. The Royal College of Ophthalmologists' clinical guidelines for diabetic retinopathy: a summary. Eye. 2013;27(2):285-287. https://doi.org/10.1038/eye.2012.287.
21. Pappot N, Do NC, Vestgaard M, Ásbjörnsdóttir B, Hajari JN, Lund-Andersen H, et al. Prevalence and severity of diabetic retinopathy in pregnant women with diabetes - time to individualize photo screening frequency. DiabetMed. 2022;39(7):e114819. https://doi.org/10.1111/dme.14819.
22. American Diabetes Association Professional Practice Committee. Management of diabetes in pregnancy: standards of medical care in diabetes - 2022. Diabetes Care. 2021;45(Suppl 1):S232-S243. https://doi.org/10.2337/dc22-s015.
23. Ong AY, Kiire CA, Frise C, Bakr Y, de Silva SR. Intravitreal anti-vascular endothelial growth factor injections in pregnancy and breastfeeding: a case series and systematic review of the literature. Eye. 2023;38(5):951-963. https://doi.org/10.1038/s41433-023-02811-6.

https://doi.org/10.52645/MJHS.2024.3.09

UDC: 616.155.194.18:616.5-002.525.2

CASE STUDY

Acute autoimmune hemolytic anemia in a patient with systemic lupus erythematosus

Vera Chirca[1*], Serghei Popa[1], Svetlana Agachi[1], Lucia Dutca[1], Valeriu Corotaş[2]

[1] Rheumatology and Nephrology Discipline, *Nicolae Testemițanu* State University of Medicine and Pharmacy, Chișinău, Republic of Moldova
[2] *Holly Trinity* Municipal Clinical Hospital, Chișinău, Republic of Moldova

ABSTRACT

Introduction. Autoimmune hemolytic anemia occurs due to the accelerated destruction of erythrocytes as a result of the dysfunction of immune system cells, which produce antibodies against the normal antigens of the membrane of hematopoietic cells. One of its causes is systemic lupus erythematosus.

Materials and methods. We present a case of a 20-year-old patient who was hospitalized with acute autoimmune hemolytic anemia, having been diagnosed with SLE at the age of 18 years. At the onset of the disease, hemolytic anemia was a differential diagnostic challenge.

Results. The differential diagnosis between primary and secondary autoimmune hemolytic anemia (AIHA) was an important step. The presence of antinuclear antibodies (ANA Hep2, Anti-dsDNA, Anti-cardiolipin, Anti-phospholipids, anti-Ro, Anti-Sm B) were important arguments in making the diagnosis. The relapse of AIHA was caused by inadequate treatment, due to a lack of compliance. Pulse therapy combined with methylprednisolone and cyclophosphamide successfully resolved the AIHA.

Conclusions. Hematological abnormalities are commonly seen in SLE patients, but hemolytic autoimmune anemia is a rare condition. A timely diagnosis of the cause of hemolytic anemia and proper treatment of lupus by correcting autoimmune disorders are crucial in disease management. Pulse therapy combined with corticosteroids and immunosuppressants is effective in acute relapses of hemolytic anemia.

Keywords: systemic lupus erythematosus, autoimmune hemolytic anemia, antinuclear antibodies, ANA, Anti-dsDNA, Anti-phospholipid, corticosteroids, immunosuppressants, cyclophosphamide.

Cite this article: Chirca V, Popa S, Agachi S, Dutca L, Corotaş V. Acute autoimmune hemolytic anemia in a patient with systemic lupus erythematosus. Mold J Health Sci. 2024;11(3):59-64. https://doi.org/10.52645/MJHS.2024.3.09.

Manuscript received: 30.04.2024

Accepted for publication: 5.09.2024

Published: 20.09.2024

[*]**Corresponding author: Vera Chirca**, Dr. resident,
Rheumatology and Nephrology Discipline,
Nicolae Testemițanu State University of Medicine and Pharmacy,
165 Ștefan cel Mare și Sfânt blvd, Chișinău, Republic of Moldova, MD 2025
e-mail: vera_tkach_2017@mail.ru

Authors' ORCID IDs
Vera Chirca – https://orcid.org/0009-0007-6435-7673
Serghei Popa – https://orcid.org/0000-0001-9348-4187
Svetlana Agachi – https://orcid.org/0000-0002-2569-7188
Lucia Dutca – https://orcid.org/0000-0002-1815-2294
Valeriu Corotaș – https://orcid.org/0009-0008-2552-4720

Key messages

What is not yet known on the issue addressed in the submitted manuscript

The submitted manuscript introduces a rare case of recurrence of acute autoimmune hemolytic anemia in a patient with systemic lupus erythematosus. The cause and triggers for this phenomenon are still unclear.

The research hypothesis

The manuscript does not explicitly state a research hypothesis, as it primarily focuses on reporting a rare case of AIHA in the course of SLE.

The novelty added by manuscript to the already published scientific literature

This manuscript contributes to the existing scientific literature by presenting a novel case of a patient with SLE, who initially presented with autoimmune hemolytic anemia, posing a diagnostic challenge. Without adequate treatment, patients are at risk of relapse with adverse consequences.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with an unclear etiology and complex pathogenesis. The immune response in SLE is directed against self-nuclear and non-nuclear nucleic acid-protein complexes [1]. Autoimmune hemolytic anemia (AIHA) is a rare autoimmune disease in which red blood cells are exposed to autoantibodies, which causes a significant decrease in their lifespan. AIHA may manifest in SLE patients at the time of diagnosis or within the first year of the disease [2]. Autoimmune hemolytic anemia manifests itself in approximately 5-10% of SLE patients [2, 3]. AIHA involves the presence of antibodies that react to heat, cold, or mixed types of reactive antibodies that are directed against antigens on the surface of red blood cells. Warm autoimmune hemolytic anemia (warm agglutinin disease) is usually manifested by asthenia and other constitutional symptoms and is diagnosed by the presence of IgG antibodies. About half of the cases of warm AIHA are recognized as secondary to the underlying disease. Warm AIHA in SLE is often associated with the presence of antiphospholipid antibodies and with an increased risk of thrombosis [4, 5].

The essential treatment of AIHA is based on suppression of autoantibody production by monotherapy or combination therapy with glucocorticoids (GC) and/or rituximab and, more rarely, with immunosuppressants such as cyclophosphamide, azathioprine. Reducing the destruction of red blood cells by splenectomy is currently considered the third-line of treatment for warm AIHA [6, 7].

Here we report a rare case of SLE with autoimmune hemolytic anemia at the onset of the disease, with relapses due to inadequate treatment in a non-compliant patient.

Case report

We report the case of a 20-year-old man, hospitalized with complaints of general weakness, asthenia, dyspnea, fever, and icteric sclera. He has a 2-year history of SLE and treatment with low dose of methylprednisolone. The onset of the disease was marked by warm autoimmune hemolytic anemia. Laboratory results showed a low level of hemoglobin, erythrocytes and haptoglobin and a high level of indirect bilirubin and lactate dehydrogenase, reticulocytosis.

