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KNOWLEDGE AND ATTITUDES TOWARDS EMERGENCY CONTRACEPTION AMONG ADOLESCENTS

INFORMISANOST I STAVOVI ADOLESCENATA U VEZI SA PRIMENOM URGENTNE KONTRACEPCIJE

Nikola SAVIĆ[1, 2], Andrea MIRKOVIĆ[3] and Slobodanka BOGDANOVIĆ VASIĆ[4]

Summary

Introduction. Emergency or postcoital contraception is a method of contraception that is used within 72 hours after unprotected intercourse. It is very important that adolescents consider emergency contraception with awareness. It is not a regular method of contraception. The aim of this study was to examine the knowledge and attitudes of adolescents towards the use of emergency contraception. **Material and Methods.** The research was a cross-sectional study that used a specially designed questionnaire for adolescents intended to assess their knowledge about emergency contraception methods. The study included an intentional sample of 108 students attending the Medical High School "Dr. Miša Pantić" in Valjevo. Participation in the study was voluntary and anonymous. **Results.** The largest number of students was informed about the indications for emergency contraception (80%, $\chi^2 = 0.004$); the respondents agreed that emergency contraception is not a regular method of contraception and should be used in cases of sexual abuse ($\chi^2 = 0.019$). Most of the respondents believe that they need additional education (N = 95, $\chi^2 = 0.032$) regarding emergency contraception methods. **Conclusion.** The analysis of the results showed that the adolescents who participated in the study need additional education about the methods of emergency contraception. It is necessary to improve the strategies of health education of adolescents on this topic.

Key words: Adolescent; Contraception; Contraception, Postcoital; Health Knowledge, Attitudes, Practice; Sexual Behavior; Reproductive Health; Surveys and Questionnaires

Sažetak

Uvod. Hitna ili postkoitalna kontracepcija je metoda kontracepcije koja se koristi do 72 sata nakon nezaštićenog odnosa. Veoma je važno da adolescenti odgovorno pristupe upotrebi hitne kontracepcije. To nije redovna metoda kontracepcije. Cilj rada bilo je ispitivanje informisanosti i stavova adolescenata u vezi sa upotrebom hitne kontracepcije. **Materijal i metode.** Istraživanje je sprovedeno u obliku studije preseka. Kao instrument istraživanja, napravljen je upitnik za adolescente koji procenjuje nivo njihovog informisanja o metodama hitne kontracepcije. Studija je obuhvatila uzorak od 108 učenika; uzorak je namerni; studija je sprovedena u Medicinskoj školi „Dr Miša Pantić" u Valjevu. Učešće u istraživanju bilo je dobrovoljno i anonimno. **Rezultati.** Najveći broj učenika u posmatranom uzorku informisan je o indikacijama za upotrebu hitne kontracepcije (80%, $\chi^2 = 0{,}004$), ispitanici su se složili da hitna kontracepcija nije redovna metoda kontracepcije i da je treba koristiti u slučajevima seksualnog nasilja ($\chi^2 = 0{,}019$). Najveći broj ispitanika smatra da im je potrebno dodatno obrazovanje (N = 95, $\chi^2 = 0{,}032$) u vezi sa metodama hitne kontracepcije. **Zaključak.** Analiza rezultata sprovedenog istraživanja ukazuje na potrebu dodatne edukacije adolescenata o metodama kontracepcije u vanrednim situacijama. Neophodno je intenzivirati strategije zdravstveno-vaspitnog rada sa adolescentima na ovu temu.

Ključne reči: adolescent; kontracepcija; postkoitalna kontracepcija; znanje o zdravlju, stavovi, praksa; seksualno ponašanje; reproduktivno zdravlje; ankete i upitnici

Introduction

Emergency or postcoital contraception is a method of contraception that can be used up to 72 hours after unprotected intercourse. Emergency contraceptive methods include the use of progestin-only pills, combined oral contraceptive pills, mifepristone and intrauterine contraceptive devices. It is very important to educate adolescents that these are not regular methods of contraception [1].

Progestin-only pills are used within 72 hours; they are highly effective and have very rare and minor side effects. The use of combined hormonal oral contraceptive pills in emergency contraception is carried out according to the Yuzpe regimen. This method consists of taking ethinyl estradiol and levonorgestrel. If taken hin 24 hours, it has high efficiency and a risk of pregnancy of only 2% [1, 2].

Mifepristone is used in many countries around the world, in China, Israel and throughout Europe and the

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United States. In the follicular phase, it inhibits follicle development, ovulation, and the endometrial secretory transformation [3].

Intrauterine devices that contain metals (copper, silver, gold) or progestogen are very effective in emergency contraception. This method can be used no later than 5 days after unprotected sexual intercourse. After emergency insertion, they can remain in the uterus and thus become a method of long-term contraception. The advantages of this method are numerous: side effects that may occur with oral emergency contraception are avoided; they can be used as long-term contraception, and may be a method of emergency contraception for breastfeeding women [1, 4, 5].

Since 2009, ulipristal acetate, a selective progesterone receptor modulator, has also been in use, which can be used up to 5 days after unprotected or risky sexual intercourse [1, 6].