Material and methods

Complete blood count revealed macrocytic anemia with Hb 49 g/L, RBC $0.98x10^{12}$/L, with no changes in platelet and white blood cell count. At the biochemical examination, hyperbilirubinemia with increase of both direct and indirect bilirubin (total bilirubin 71.4 µmol/L, direct bilirubin 20.71 µmol/L and indirect bilirubin 50.69 µmol/L), hypertransaminasemia (ALT 219.8 U/L, AST 178.1 U/L), decreased serum haptoglobin (0.590 g/L) and increased lactate dehydrogenase (LDH 556.4 U/L) activity were observed. The diagnose of systemic lupus erythematosus was established in accordance with the 2019 EULAR/ACR classification criteria for SLE [8-10].

Results

An 18-year-old male patient presented to the emergency unit with generalized weakness, dizziness, arthralgia, and abdominal pain. The symptoms appeared a week ago and were accompanied by a fever of 38-39°C. At the physical examination, the following were observed: pale skin, icteric sclera, local hyperemia on the fingers, ulceration in the area of the right big toe, skin peeling at the level of the fingers and toes, subacute skin rash and edema of the lower limbs. Auscultation of the lungs revealed rough vesicular breathing, dry murmurs bilaterally in basal area. The heart sounds were clear and rhythmic. Palpation of the abdomen caused pain in the epigastric region. The liver was enlarged (10 cm bellow the edge of the right rib). The spleen was enlarged to 10 cm in longitudinal diameter. Vital signs at admission: temperature 37.9°C, pulse 78 /min, BP 125/80 mmHg, RR 19 per minute and SpO_2 99%. Due to severe anemia, the patient was hospitalized in the intensive care unit, where an erythrocyte mass transfusion was performed during the first 3 days (6 doses of erythrocyte concentrate).

After the improvement of the hematological indices, the patient was transferred to the rheumatology department. Physical examination showed urticaria, local hyperemia in the hands, ulceration in the area of the right big toe, peeling of the skin in the fingers and toes, signs of pruritus in the lower extremities, photosensitivity, subacute skin rash. From the patient's medical history, it was found that the patient was diagnosed with SLE with antiphospholipid syndrome accompanied by autoimmune hemolytic anemia 3 years ago. At the onset, he presented with general asthenia, vertigo, nausea, vomiting, asthenia and fever. As the hemoglobin level was very low (72 g/l), differential diagnostic measures were taken (sternal puncture with bone marrow investigation and immunological studies). The association of hemolytic anemia with positive antinuclear antibodies (ANA on Hep2 cells, anti-dsDNA antibodies, anti-cardiolipins, anti-phospholipids, anti-Ro, Anti-Sm-B in diagnostic titer and anti-histones, Anti-Mi-2β, anti-nucleosomes, anti-RNP, Anti-Ku, anticentromere in small titer), provided strong evidence for the diagnosis of SLE according to the 2019 EULAR/ACR classification criteria of systemic lupus erythematosus. Treatment with glucocorticosteroids was initiated with a dose of 60 mg/day of Prednisone equivalent, with dose tapering in outpatient settings after stabilization of the condition. The patient did not comply with the medical prescriptions, and rapidly reduced the dose of Methylprednisolone eventually discontinuing it completely. Upon discontinuation of treatment, symptoms of clinical exacerbation and signs of hemolytic anemia reappeared.

During the last hospitalization, measures were taken to rule out digestive hemorrhage and assess the extent of internal organ damage. Fibrogastroduodenoscopy revealed catarrhal gastritis without signs of hemorrhage, and the abdominal ultrasound examination revealed hepatomegaly and splenomegaly. No obvious changes on transthoracic echocardiography. X-ray examination of the chest demonstrates interstitial lung involvement (Fig. 1).

Laboratory results are presented in Tables 1 and 2.

Table 1. Hematological parameters of patient during hospitalization

Parameter	Date						Reference range	Units
	15.03	16.03	17.03	18.03	19.03	22.03		
Hemoglobin	49	61	76	92	102	100	130-170	g/L
Hematocrit	13.4	17	21	25	28.7	28.6	39-54	%
Red blood cells	0.89	1.31	1.7	2.1	2.49	2.54	4.0-6.0	*10^12/L
Platelets	205	155	118	126	160	238	150-450	*10^9/L
MCV	150.6	132.3	123.7	118.3	115.3	112.6	78-95	fL
MCH	55.1	46.9	45.0	43.2	41.0	39.4	27-36	pg
MCHC	36.6	35.5	36.4	36.5	35.5	35.0	32-36	g/dL
PDW	9.5	9.3	9.3	11.0	10.4	9.6	11-16.6	fL
MPV	10.0	9.9	9.7	10.1	10.0	9.5	7.4-11.0	fL
P-LCR	23.6	23.3	22.3	25.7	24.1	20.8	13-43	%
White blood cells	12.45	6.7	3.9	3.5	3.92	4.83	3.6-10.0	*10^9/L
Neutrophils	82.9	72	56	55	66.7	65.2	42.2-75.2	%
Eosinophils	0.2	0.6	2.1	3	3.6	0.0	0-4.0	%
Basophiles	0.2	0.0	0.3	0.3	0.3	0.0	0-0.6	%
Monocytes	6.3	8	10	11	7.7	11.6	2.2-8.0	%
Lymphocytes	10.4 1.29	19 1.29	31 1.22	31 1.07	21.7 0.85	23.2 1.12	20.5-45.0 1-4	% *10^9/L)
ESR		27	26	24	6	5		mm/h
Reticulocytes					170.9		0.2-1.0	%
Morphology	Macrocytosis				Macrocytosis Reticulocytosis Anemia	Macrocytosis Anisocytosis		

Note: MCV - mean corpuscular volume; MCH - mean corpuscular hemoglobin; MCHC - mean corpuscular hemoglobin concentration; PDW - platelet distribution width; MPV - mean platelet volume; P-LCR - platelet-large cell ratio; ESR - erythrocyte sedimentation rate.

Table 2. Biochemical parameters of patient during hospitalization

Parameter	Date					Reference range	Units
	15/03	16/03	17/03	18/03	22/03		
Total bilirubin	71.4	54.4	39.2	33.9	14.57	2.0-21.0	µmol/L
Direct bilirubin	20.71	16.4	13.7	11.4		<5.13	µmol/L
Indirect bilirubin	50.69	38.0	25.5	22.5		<16.4	µmol/L
AST	178.1	123	68	37	12.7	<35	U/L
ALT	219.8	160	109	74	22.9	<45	U/L
Urea	9.27	8.3	6.5	5.7	7.70	2.8-7.2	mmol/L
Creatinine	134.3	106	72	58	47.9	70-115	µmol/L
Amylase	63.7					28-100	U/L
Albumin					28.6	35-53	g/l
y-GT					34.0	11-50	U/L
LDH					556.4	240-480	U/L
CRP					2.7	<5	mg/L
RF					6.0	0-15	IU/mL
Na					142.0	130-157	mmol/l
K					4.18	3.6-5.-	mmol/l
Haptoglobin					0.590	0.9-2.2	g/L

Note: AST – aspartate aminotransferase; ALT- alanine aminotransferase; y-GT - gamma-glutamyl transpeptidase; LDH - lactate dehydrogenase; CRP – C-reactive protein; RF – rheumatoid factor; Na - sodium; K - potassium.

The physical examination revealed clinical signs characteristic of the evolution of systemic lupus erythematosus, such as acute photosensitive skin rash, necrotizing vasculitis in the fingers, scratching lesions and livedo reticularis (Fig. 2)

In the rheumatology department, high doses of glucocorticoids (Methylprednisolone 250 mg intravenously for 3 days as pulse therapy) were initiated, followed by prolonged treatment with Prednisolone 40 mg/day *per os* with dose adjustment depending on the effectiveness of the treatment measured by validated tools.

On the third day after the installation of the peripheral venous catheter (ulnar vein) pain, swelling and hyperemia in the area of the venipuncture appeared. The catheter was

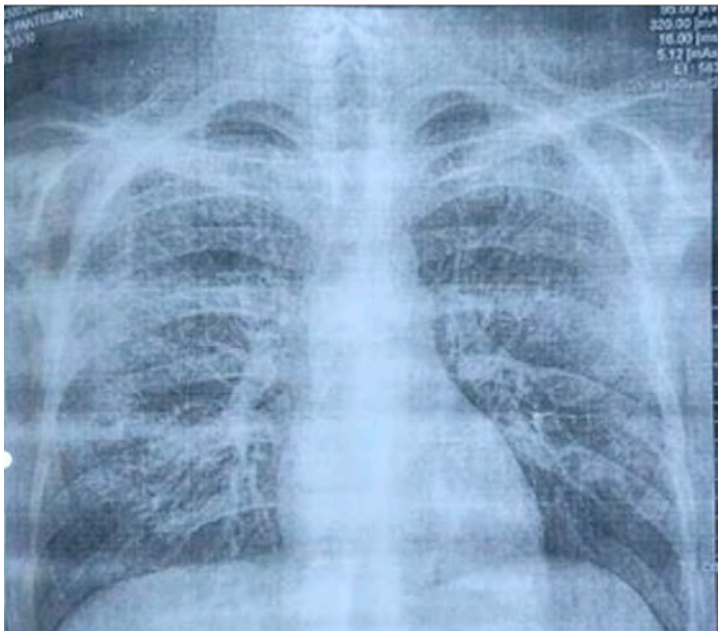


Fig 1. Chest X-ray with diffuse interstitial lung involvement most characteristic for lupus pneumonitis

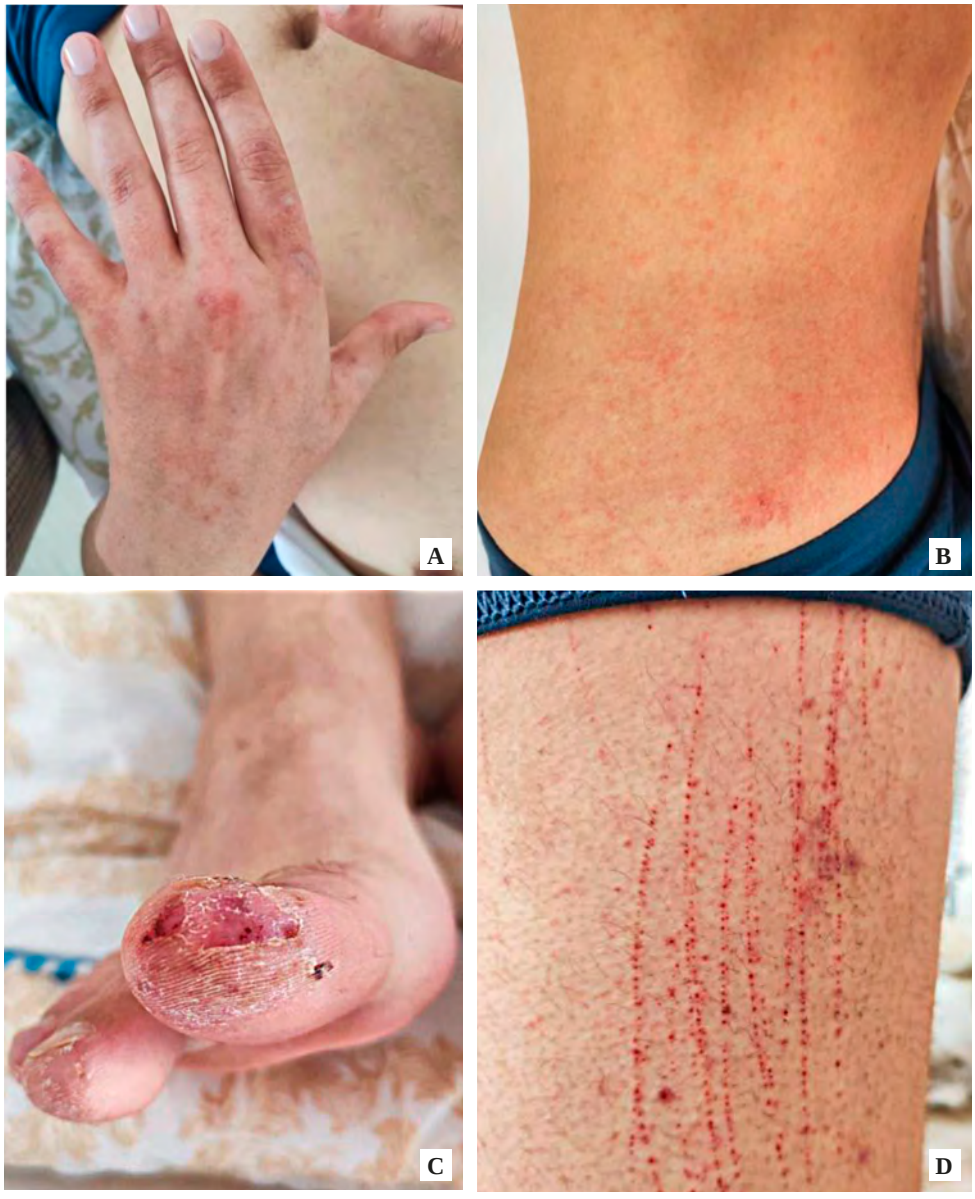


Fig 2. Skin manifestations observed in the patient
A, B - subacute skin rash, C - necrotizing digital vasculitis, D - scratching lesions

removed, and the vascular Doppler examination detected a non-occlusive thrombosis of the veins of the upper arm. Administration of Clexane at a dose of 2000 Un/day resolved this process.