It is especially important to use emergency contraception after sexual assaults and in rape victims [7, 8]. Emergency contraception can effectively prevent unwanted pregnancies, yet its wider use has not yet led to a significant decline in the abortion rate at the population level [9]. Most women, in a large number of countries, get emergency contraception at pharmacies without a prescription, but they should be advised to visit a gynecologist and start using regular contraception. Emergency contraception has a number of advantages over intentional termination of pregnancy. The United Nations Commission on Life-Saving Commodities for Women and Children listed emergency contraception as one of its 13 "overlooked life-saving commodities" that could save lives of 6 million women and children (United Nations International Children's Emergency Fund, 2012) [10, 11]. Young adolescent girls often decide to use oral emergency contraception and it is extremely important to provide health education to this population at appropriate opportunities [12]. Emergency contraception plays a significant role in the prevention of adolescent pregnancies and prevention of abortion complications [13]. Intrauterine devices are the most effective method of emergency contraception but they are recommended to older women who have already fulfilled their reproductive role and need long-term contraception, which is effective for years [14, 15].

The aim of the research was to examine the knowledge and attitudes of adolescents on the use of emergency contraception.

Material and Methods

The research was a cross-sectional study using a specially designed questionnaire for adolescents intended to assess their knowledge about emergency contraception methods. The research instrument consisted of two parts: the first part examined the sociodemographic characteristics of the respondents and the second part was a five-point Likert scale questionnaire where students expressed their level of agreement with the statements discussed. The study included a sample of 108 students attending the Medical High School "Dr. Miša Pantić" in Valjevo, in the period April - May 2021. The study sample was intentional, including students of health and social care. Participation in the study was voluntary and anonymous. The research was approved by the competent authorities of the institution (Record number of consent for conducting a scientific study: 152/1).

The inclusion criteria were personal consent to participate in the survey and giving answers to all the questions in the questionnaire. The exclusion criteria were no wish to participate in the research and the desire of adolescents not to give answers to all the questions in the questionnaire. Prior to the start of research, the respondents were informed about the study itself orally and in writing. Students were given instructions on how to fill out the questionnaire. The questionnaires were distributed and collected personally by the researchers.

Statistical data processing included methods of descriptive and inferential statistics using the χ^2 test and Fisher's exact test. The data were analyzed by the Statistical package for the social sciences for Windows. The obtained results are presented in tables and graphs.

Results

The most important sociodemographic characteristics of the respondents in the observed sample are shown in **Table 1**. Knowledge and attitudes about emegency contraception among adolescents are shown in **Table 2.**

The largest number of respondents answered that they need additional education (N = 95, $\chi^2 = 0.032$) on the methods of emergency contraception. There is a statistically significant difference in the answers of the respondents and a positive attitude towards health education of adolescents **(Graph 1)**.

Table 1. Sociodemographic characteristics of the respondents
Tabela 1*. Sociodemografska struktura ispitanika*

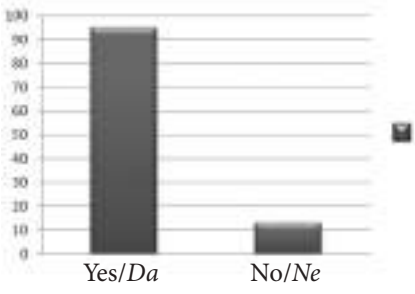
Variables/*Varijable*	No/*Broj*	%	P*
Gender/*Pol*			
Female/*Ženski*	88	81%	0.345
Male/*Muški*	20	19%	
Age/*Starosno doba*			
The third year of secondary school/*Treći razred srednje škole*	47	44%	0.344
The fourth year of secondary school/*Četvrti razred srednje škole*	61	56%	

*Fisher's exact test/*Fišerov egzaktni test*

Table 2. Adolescents' knowledge and attitudes about emergency contraception
Tabela 2*. Informisanost i stavovi adolescenata o urgentnoj kontracepciji*