As can be seen in the case presented by us, not all the elements of AIHA are manifest. Its peculiarities include anemia with macro- and anisocytosis, hyperbilirubinemia, hypohaptglobinemia and increased liver enzymes (AST, ALT, LDH), with an absence of thrombocytopenia. The presence of AIHA is associated with a more severe course of the disease, onset at a young age and multisystemic involvement (pulmonary, joint, vascular, thrombotic events). Non-compliance worsens the symptoms, futher endangering the patient's life.

Discussion

SLE is a systemic autoimmune disease in which tolerance to one's own antigens is lost. Autoantibodies cause cell and tissue destruction through cytotoxicity reactions or the formation of immune complexes. It can affect any organ, the initial symptoms are often non-specific, and the correct diagnosis is difficult. Women of childbearing age are more frequently affected, only approximately 10% of patients are men [1].

Autoimmune hemolytic anemia may be the first manifestation of systemic lupus erythematosus and can occur several years before the diagnosis of SLE is established. For differential diagnosis, the authors recommend the determination of SLE (specific antinuclear antibody) marker tests in the presence of symptoms characteristic of the disease, using the 2019 EULAR/ACR diagnostic criteria. Among these criteria is autoimmune hemolytic anemia (which contributes 4 points in favor of the diagnosis of SLE) [8-10]. Hemolytic anemia in patients with SLE is rare and is possibly caused by anti-erythrocyte or microangiopathic antibodies [2-5].

Autoimmune hemolytic anemia in patients with SLE can be the cause of various complications and multi-organ damage. The risk of ischemia and thrombotic events should not be overlooked, as the products of hemolysis are toxic to several cell types and tissues. Excess iron and hemoglobin can also affect the kidneys, especially in those with lupus nephritis.

González LA *et al.* in a Latin American cohort study (2023) on a group of 1364 patients with lupus, mentions that severe AIHA is observed in about 3.6% of patients, particularly at the onset of the disease. Male sex and high activity of the disease are risk factors for its development. The authors hypothesize that hematological manifestations in a patient with SLE could predict the occurrence of AIHA in the near future [11].

Turk E. *et al.* (2024) in a large Nationwide Inpatient Sample (NIS), conclude that AIHA contributes to the increased mortality of patients with SLE due to acute myocardial infarction, cerebral stroke.They emphasize that AIHA must be promptly diagnosed in patients with lupus, considering it an unfavorable risk factor related to patient mortality [6].

At present, there is no broad consensus on the treatment of SLE patients. It depends on the clinical manifestations and activity of the disease, damage to life-threatening organs (lungs, heart, kidneys, nervous system). Most authors consider the use of corticosteroids in patients with AIHA to be appropriate, with a gradual reduction of the dose once a stable clinical effect is achieved, in order to reach an adequate maintenance dose. The role of immunosuppressors in the treatment of AIHA is not well defined. Some authors show the efficacy of Rituximab in the treatment of patients with SLE and AIHA [7].

Conclusions

The particularities of this clinical case confirm the severity of the evolution of systemic lupus erythematosus in association with autoimmune hemolytic anemia. Intensive treatment with corticosteroids along with erythrocyte mass transfusions for the correction of anemia at the onset of this syndrome, as well as in cases of relapse, is effective in most instances. Once the desired effect is achieved, the dose of CS should be gradually reduced until an effective maintenance dose is reached. In refractory cases, it is necessary to consider the administration of immunosuppressors, such as Rituximab. Further research is needed to evaluate predictive factors, as well as to discover new drugs effective in patient management.

Competing interests

None declared.

Authors' contribution

SP, SA devised the main conceptual ideas of the paper. VT, LD drafted the manuscript. LD, VT, VC collected the data from patient. All authors reviewed the manuscript and approved the final version.

Informed consent for publication

Obtained.

Funding

None.

References

1. Systemic lupus erythematosus. In: Groppa L, Popa S, Rotaru L, et al. Rheumatology and nephrology: Textbook. Chişinău: Lexon Prim; 2019. p. 98-120. ISBN 978-9975-3344-1-9.
2. Domiciano DS, Shinjo SK. Autoimmune hemolytic anemia in systemic lupus erythematosus: association with thrombocytopenia. Clin Rheumatol. 2010 Dec;29(12):1427-31. doi: 10.1007/s10067-010-1479-2.
3. Lu Y, Huang XM. Autoimmune hemolytic anemia as an initial presentation in children with systemic lupus erythematosus: two case reports. J Int Med Res. 2022 Aug;50(8):3000605221115390. doi: 10.1177/03000605221115390.
4. Kokori SI, Ioannidis JP, Voulgarelis M, Tzioufas AG, Moutsopoulos HM. Autoimmune hemolytic anemia in patients with systemic lupus erythematosus. Am J Med.

2000;108(3):198-204. https://doi.org/10.1016/S0002-9343(99)00413-1.
5. Gormezano NWS, Kern D, Pereira OL, et al. Autoimmune hemolytic anemia in systemic lupus erythematosus at diagnosis: differences between pediatric and adult patients. Lupus. 2017;26(4):426-430. doi: 10.1177/0961203316676379.
6. Turk E, Deenadayalan V, Obeidat K, Rodriguez P. Outcomes of autoimmune hemolytic anemia in patients with systemic lupus erythematosus: a nationwide inpatient sample study [abstract]. Arthritis Rheumatol. 2022;74(Suppl 9) [cited 2024 Apr 12]. Available from: https://acrabstracts.org/abstract/outcomes-of-autoimmune-hemolytic-anemia-in-patients-with-systemic-lupus-erythematosus-a-nationwide-inpatient-sample-study/
7. Pavo-Blanco M, Novella-Navarro M, Cáliz-Cáliz R, Ferrer-González MA. Rituximab in refractory autoimmune hemolytic anemia in systemic lupus erythematosus. Reumatol Clin. 2018;14(4):248-249. doi: 10.1016/j.reumae.2017.07.007.
8. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol. 2019 Sep;71(9):1400-1412. doi: 10.1002/art.40930.
9. Ameer M, Chaudhry H, Mushtaq J, et al. An overview of systemic lupus erythematosus (SLE) pathogenesis, classification, and management. Cureus. 2022;14(10):e30330. doi: 10.7759/cureus.30330.
10. Fanouriakis A, Tziolos N, Bertsias G, et al. Update in the diagnosis and management of systemic lupus erythematosus. Ann Rheum Dis. 2021;80:14-25. https://doi.org/10.1136/annrheumdis-2020-218272.
11. González LA, Alarcón GS, Harvey GB, et al. Predictors of severe hemolytic anemia and its impact on major outcomes in systemic lupus erythematosus: data from a multiethnic Latin American cohort. Lupus. 2023;32(5):658-667. doi: 10.1177/09612033231163745.

MJHS Moldovan Journal of Health Sciences
REVISTA DE ȘTIINȚE ALE SĂNĂTĂȚII DIN MOLDOVA

AUTHORS STATEMENT FOR PUBLICATION

Manuscript title:

Corresponding author's full name, e-mail address and tel.:

Please note that all contributing authors are obligated to sign *Authors statement for publication* form otherwise the manuscript will not be published.

Please fill in the table below according to following:

- list the authors in order in which they are stated in manuscript,
- each author should sign this document (on designated place in the table). By signing this form authors take full responsibility for all statements it contains.

No.	Author's full name	Author's signature	Date
1.			
2.			
3.			
4.			
5.			
6.			
7.			

AUTHORSHIP STATEMENT:

According to International Committee of Medical Journal Editors (ICMJE): "An author is considered to be someone who has made substantive intellectual contributions to a published study, takes responsibility and is accountable for what is published. ***All persons listed as authors in the manuscript must meet ALL of the following four criteria for authorship****" (available at: https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html)*

Please fill the table with the initials of each author (e.g., AB for Adrian Belîi) regarding authors contribution to specific component of research. The initials of each author must appear at least once in each of the four criteria below:

Criteria	Component of the research	Author's initials
1.	substantial contribution to conception and design of the work	
	substantial contribution to acquisition of data	
	substantial contribution to analysis and interpretation of data	
2.	drafting the article	
	critically reviewing the article for important intellectual content	
3.	final approval of the version to be published	
4.	taking responsibility and being accountable for all aspects of the work	

All persons who have made substantial contributions to the work (technical editing, writing assistance, general administrative support, financial and material support) **but do not meet all four criteria for authorship** are listed in *Acknowledgments* section and have given us their written permission to be named.

☐ Yes
☐ No
☐ We have not received substantial contributions from non-authors.

ORIGINALITY OF THE WORK STATEMENT:

Editorial board of the Moldovan Journal of Health Sciences strongly promotes research integrity and aims to prevent any type of scientific misconduct according to Committee on Publication Ethics (COPE) flowcharts. (available at: https://publicationethics.org/guidance/Flowcharts)

Please thick the box if the following statements are correct to the best of your knowledge:

☐ the manuscript is not previously published in the same or very similar form in other journal (previous publishing does not apply to abstract or poster presentations at a professional meeting)
☐ the manuscript is not currently under consideration in other journals (that does not apply for manuscripts that have been rejected by other journals)

RESEARCH ETHICS:

According to International Committee of Medical Journal Editors (ICMJE), the research project that involves human subjects must be conducted in accordance with the Helsinki Declaration and approved by the independent local, regional, or national review body or ethics committee.

Ethical approval

Reported research was approved by institutional/national ethics committee:

☐ Yes
☐ No
☐ Not applicable

If yes, please state the name of the approving ethics committee, the protocol number and the date of evaluation: _____

If no, please provide further details: _____

Informed consent

According to International Committee of Medical Journal Editors (ICMJE): „Patients have a right to privacy that should not be violated without informed consent. Identifying information, including names, initials, or hospital numbers, should not be published in written descriptions, photographs, or pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication." (available at: https://www.icmje.org/icmje-recommendations.pdf)

The appropriate informed consent was obtained from all research participants:

☐ Yes
☐ No
☐ Not applicable

If no, please explain: _____

CONFLICT OF INTEREST STATEMENT:

All authors have disclosed all relationships/activities/interests that are related to the content of this manuscript by completing the ICMJE Disclosure Form.

☐ Yes
☐ No

☐ Provide the statement: _____

OR

☐ Nothing to declare.

Date (dd/mm/yyyy) _____

Corresponding author's signature _____

Please, send this filled and scanned form to: editor.mjhs@usmf.md

MJHS Moldovan Journal of Health Sciences
REVISTA DE ȘTIINȚE ALE SĂNĂTĂȚII DIN MOLDOVA

[Revised May, 2023]

GUIDE FOR AUTHORS

Moldovan Journal of Health Sciences is an open access, double blind peer reviewed medical journal, published quarterly. The journal accepts for publication **original research papers**, **review articles**, **case reports**, **letters to the editor**, **In memoriam** and **book reviews**.

The *Moldovan Journal of Health Sciences* follows the ***Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals*** set out by the **International Committee of Medical Journal Editors (ICMJE)** and publication ethics practices suggested by the **Committee on Publication Ethics** (**COPE)**.

GENERAL GUIDELINES

• The manuscripts should be written in **English**;
• Each manuscript must be accompanied by *Authors statement for publication form* signed by all authors;
• The manuscript, including the title page, abstract and keywords, main text, references, figure captions, and tables should be typed in Times New Roman 12-point size font and 1,5 line spacing, with 2 cm margins all around and saved as one file;
• Each figure should be submitted also as separate file in one of the following formats: ".jpeg", ".tiff", ".eps", ".ppt", ".pptx". Scanning resolution should be at least 300 dpi;
• Written permission from the copyright owners must be obtained to reproduce the figure or other material published before, and the original source should be cited in the figure caption or table footnote;
• Use only standard abbreviations and be sure to explain all of them the first time they are used in the text;
• Use Systeme International (SI) measurements;
• Use generic names for drugs, devices and equipment. When brand-names are mentioned in the manuscript, the complete name and location of the manufacturer must be supplied;
• References should be numbered in the order in which they appear in the text. At the end of the article the full list of references should follow the Vancouver style.

MANUSCRIPT SUBMISSION

Manuscripts must be submitted in electronic version to the e-mail: editor.mjhs@usmf.md.
A submitted manuscript should be accompanied by *Authors statement for publication form* signed by all authors (a template is provided by editor).
The corresponding author must ensure that all authors have disclosed all relationships/activities/interests that are related to the content of the manuscript by completing the ICMJE Disclosure Form. The summarized statement regarding Conflict of interest must be provided in *Authors statement for publication form* and in the Title page.
The corresponding author holds full responsibility for the submission and correspondence with the editor during the peer-review and publication process. All correspondence, including notification of the Editor's decision and requests for revisions, will be made by e-mail.

MANUSCRIPT ORGANIZATION

Manuscripts should be organized as follows. Instructions for each element appear below the list.

TITLE PAGE	> Article title / Short title > Authors information (full names, academic titles, ORCIDs, affiliations) > Corresponding author's contact details > Authors' contributions > Acknowledgments and funding > Conflict of interest > Article highlights > Word count (for Main text and Abstract)
ABSTRACT AND KEYWORDS	> Structured abstract > Keywords > Clinical trial registration information
MAIN TEXT AND REFERENCES	> Introduction > Materials and methods > Results > Discussion > Conclusions > References
TABLES AND FIGURES	> Tables are inserted immediately after the first paragraph in which they are cited > Figure captions are inserted immediately after the first paragraph in which the figure is cited. Figures should be submitted also as separate files.