Variables *Varijable*	Absolutely disagree/*Apsolutno se ne slažem*	Disagree *Ne slažem se*	Neutral *Niti se slažem, niti se ne slažem*	Agree *Slažem se*	Absolutely agree *Apsolutno se slažem*	Total N *Ukupan broj*	P*
Emergency contraception is used in case of unprotected intercourse, condom breaking or slipping *Urgentna kontracepcija se koristi u slučaju nezaštićenog polnog odnosa, pucanja ili spadanja kondoma*							
Female/*Ženski*	3	6	8	26	45	88	0.004
Male/*Muški*	1	0	4	6	9	20	
Emergency contraception is most often used up to 72 hours after unprotected sexual intercourse *Urgentna kontracepcija se najčešće primenjuje do 72 časa nakon nezaštićenog polnog odnosa*							
Female/*Ženski*	2	11	17	23	35	88	0.162
Male/*Muški*	1	2	5	5	7	20	
Emergency contraception can be used as a regular method of contraception *Urgentna kontracepcija se može koristiti kao redovna metoda kontracepcije*							
Female/*Ženski*	3	4	8	6	67	88	0.230
Male/*Muški*	0	1	1	4	14	20	
Emergency contraception should be used in cases of rape, in victims of sexual assault *Urgentnu kontracepciju bi trebalo primeniti u slučajevima silovanja, kod žrtava seksualnog nasil*ja							
Female/*Ženski*	5	3	6	34	40	88	0.019
Male/*Muški*	1	1	2	6	10	20	
Emergency contraception involves the use of progestin-only pills *Urgentna kontracepcija obuhvata primenu pilula koje sadrže samo progestin*							
Female/*Ženski*	10	9	11	16	42	88	0.791
Male/*Muški*	2	3	2	5	8	20	
Emergency contraception includes combined hormonal contraceptive pills for oral use *Urgentna kontracepcija obuhvata kombinovane hormonske kontraceptivne tablete za oralnu primenu*							
Female/*Ženski*	7	12	10	24	35	88	0.004
Male/*Muški*	1	1	2	3	13	20	
Emergency contraception includes contraceptive methods such as intrauterine devices *Urgentna kontracepcepcija obuhvata kontraceptivne metode kao što je intrauterini uložak*							
Female/*Ženski*	15	14	17	13	29	88	0.822
Male/*Muški*	2	3	5	3	7	20	
Emergency contraception includes barrier methods (male and female condom, diaphragm) *Urgentna kontracepcija obuhvata barijerne metode (muški i ženski kondom, dijafragmu)*							
Female/*Ženski*	44	13	19	9	3	88	0.335
Male/*Muški*	8	5	4	2	1	20	
Oral use of emergency contraception may cause side effects such as nausea, vomiting, bleeding, menstrual disorders *Oralna primena urgentne kontracepcije može dati neželjene efekte kao što su muka, povraćanje, krvarenje, poremećaj menstrualnog ciklusa*							
Female/*Ženski*	0	3	9	28	48	88	0.006
Male/*Muški*	1	1	4	5	9	20	
Emergency oral hormonal contraception can only be obtained with a doctor's prescription *Urgentna oralna hormonska kontracepcija se može dobiti samo uz lekarski recept*							
Female/*Ženski*	5	3	8	35	37	88	0.017
Male/*Muški*	1	1	3	6	9	20	
Emergency contraception is safer than abortion/*Urgentna kontracepcija je bezbednija od abortusa*							
Female/*Ženski*	2	7	9	29	41	88	0.029
Male/*Muški*	0	4	1	4	11	20	
Emergency contraception is used only in special cases, preference should be given to methods of regular contraception/*Urgentna kontracepcija se koristi samo u posebnim slučajevima, prednost treba dati metodama redovne kontracepcije*							
Female/*Ženski*	5	10	12	16	45	88	0.584
Male/*Muški*	1	2	3	6	8	20	
It is obligatory to consult a gynecologist about the use of emergency contraception *O primeni urgentne kontracepcije obavezno se treba konsultovati sa lakarom ginekologom*							
Female/*Ženski*	8	7	16	19	38	88	0.256
Male/*Muški*	2	3	4	5	6	20	

*χ^2test/χ^2 *test*



Graph 1. Distribution of respondents expressing the need for additional education on emergency contraception
Grafikon 1*. Distribucija ispitanika prema iskazanoj potrebi o dodatnoj edukaciji u vezi sa urgentnom kontracepcijom*

Discussion

The largest number of students in the observed sample was informed about the indications for emergency contraception (80%); the answers to this question showed that there is a statistically significant difference in the degree of agreement among the respondents ($\chi^2 = 0.004$) and similar results were obtained in a study conducted among adolescents attending the Academy of Vocational Studies in Šabac [16]. A majority of the respondents agreed that emergency contraception is not a regular method of contraception and it should be used in cases of sexual assault and rape ($\chi^2 = 0.019$). More than half of the female respondents (58%) are better informed about emergency contraceptive methods that contain progestin. The female respondents were better informed on this topic just like in other scientific studies, such as a research conducted at the University of Fort Hare [17]. More than half of the respondents (52%) were not informed that intrauterine devices can also be a method of emergency contraception. Most respondents were informed that emergency contraception is not a barrier method of contraception, such as condoms, diaphragms and cervical caps. There was a statistically significant difference in the responses of the subjects regarding the side effects of oral emergency contraception ($\chi^2 = 0.006$); however, a large number of subjects were familiar with the potential side effects. This issue has been highlighted in numerous scientific papers with an emphasis on the fact that adolescents should be acquainted with the advantages and disadvantages of emergency contraception [18]. There is a statistically significant difference in the answers of the respondents when it comes to the procurement of emergency contraception; more than half of the respondents were not informed that oral emergency contraception can be obtained without a prescription in pharmacies ($\chi^2 = 0.017$). This is in accordance with numerous studies conducted in this domain [16]. Numerous papers have studied the availability of emergency contraception to adolescents; a research of the Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana, in their 2017 study reported that in a sample of 979 pharmacies, emergency contraception was available to adolescents in 83% [19]. In countries where emergency contraception is unavailable in pharmacies there is a high abortion rate during adolescence [20]. There is a statistically significant difference in the answers concerning the claim that urgent contraception is safer than abortion, i.e. intentional termination of pregnancy ($\chi^2 = 0.029$). Most respondents believe that preference should be given to regular contraceptive methods and that a gynecologist should be consulted regarding the application of emergency contraception methods. This is in line with the results of other studies, which also confirm the awareness of adolescents about the importance of consulting doctors and health professionals regarding the use of emergency contraception. The results coincide with the results of a study conducted in adolescents from Berlin by the Institute of Social Medicine in Berlin [21]. Numerous studies indicate that young people accept the authority of health workers when it comes to emergency contraception [22]. Most respondents agree that adolescent need additional health interventions and education on the topic of emergency contraception ($N = 95$, $\chi^2 = 0.032$). This is also in accordance with other studies with a similar sample structure [23–25].

Conclusion

In the observed sample, female respondents were more informed about the methods of emergency contraception. Adolescents generally need to be better informed on this topic, in order to preserve and improve their reproductive health. The need for more extensive health education on emergency contraception was noticed by adolescents themselves and they mostly believe that preventive interventions are necessary.