TITLE PAGE. *Moldovan Journal of Health Sciences* adheres to a **double-blinded peer-review policy**. The title page must be separated from the main text of the article. **The main text of the article must not include information about the authors**.
> ***Article title*** should be concise, relevant to the content of the manuscript, and reflect the study design (up to 25 words). Abbreviations are not allowed. *Short title* (to be used as a running title) can be a maximum of 8 words.
> ***Author information***. Authors should be listed in order of their contribution to the paper. Members of the research group who do not meet the formal criteria of the authorship, but have had some contribution to the paper, may be mentioned in the "Acknowledgements and funding" section.
Each author's full name, academic titles, the ORCID iD and the affiliation (the full name of department, institution, city and country) should be provided.

Example:

Lilian Șaptefrați, MD, PhD, Professor, https://orcid.org/0000-0003-2779-718X, Department of Histology, Cytology And Embryology, *Nicolae Testemitanu* State University of Medicine and Pharmacy, Chisinau, Moldova.

> *Corresponding author's contact details*. Mark the corresponding author with an asterisk and provide in a separate paragraph full contact information, including full name, academic degrees, address (institutional affiliation, city, and country), e-mail address and telephone number.

> *Authors' contributions*. The contributions of all authors must be described, please follow the suggested format: *"HW conceived the study and participated in study design and helped drafting the manuscript. MG performed the processing of specimens and tissue culture methods and drafted the manuscript. TK performed immunofluorescence tests. PN participated in staining and flow-cytometry. AR participated in the study design and performed the statistical analysis. All the authors reviewed the work critically and approved the final version of the manuscript".*

> *Acknowledgements and funding*. People who contributed to the study design, data collection, analysis and interpretation, manuscript preparation and editing, offered general or technical support, contributed with essential materials to the study, but do not meet ICMJE authorship criteria will not be considered as authors, but their contribution will be mentioned in section "Acknowledgements and funding". Also in this section must be specified the sources of work funding. Mention of persons or institutions who have contributed to the work and manuscript can be made only after obtaining permission from each of them.

> A ***Conflict of interest*** statement should summarize all aspects of any conflicts of interest included on the ICMJE form. If there is no conflict of interest, this should also be explicitly stated as „none declared".

> *Article highlights* states the main ideas of the paper: What is not yet known on the issue addressed in the submitted manuscript (described in 1-3 sentences); The research hypothesis (described in 1-2 sentences); The novelty added by manuscript to the already published scientific literature (limited to 1-3 sentences).

> *Word count* for Main body text and Abstract should be provided. The volume of the manuscript text should not exceed 6000 words, and Abstract – 350 words.

ABSTRACT AND KEYWORDS

The *Abstract* should provide the context or background for the study and should state the study's purpose, basic procedures, significant results, main findings, and principal conclusions. The summary text should not exceed 350 words organized according to the following headings: *Introduction, Materials and methods, Results, Conclusions*. These headings may be adapted in the case of theoretical papers and reviews. The abstract should not contain any undefined abbreviations or citations.

Keywords. Immediately after the abstract, provide 4-6 keywords that are representative for the contents of the article. For the selection of keywords, refer to Medical Subject Headings (MeSH) in PubMed (https://www.ncbi.nlm.nih.gov/mesh/).

If the article reported the results of a clinical trial, please indicate at the end of the abstract the Name of trial database where registered, unique *clinical trial registration number* and date registered.

MAIN TEXT AND REFERENCES

Original research articles are usually organized according to the IMRAD format: *Introduction, Methods, Results, Discussion,* and *Conclusions.* Other types of articles, such as meta-analyses, case reports, narrative reviews, and editorials may have less structured or unstructured formats.

> Introduction

The Introduction section should: provide a context or background for the study that would allow readers outside the field to understand the purpose and significance of the study; define the problem addressed and explain why it is important; include a brief review of recent literature in the field; mention any relevant controversies or disagreements existing in the field; formulate research hypothesis and present the main and secondary assessed outcomes; conclude with the research' propose and a short comment whether the purpose has been achieved. The Introduction should not contain either results or conclusions.

> Materials and methods

The *Materials and methods* section should present in sufficient details all carried out procedures. Here should be described protocols and supporting information on the used methods. It will include study design, subjects' recruitment procedure, clear description of all interventions and comparisons and applied statistics (*Selection and Description of Participants, Technical Information, Statistics*). The Methods section should be sufficiently detailed such that others with access to the data would be able to reproduce the results. For studies on humans or animals a statement about ethical approval and informed consent of study subjects should be include. Please specify date and number of Ethics Committee (EC) decision, chair of the EC as well as institution within EC is organized.

> Results

Authors must present results logically using text, tables, and figures, giving the main or most important findings first. Results should be explained (not justified or compared in this section) and include fundamental statements related to hypothesis behind the study.

> Discussion

The data should be interpreted concisely without repeating materials already presented in the *Results* section. Describe the impact, relevance and significance of the obtained results for the field. The results are compared with those from previous publications and

draw potential future research directions. Discussions should include important interpretations of the findings and results compared with previous studies. In addition, study limitations and potential bias should be mentioned.

> Conclusions

This section should conclude laconically entire study, and highlight the added-value brought on the studied issue. The conclusions should not provide new information or double (repeat) those presented in the *Results* section.

> References

Moldovan Journal of Health Sciences uses the reference style outlined by the International Committee of Medical Journal Editors (www.icmje.org), also known as "Vancouver style". Example formats are listed below.

In-text reference citations should be numbered consecutively, identified by Arabic numerals in square brackets [ ]. References should be listed at the end of the manuscript and numbered in the order in which they are first mentioned in the text. Every reference cited in the text is also present in the reference list (and vice versa). Journals titles should be abbreviated according to the Index Medicus.

It may be cited only articles or abstracts that have been published and are available through public servers. Personal communications, manuscripts in preparation, and other unpublished data should not be included in the reference list, but may be mentioned in parentheses in the text as "unpublished data" or "unpublished observations", indicating the involved researchers. It is of manuscript authors' responsibility to obtain the permission to refer to unpublished data.

The references in the Cyrillic, Greek, Arabic scripts should be transliterated into Latin script using the ALA-LC Romanization Tables.

Non-English titles must be followed by the English translation in square brackets.

All electronic references should include active and available URLs and the access date.

Examples of references

Journal article

Belîi A, Cobâleţchi S, Casian V, Belîi N, Severin G, Chesov I, Bubulici E. Les aspects pharmacoéconomiques dans la gestion de la douleur périopératoire [Pharmaco-economic aspects of perioperative pain management]. Ann Fr Anesth Reanim. 2012;31(1):60-6. French. doi: 10.1016/j.annfar.2011.09.008.

Book

Razin MP, Minaev SV, Turabov IA. Detskaia khirurgiia [Pediatric surgery]. 2nd ed. Moscow: Geotar-Media; 2020. 696 p. Russian.

Chapter in a book

Steiber AL, Chazot C, Kopple JD. Vitamin and trace element needs in chronic kidney disease. In: Burrowes J, Kovesdy C, Byham-Gray L, editors. Nutrition in kidney disease. 3rd ed. Cham: Humana Press; 2020. p. 607-623.

Conference paper

Ojovan V. Medical rehabilitation of children with type 1 diabetes: medical bioethical and psychosocial aspects. In: MedEspera: 9th International Medical Congress for Students and Young Doctors, 12-14 May 2022, Chisinau, Republic of Moldova: Abstract book. Chișinău; 2022. p. 77.

Website reference

World Health Organization (WHO). Therapeutics for Ebola virus disease [Internet]. Geneva: WHO; 2022 [cited 2022 Sep 5]. Available from: https://www.who.int/publications/i/item/9789240055742

TABLES AND FIGURES

Tables should be numbered consecutively with Arabic numerals, and be cited in text. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Tables must be submited as editable text and not as images. Each table should be completely informative in itself, and the data presented in it do not duplicate the results described elsewhere in the article.

The label "Table 1" and a short descriptive title should be provided above the table. Legends, notes, and any abbreviations used in the table should be explained below the table in a footnote. Applied statistical tests and the type of presented data should be also mentioned. Please follow the example:

Table 1. Intra-anesthetic and immediately post-extubation adverse events

	Experimental Cohort (n=100)	Control Cohort (n=100)	p
Dysrhythmia	6.0%	30%	0.49
Hemodynamic instability	7.0%	1.0%	0.034
Prolonged awakening*	11.0%	4.0%	0.19
PONV post-intubation	8.0%	27.0%	0.007
Strong pain on awakening	17.0%	19.0%	1.0

Note: *Unusually slow awaking, after that cerebral concentration of the anesthetic reach the under hypnotic level.
Used statistical analysis: Fisher's exact test.

Figures (photographs or radiographs, drawings, graphs, bar charts, flow charts, and pathways) should be submitted in a suitable format for print publication. Figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints. Figures' quality should assure the visibility of details. The following file formats are accepted: ".jpeg", ".tiff", ".eps" (preferred format for diagrams), ".ppt", ".pptx" (figures should be of the size of a single slide), with a resolution of at least 300 dpi.
Figures will be included in the main manuscript, and also submitted as separate files. The file title should include the figure number and an identifiable short title.
Figures should be numbered consecutively according to the order in which they have been cited in the text. Write the label **Fig. 1** and a short descriptive title under the figure. Figure's legend should describe briefly the data shown. Figure's description should not repeat the description in the text of the manuscript. When used symbols, arrows, numbers or letters to describe parts of the figure, explain clearly each one of them in the legend. Explain the internal scale and identify the staining method of the photomicrographs.
If a table or figure has been published before, the authors must obtain written permission to reproduce the material in both print and electronic formats from the copyright owner and submit it with the manuscript. The original source should be cited in the figure caption or table footnote. For example, "Reprinted with permission from Calfee DR, Wispelwey B. Brain abscess. Semin Neurol. 2000;20:357." ("Data from . . ." or "Adapted from . . ." may also be used, as appropriate).

ETHICAL ISSUES & RESEARCH REPORTING GUIDELINES

Definition of Authorship

As stated in the guidelines of the International Committee of Medical Journal Editors (ICJME), all persons listed as authors in the manuscript must meet **ALL of the following criteria** for authorship:

1. substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. drafting the work or reviewing it critically for important intellectual content; AND
3. final approval of the version to be published; AND
4. agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements and funding

All contributors, members of the research group who do not meet the criteria for authorship as defined above should be listed in an acknowledgments section. All financial and material support for the conduct of the research and/or preparation of the article from internal or external agencies, including commercial companies, should be clearly and completely identified.

AI in scientific writing

Authors must disclose the use of Artificial Intelligence or (AI)-assisted technologies in the writing process by adding a statement at the end of their manuscript in the core manuscript file, before the References list. The statement should be placed in a new section entitled *„Declaration of Generative AI and AI-assisted technologies in the writing process"*. For example, *„The author(s) used [AI service/ tool name] in order to [reason]. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication"*. If there is nothing to disclose, there is no need to add a statement. AI and AI-assisted technologies should not be listed as an author or co-author, or be cited as an author.

Conflict of interest disclosure

All authors must disclose any financial, personal or professional relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest are financial support from, or connections to, pharmaceutical companies, political pressure from interest groups, and academically related issues. If there is no conflict of interest, this should also be explicitly stated as none declared.

Copyright, open access, and permission to reuse

Duplicate publication

Material submitted to *Moldovan Journal of Health Sciences* must be original. Submitted manuscript must not have been previously published elsewhere (except as an abstract or a preliminary report), and must not be under consideration by another journal. Related manuscripts under consideration or in press elsewhere must be declared by authors at the time of submission in the cover letter. Dual publication or redundant publication is unethical. For more details please refer to the COPE guidelines on http://www.publicationethics.org.

Plagiarism

Authors should submit only original work that is not plagiarized, and has not been published or being considered elsewhere. Appropriate softwares may be used by the editorial office to check for similarities of submitted manuscripts with existing literature. If the submitted manuscript violates copyright policies; it can be suspended or dismissed, regardless of the stage of the publishing process.

Copyright license

Reproduction of previously published contents

If the submitted manuscript used or reproduced information/material previously published or copyrighted is the responsibility of the corresponding author to obtain a written permission from the copyright owner and properly cite the original source. In order to maintain transparency, it is recommended to submit the permission, as a copy, along with the manuscript.

Self-Archiving

Authors are encouraged to submit the final version of the accepted, peer-reviewed manuscript to their funding body's archive for public release immediately upon publication and to deposit the final version on their institution's repository. Authors should cite the publication reference and DOI number on any deposited version, and provide a link from it to the published article on the journal's website https://cercetare.usmf.md/ro/revista-mjhs/Arhiva-MJHS.

Research reporting guidelines

Moldovan Journal of Health Sciences adheres to the ethical standards described by the Committee on Publication Ethics (COPE) and the International Committee of Medical Journal Editors (ICMJE). Authors are expected to adhere to these standards. Manuscripts submitted to the journal should conform to the **ICMJE Recommendations** and the following guidelines as appropriate:

- STROBE guidelines for observational studies;
- CONSORT guidelines for clinical trials;
- PRISMA guidelines for systematic reviews and meta-analyses;
- STARD guidelines for diagnostic studies;
- CARE statement for clinical cases;
- SAGER guidelines for reporting of sex and gender information in study design, data analyses, results and interpretation of findings.