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PERINATAL FOLLOW UP AND NEONATAL OUTCOMES OF PREGNANCIES WITH OBSTETRIC CHOLESTASIS

PERINATALNO PRAĆENJE I NEONATALNI ISHODI U TRUDNOĆAMA SA OPSTETRIČKOM HOLESTAZOM

Anita KRSMAN[1, 2], Branislava BATURAN[1, 2], Ana LAZAREVIĆ[3], Zorica GRUJIĆ[1, 2], Đorđe PETROVIĆ[1, 2] and Isidora DICKOV[1]

Summary

Introduction. Obstetric cholestasis is the most common liver disease during pregnancy, which is predominantly associated with fetal complications. **Material and Methods.** This retrospective study included a total of 44 pregnant women with obstetric cholestasis who gave birth at the Clinic of Obstetrics and Gynecology, Clinical Center of Vojvodina, Novi Sad, from January 1, 2014 to December 31, 2018. **Results.** The average maternal age was 34 years. The mean gestational age at diagnosis of obstetric cholestasis was 31 weeks, and at the time of delivery 35 weeks of gestation. Abdominal pruritus was the main symptom of the disease affecting 72.72% of patients. The mean bile acid level in the blood at the time of diagnosis was 25.26 μmol/L. Twenty nine patients (65.90%) gave birth vaginally, while 15 (34.09%) underwent cesarean section. The main maternal complication was postpartum hemorrhage. The average blood loss was 567 ml. There were no maternal deaths or stillbirths. The average newborn birth weight was 2830 g. Respiratory distress syndrome was diagnosed in 8 newborns (15.09%). The mean Apgar score at 1minute was 7, while at 5 minutes it was 9. **Conclusion.** Individual approach, continuous clinical and laboratory monitoring with adequate therapeutic treatment are necessary in patients with obstetric cholestasis.

Key words: Cholestasis; Infant, Newborn; Risk Factors; Perinatal Care; Pregnancy Outcome; Pregnancy Complications; Signs and Symptoms

Sažetak.

Uvod. Opstetrička holestaza je najčešća bolest jetre u trudnoći, koja je povezana sa komplikacijama prvenstveno po plod. **Materijal i metode.** Retrospektivna studija obuhvatila je 44 trudnice sa opstetričkom holestazom, porođene na Klinici za ginekologiju i akušerstvo Kliničkog centra Vojvodine u Novom Sadu, u periodu od 1. januara 2014. do 31. decembra 2018. godine. **Rezultati.** Prosečna starost majki iznosila je 34 godine. Prosečna gestacijska starost trudnoća u vreme postavljanja dijagnoze bila je 31 nedelja, a u vreme porođaja 35 gestacijskih nedelja. Svrab je bio dominantan simptom bolesti i najčešće se pojavljivao u predelu trbuha (72,72%). Prosečna vrednost žučnih kiselina u krvi u momentu postavljanja dijagnoze bila je 25,26 μmol/L. Dvadeset devet pacijentkinja (65,90%) porođeno je vaginalnim putem, dok je 15 (34,09%) trudnica porođeno carskim rezom. Glavna maternalna komplikacija bila je postpartalno krvarenje. Prosečan gubitak krvi bio je 567 ml. Nije bilo maternalnih smrti ni mrtvorođene dece. Prosečna telesna masa na rođenju iznosila je 2.830 g. Respiratorni disters sindrom dijagnostikovan je kod osmoro novorođenčadi (15,09%). Prosečna ocena po Apgaru u prvom minutu iznosila je 7, dok je u petom minutu bila 9. **Zaključak.** Individualni pristup, kontinuirano kliničko i laboratorijsko praćenje uz adekvatan terapijski tretman neophodni su kod pacijentkinja sa opstetričkom holestazom.

Ključne reči: holestaza; novorođenče; faktori rizika; perinatalna nega; ishod trudnoće; komplikacije u trudnoći; znaci i simptomi

Introduction

Obstetric cholestasis (OC) is the most common liver disease during pregnancy [1]. In the absence of other liver pathology, it is defined as pruritus with abnormal liver function which resolves following delivery [1]. The OC was first described in 1883 by Ahlfeld as jaundice in pregnancy that receded spontaneously after childbirth [2]. The OC is a multifactorial condition of pregnancy, but its pathogenesis is not well defined. A genetic predisposition, hormonal and environmental factors have a significant role in the etiology of OC [3]. Studies have shown that in patients with familial OC, there are variations in several genes encoding hepatobiliary transport proteins, as well as in the major bile acid receptor, farnesoid X receptor [4]. This condition may repeat in subsequent pregnancies [5]. The role of hormonal

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Abbreviations
OC – obstetric cholestasis
IUGR – intrauterine growth restriction
RDS – respiratory distress syndrome

and environmental factors in the etiology of OC has also been described. The role of estrogen and progesterone in the etiology of OC has been proven, so this condition is more common in women with multifetal pregnancies and after oral progesterone treatment [6]. Special caution and monitoring is needed in patients with OC because of the risk of poor perinatal outcome such as: premature birth, meconium in the amniotic fluid, fetal bradycardia, fetal distress, and unfortunately intrauterine fetal death and stillbirth [7]. Intrahepatic cholestasis in pregnancy may be associated with significant vitamin K deficiency, severe coagulopathy and consequent life-threatening bleeding [8, 9]. The risk of adverse perinatal outcomes can be reduced by active treatment, including medications, antenatal fetal monitoring and elective early delivery. The aim of our study was to determine the maternal and neonatal outcomes in pregnancies with OC.