Ethical approval and Informed consent

If the research project involves human subjects or animals, authors must state in the manuscript that the study was approved by the Ethics Committee of the institution within which the research work was undertaken (the protocol number and the date of evaluation should be provided). Patients' identifying information should not be published in written descriptions and photographs, unless the information is essential for scientific purposes and the patient gave written informed consent for publication. The authors must include a statement confirming that informed consent was obtained from all identifiable study participants (or that no informed consent was required).

Clinical trial registration

The *Moldovan Journal of Health Sciences* follows the trials registration policy of the ICMJE (www.icmje.org) and considers only trials that have been appropriately registered in a public registry prior to submission. Any research that deals with a clinical trial should be registered with a primary national clinical trial registration site, or other primary national registry sites accredited by the World Health Organization (https://www.who.int/ictrp/network/primary/en/). The clinical trial registration number should be provided at the end of the Abstract.

Data access and responsibility

The corresponding author should indicate that he or she had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

FOR MORE DETAILS, PLEASE CONTACT:

Editor-in-chief: **Serghei Popa**, PhD, university professor
tel: +373 60907799
e-mail: editor.mjhs@usmf.md

SPONDI-LIZ

cremă

Medicament combinat pentru tratament local cu acțiune antiinflamatoare, antitrombotică și analgezică.

STOP durerilor

- articulare
- musculare
- de spate
- post-traumatice

Acesta este un medicament. Citiți cu atenție prospectul.
Dacă apar manifestări neplăcute, adresați-vă medicului sau farmacistului.
Numărul de înregistrare 25299 din 07.02.2019

MYDOCALM® LONG

tolperisonă 450 mg, miorelaxant original

ÎNCREDERE ÎN ORICE MIȘCARE

Denumirea comercială a medicamentului: Mydocalm Long 450 mg comprimat cu eliberare prelungită. **Compoziția calitativă și cantitativă:** Fiecare comprimat cu eliberare prelungită conține 450 mg clorhidrat de tolperison. **Indicații terapeutice:** Tratamentul simptomatic al spasticității după accident vascular cerebral la adulți. **Doze și mod de administrare**: Doze: Doza orală zilnică recomandată este de 450 mg (un comprimat) o dată pe zi. *Pacienți cu insuficiență renală*: pacienții cu insuficiență renală trebuie să fie supuși monitorizării regulate a funcției renale. Nu se recomandă administrarea Mydocalm Long pacienților cu insuficiență renală moderată. Alte forme de dozare sau concentrații ale tolperisonului pot satisface mai bine nevoile acestui grup. Administrarea tolperisonului nu este recomandată la pacienții cu insuficiență renală severă. *Pacienți cu insuficiență hepatică:* pacienții cu insuficiență hepatică trebuie să fie supuși monitorizării regulate a funcției hepatice. Alte forme de dozare sau concentrații ale tolperisonului pot satisface mai bine nevoile acestui grup. Administrarea tolperisonului nu este recomandată la pacienții cu insuficiență hepatică severă. *Pediatrie:* Siguranța și eficacitatea tolperisonului la copii și adolescenți cu vârsta sub 18 ani nu au fost stabilite. Mod de administrare: Administrare orală. Medicamentul trebuie administrat după masă, fără a mesteca sau zdrobi comprimatul, cu un pahar cu apă. Aportul alimentar insuficient poate scădea biodisponibilitatea tolperisonului.**Contraindicații:** Hipersensibilitate la substanța activă (tolperison) sau la substanța înrudită chimic eperizonă, sau la oricare dintre excipienți. Miastenia gravis. Sarcina si alaptarea. **Atenționări și precauții speciale pentru utilizare:** Reacții de hipersensibilitate: Cele mai frecvente reacții adverse legate de tolperison, raportate după punerea pe piață, au fost reacțiile de hipersensibilitate. Reacțiile de hipersensibilitate au variat de la reacții cutanate ușoare la reacții sistemice severe, inclusiv șoc anafilactic. Simptomele pot include eritem, erupții cutanate, urticarie, prurit, angioedem, tahicardie, hipotensiune arterială sau dispnee. Pacienții cu hipersensibilitate la alte medicamente sau cu antecedente de alergie pot pot fi expuși la un risc mai mare. În caz de hipersensibilitate cunoscută la lidocaină se impune o prudență crescută în timpul administrării de tolperison, din cauza posibilelor reacții alergice încrucișate. Pacienții trebuie sfătuiți să rămână vigilenți la apariția simptomelor de hipersensibilitate, să întrerupă imediat administrarea tolperisonului, și să solicite imediat asistență medicală în cazul în care apar astfel de simptome. Tolperison nu mai trebuie să fie administrat încă o dată după un episod de hipersensibilitate la tolperison. **Reacții adverse:** Rezumatul profilului de siguranță: Clasele de organe ale sistemului cel mai frecvent vizate sunt: Tulburări ale pielii și țesutului subcutanat, Tulburări generale, Tulburări neurologice și Tulburări gastro-intestinale. Din datele după punerea pe piață, reacțiile adverse de hipersensibilitate asociate cu administrarea tolperisonului reprezintă aproximativ 50-60% din cazurile raportate. Majoritatea cazurilor reprezintă afecțiuni ușoare și autolimitate. Reacții de hipersensibilitate care pun viața în pericol sunt raportate foarte rar. Mai puțin frecvente (de la > 1/1 000 la < 1/100): anorexie, insomnie, tulburări de somn, cefalee, amețeală, somnolență, hipotensiune arterială, disconfort abdominal, diaree, gură uscată, dispepsie, greață, slăbiciune musculară, mialgie, dureri la nivelul extremităților, astenie, indispoziție, oboseală. **Data și numărul autorizației de punere pe piață:** Nr.29323 din 02.10.2023. **Statutul legal:** cu prescripție medicală. **Data revizuirii textului:** Octombrie 2023. *Acest material publicitar este destinat persoanelor calificate să prescrie, să distribuie și/sau să elibereze medicamente. Pentru informații complete vă rugăm să consultați rezumatul caracteristicilor produsului. Informații detaliate privind acest medicament sunt disponibile pe site-ul Agenției Medicamentului și Dispozitivelor Medicale (AMDM) http://nomenclator.amdm.gov.md/*

Pentru mesaje de siguranță și informații medicale: e-mail: drugsafety.md@gedeonrichter.com sau tel.: (022) 20-21-90.

Societatea pe Acțiuni de Tip Deschis Fabrica de Produse Chimice "GEDEON RICHTER" Budapesta,
Sucursala Chișinău, str. A. Puşkin, 47/1, bl. A, of.1; Tel.: (022) 22-14-49; (022) 22-26-71; www.gedeonrichter.md

GEDEON RICHTER