Material and Methods

This observational, descriptive cross-sectional retrospective study reviewed clinical outcomes of pregnant women with OC who gave birth at the Department of Obstetrics and Gynecology, Clinical Center of Vojvodina, Novi Sad in the period of five years (2014 – 2018). In the absence of other liver diseases, the diagnosis of OC was confirmed based on the presence of pruritus with abnormal liver function test results. The disease was diagnosed in pregnant women with pruritus and elevated bile acid levels (≥ 14 μmol/L) and/or elevated liver enzymes, without a chronic liver disease or dermatological diseases. The following maternal parameters were analyzed: age, mode of conception, gestational age at the time of OC diagnosis, mode of delivery, and gestational age at delivery. The following fetal and neonatal parameters were examined: intrauterine growth restriction (IUGR), stillbirth, gestational age at delivery, birth weight, Apgar score, and respiratory distress syndrome (RDS). We also evaluated complications (hemorrhage and blood transfusion) and laboratory parameters of liver function and bile acid values at the time of OC diagnosis. The time and mode of delivery depended on maternal complications and fetal condition. Exclusion criteria were: pruritus due to skin disorders, gall bladder and biliary disorder, preeclampsia, and patients with incomplete medical data. The collected data were presented in the form of median values and relative numbers (measure of variability). Statistical data processing was performed using the programs Microsoft Excel 2013.

Results

During the study period, 44 pregnant women with OC gave birth to 53 live babies after 24 weeks of gestation. The mean maternal age was 34 years (range 20 – 39 years) **(Table 1)**. The average gestational age at diagnosis of OC and at the time of delivery was 31 and 35 gestational weeks. There were 31 (70.45%) spontaneous pregnancies and 13 (29.55%) pregnancies conceived by *in vitro* fertilization. Pruritus was the main symptom of the disease and it most commonly affected the abdomen (72.72%). The mean values of alanine transaminase, aspartate transaminase and alkaline phosphatase were 249.32 U/L; 154,53 U/L and 241,06 μmol/L, respectively **(Table 2)**. The mean value of bile acid at the time of diagnosis was 25, 26 μmol/L. The mean total serum bilirubin level was 22,4 μmol/L. In terms of the mode of delivery, 29 patients (65.90%) underwent vaginal delivery, while 15 (34.09%) pregnancies were completed by cesarean section. Six patients (13.63%) gave birth before 34 weeks by emergency cesarean section and 18 patients (40.90%) gave birth after 34 weeks, but still prematurely (before 37 weeks of gestation). The main maternal complication was postpartum hemorrhage. The average blood loss during delivery was 567 ml. Two

Table 1. Characteristics of study population
Tabela 1. *Karakteristike ispitivane populacije*

Characteristics/*Karakteristike*	
Age (years, mean)/*Godine života (prosek)*	34
Parity (range)/*Paritet (raspon)*	1–4
Mode of conception/*Način začeća*	
Spontaneous/*Spontani*	31 (70.45%)
In vitro fertilization/*In vitro oplodnja*	13 (29.55%)
Gestational age at diagnosis (weeks, mean)/*Gestacijska starost u vreme postavljanja dijagnoze (nedelje, prosek)*	31
Mode of delivery/*Način porođaja*	
Vaginal/*Vaginalni*	29 (65.90%)
Cesarean section/*Carski rez*	15 (34.09%)
Intra and postpartum hemorrhage/*Intra i postpartalno krvarenje*	3 (6.81%)
Blood transfusion/*Transfuzija krvi*	3 (6.81%)
Intrauterine growth retardation/*Intrauterini zastoj u rastu*	2 (4.54%)
Gestational age at delivery (weeks, mean)/*Gestacijska starost na porođaju (nedelje, prosek)*	35.86
Delivery < 37 weeks of gestation/*Porođaj < 37. gestacijske nedelje*	18 (40.9%)
Delivery < 34 weeks of gestations/*Porođaj < 34. gestacijske nedelje*	6 (13.63%)

Table 2. Laboratory findings in patients with OC in our study
Tabela 2. *Laboratorijski nalazi pacijentkinja sa opstetričkom holestazom u našoj studiji*

Variables/*Varijable*	$\bar{X}$
Total bile acid at diagnosis (μmol/L)/*Ukupne žučne kiseline prilikom dijagnoze (μmol/L)*	25.26
Alanine transaminase at diagnosis (U/L)/*Alanin transaminaza prilikom dijagnoze (U/L)*	249.32
Aspartate transaminase at diagnosis (U/L)/*Aspartat transaminaza prilikom dijagnoze (U/L)*	165.54
Total bilirubin at diagnosis (μmol/L)/*Ukupni bilirubin prilikom dijagnoze (μmol/L)*	22.4
Alkaline phosphatase at diagnosis (μmol/L)/*Alkalna fosfataza prilikom dijagnoze (μmol/L)*	241.06

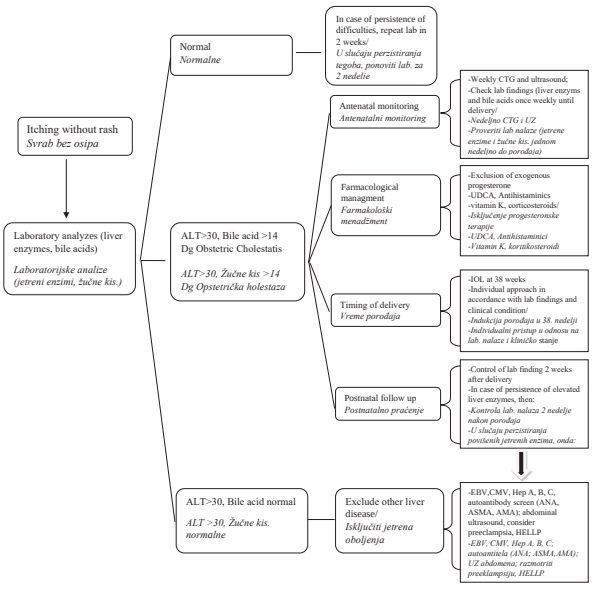
Table 3. Characteristics of newborns of mothers with obstetric cholestasis
Tabela 3. *Karakteristike novorođenčadi majki sa opstetričkom holestazom*

Characteristics/*Karakteristike*	
Respiratory distress syndrome/*Respiratorni distres sindrom*	8 (15.09%)
Premature babies/*Prevremeno rođena deca*	
< 34 gestational weeks/< *34. gestacijske nedelje*	14 (26.41%)
< 37 gestational weeks/< *37. gestacijske nedelje*	28 (52.83%)
Stillbirth/*Mrtvorođeni*	0
Mean body weight/*Prosečna telesna masa na rođenju (g)*	2830 g
Apgar score at 1 minute (mean)/*Apgar skor 1. minuta (prosek)*	7
Apgar score at 5 minutes (mean)/*Apgar skor nakon 5. minuta (prosek)*	9

patients (4.54%) had a blood loss over 1500 ml. Three patients (6.81%) received blood transfusion. There were no maternal deaths or stillbirths. The average birth weight of newborns was 2830 g **(Table 3).** The mean Apgar score at 1 minute was 7, while at 5 minutes it was 9. There were 8 neonates (15.09%) with RDS. The IUGR was diagnosed in 2 cases (4.54%). There were no intrauterine fetal deaths.

Discussion

In this study, we presented the outcomes of 44 pregnancies complicated by OC during a five year period. The mean maternal age in our study was 34 years. Few studies have shown that older maternal age is a risk factor for OC [10]. The majority of the patients were primigravida (65.9%). Symptoms of OC appeared between 27 and 39 weeks of gestation, which confirms the claims that the disease is most often diagnosed in the second and third trimesters of pregnancy [8, 11]. All patients had pruritus as the dominant symptom of the disease. It commonly occurs between 25 – 32 weeks of gestation. Studies have shown that itching is most intense at night and it is associated with insomnia. Since this is a retrospective study, we did not examine the occurrence of itching in relation to the time of day. In relation to location, patients mostly reported abdominal pruritus (72.72%), 8 patients (18.18%) said that palms and soles were the places of the most intense itching and only 4 patients (9.09%) reported itching all over the body. Our results are consistent with results found in other studies [12]. In the absence of other skin changes, skin excoriations from scratching were most often observed. After the diagnosis of OC, continuous monitoring (active management) of these patients is required, which includes pharmacological therapy, antenatal monitoring with a decision on the type and time of delivery. Ursodeoxycholate, which decreases maternal symptoms and serum bile acid levels, is widely used for the treatment of OC [13]. It is currently the most effective treatment for pruritus in OC [14]. The patients were recommended a course of ursodeoxycholate, 10 – 15 mg/kg/d, taken orally and divided into 2 – 3 doses/day. Antihistamines (chlorpheniramine) and topical agents with menthol may be useful in the treatment of pruritus. The average gestational age at birth was 35 weeks of gestation, which is in accordance with the literature data [15]. Active management is usually rec-



Graph 1. Protocol on management of obstetric cholestasis at the Clinic of Obstetrics and Gynecology, Clinical Center of Vojvodina, Novi Sad
Grafikon 1. *Protokol dijagnostike i terapije opstetričke holestaze na Klinici za ginekologiju i akušerstvo, Kliničkog centra Vojvodine, Novi Sad*

ommended to prevent the risk of intrauterine death and routine delivery at 37 to 38 weeks of gestation [16, 17]. There are still different recommendations about the time of delivery of patients with OC. It is believed that the time of delivery should be decided individually, taking into account the risk of premature birth, on the one hand, and the risks posed by continued pregnancy on the other hand [18]. The Department of Obstetrics and Gynecology (Clinical Centre of Vojvodina) has a specific protocol (continuous monitoring, therapy and postpartum control) **(Graph 1)**. During the process of decision making, special attention is paid to the level of bile acids because the concentration ≥ 40 μmol/L may be associated with higher chance of poor outcome [19]. The dominant mode of delivery in our study was vaginal (65.9%) and 15 patients underwent cesarean section (34.1%): 9 elective and 6 emergency cesarean sections. There were 3 patients with postpartum hemorrhage (6.81%), which is low in comparison with study of Pokrhel et al. [11]. Out of 53 neonates, RDS was diagnosed in 8 (15.09%). In terms of prematurity, 52.83% of babies were born before 37 weeks, and 14 babies (26.41%) were born before 34 weeks of pregnancy. Much higher incidence of preterm deliveries was reported in the studies of Dodampahala et al. (76.4%) and Bacq et al. (60%) [20, 21]. Adverse pregnancy outcomes and fetal complications are most common with elevated bile acids ≥ 40 μmol/L [12]. There were no intrauterine deaths or stillbirths in our study. Studies from the literature data also show no intrauterine deaths or stillbirths [22, 23].

Conclusion

The diagnosis of obstetric cholestasis is a significant problem, primarily due to potential fetal complications. Careful monitoring, individual approach, and timely response are necessary to avoid adverse outcomes in pregnancies with obstetric cholestasis.

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NUTRITIONAL STATUS OF PREGNANT WOMEN – EFFECTS ON THE COURSE AND PREGNANCY OUTCOME

TELESNA UHRANJENOST TRUDNICA – EFEKAT NA TOK I ISHOD TRUDNOĆE

Isidora ĐOZIĆ[1], Edita STOKIĆ[2, 3] and Jelena NIKOLIĆ[1, 2]

Summary

Introduction. In recent decades, obesity has taken on epidemic proportions and is becoming one of the most significant public health problems today. The results of clinical and epidemiological studies show that obese pregnant women can be considered a high risk group, given the increased risk of maternal and fetal complications. The aim of this study was to examine the relationship between pregnant women's nutritional status and the development of arterial hypertension, gestational diabetes and obstetric cholestasis during pregnancy, as well as the impact of pregnant women's nutritional status on newborn birth weight and vital parameters at birth, assessed by Apgar score. **Material and Methods**. This retrospective study included 71 pregnant women who were divided into two groups, depending on the nutritional status. The first group included 28 pregnant women with a body mass index < 25 kg/m² or less, whereas the second group included obese pregnant women with a body mass index > 30 kg/m² or more. Birth protocol data were used for the newborns. **Results.** In obese pregnant women, the termination of pregnancy by cesarean section was statistically significant more frequent ($p < 0.05$). Newborns of obese mothers had a statistically lower Apgar score at 5 minutes, while higher body weight of newborns and a lower Apgar score at 1 minute were at the limit of statistical significance ($p = 0.068$). Arterial hypertension was more common in obese pregnant women ($p = 0.014$), while gestational diabetes ($p = 0.42$) and obstetric cholestasis ($p = 0.51$) were more common in obese pregnant women, but without statistical significance. **Conclusion**. Obesity in pregnancy is a risk factor for the development of hypertension, a higher incidence of cesarean section, and a lower Apgar score of newborns.

Key words: Obesity; Pregnancy; Risk Factors; Hypertension; Diabetes, Gestational; Cholestasis; Cesarean Section; Apgar Score; Pregnancy Outcome

Sažetak

Uvod. Poslednjih decenija gojaznost poprima epidemijske razmere i postaje jedan od najznačajnijih javnozdravstvenih problema današnjice. Rezultati kliničkih i epidemioloških studija pokazuju da se gojazne trudnice mogu smatrati „rizičnom grupom" s obzirom na povećan rizik od maternalnih i fetalnih komplikacija. Cilj rada bilo je ispitivanje povezanosti stepena telesne uhranjenosti trudnica sa razvitkom arterijske hipertenzije, gestacijskog dijabetesa i opstretičke holestaze tokom trudnoće, kao i uticaja stepena uhranjenosti trudnica na porođajnu masu novorođenčeta i vitalne parametre na rođenju, ocenjene kroz Apgar skor. **Materijal i metode.** Istraživanje je sprovedeno u vidu retrospektivne studije kod 71 trudnice, podeljene u dve ispitivane grupe u zavisnosti od stepena uhranjenosti. Prvu grupu činilo je 28 trudnica čiji je indeks telesne mase < 25 kg/m², dok su drugu grupu činile gojazne trudnice sa indeksom telesne mase > 30 kg/m². Iz protokola novorođenčadi korišćeni su podaci o novođenčadi. **Razultati.** Kod gojaznih trudnica statistički je signifikantno češće završavanje trudnoće carskim rezom ($p < 0,05$). Novorođenčad gojaznih majki imaju statistički signifikantan niži Apgar skor u petom minutu, dok su veća telesna masa novorođenčadi i niži Apgar skor u prvoj minuti na granici statističke signifikantnosti ($p = 0,068$). Arterijska hipertenzija je češća kod gojaznih trudnica ($p = 0,014$), dok su gestacijski dijabetes ($p = 0,42$) i opstetrička holestaza ($p = 0,51$) češći kod gojaznih trudnica, ali nisu dostigli statističku značajnost. **Zaključak.** Gojaznost u trudnoći predstavlja faktor rizika za nastanak hipertenzije, veću incidenciju operativnog završavanja trudnoće i niži Apgar skor novorođenčeta.

Ključne reči: gojaznost; trudnoća; faktori rizika; hipertenzija; gestacijski dijabetes; holestaza; carski rez; Apgar skor; ishod trudnoće

Introduction

Obesity is a disease characterized by an increase in body weight caused by excessive accumulation of body fat. It is a significant risk factor for the development of numerous chronic conditions.

Obesity is becoming one of the most significant public health problems today. The increase in the incidence of obesity worldwide has a different distribution; in some parts of the world obese people account for 20 – 40% of the population, while in other parts it is observed that every second person is obese [1–3]. Obesity is a consequence of various etiopathogenic factors: genetic factors, regulation of hunger and satiety, energy imbalance, various endocrine-metabolic factors, psychological factors, and socio-economic status [4]. The hyperalimentation obesity is mostly the consequence of dispro-

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Abbreviations

BMI – body mass index
WG – weeks of gestation
CS – cesarean section
WHO – World Health Organization

portionate intake and consumption of energy. Increased caloric intake (high energy and fast food, large portions, etc.) on the one hand and reduced physical activity (sedentary lifestyle, use of computers and new technologies, etc.) on the other, are the most common causes of obesity [1].

In order to get a more accurate picture of the degree of obesity, the World Health Organization (WHO) introduced the body mass index (BMI) as an indicator of the degree of obesity [5]. In Europeans, obesity is believed to account for 85% of the risk for developing type 2 diabetes, 2.35% of ischemic heart disease, and 55% of arterial hypertension [1]. Adipose tissue was considered as a passive energy reservoir of the body, but its significant endocrine activity has been discovered in the 20th century. It secretes more than 50 peptide mediators, adipocytokines, such as leptin, resistin, adiponectin, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), visfatin and a number of others, many of which are still in the research phase [6]. The name leptin is derived from the Greek word "leptos" which means slender, thin. The main function of leptin is to regulate body weight by informing the central nervous system (CNS) about the body's total energy reserves. Obese pregnant women with higher BMI values and a higher amount of adipose tissue have a high value of leptin, which leads to insulin resistance and the development of gestational diabetes [7]. Adiponectin is the main adipocytokine with positive metabolic effects. It reduces insulin resistance, the concentration of free fatty acids, lowers glycemia, and reduces atherogenesis [8]. Visfatin has insulomimetic effects and it lowers blood glucose levels. Interestingly, visfatin acts by binding to the insulin receptor [6]. Resistin is known to produce adipose tissue and some studies show that serum resistin levels increase with obesity [9].

The effects of obesity are manifested in almost every aspect of a woman's reproductive life including metabolic and reproductive complications; results of clinical and epidemiological studies show that obese pregnant women are considered to be a "risk group" given the increased risk of maternal complications such as gestational diabetes, hypertension, thromboembolic complications, peripartum complications, and increased incidence of surgical delivery. There is also an important problem in clinical practice - difficult visualization of fetal morphology during ultrasound examination, difficult access during surgery, problems with intubation, complications of wound healing, etc. [10]. Accumulation of fat mass in central depots leads to more frequent insulin resistance and disorders of adipocytokine secretion, which increases the risk of gestational diabetes [11]. Arterial hypertension is one of the most common disorders in pregnancy. Gestational hypertension is a blood pressure ≥ 140/90 mmHg that occurs after the 20th week of gestation in women who did not have hypertension before pregnancy, and blood pressure values are normalized 6 weeks after delivery [12]. Arterial hypertension in pregnancy is a common cause of preterm birth, surgical termination of pregnancy and premature birth [13]. Fetal complications of maternal obesity are hyperglycemia, traumatic birth as a consequence of macrosomia (birth weight over 4000 g), neonatal jaundice, increased risk of congenital anomalies, and premature birth [14].

The aim of this study was to examine the relationship between pregnant women's nutritional status and the incidence of maternal complications**,** manner of childbirth, neonatal birth weight, as well as the vital parameters at birth.

Material and Methods

The retrospective study included 71 pregnant women that were hospitalized after the 37 weeks of gestation (WG) at the Clinic of Gynecology and Obstetrics of the Clinical Center of Vojvodina. Pregnant women gave birth in the period from January 2011 to January 2015. The subjects were divided into two groups, depending on the nutritional status: the first group included 28 pregnant women with normal body weight and a BMI < 25 kg/m², while the second group included 43 obese pregnant women with a BMI > 30 kg/m². Anthropometric data on the body height, body weight, weight gain (during the current pregnancy), existence of arterial hypertension, gestational diabetes, and obstetric cholestasis were gathered from the medical history. The neonatal protocol included data related to newborns: body length, body weight at birth, and Apgar scores at 1 and 5 minutes after birth. A t-test was used for parametric data (measured quantities). For nonparametric data, the χ square test was used, i.e. Fisher's exact test. The threshold of statistical significance was $p \leq 0.05$.

Results

The average age of respondents was 29.92 ± 5.78 years (minimum 18, maximum 43 years). The average gestational age of the examined group was 39.35 ± 1.01; 37 – 41 WG. The mean body weight of respondents was 82.68 ± 15.35 kg (54 kg – 121 kg). The average BMI was 30.10 ± 5.98 kg/m² (21.09 kg/m² – 45.12 kg/m²). The average weight gain during pregnancy in all subjects was 14.51 ± 6.32 kg (8 kg – 35 kg).

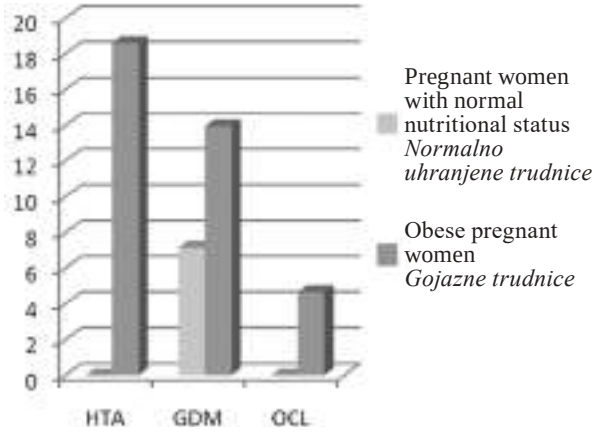
During pregnancy, 11.27% of subjects had arterial hypertension, 11.27% had gestational diabetes, 2.82% had obstetric cholestasis, and in 43.94% the pregnancy was completed by cesarean section **(Table 1)**.

There were a total of 71 newborns, with an average body length of 49.99 ± 2.16 cm (45 cm – 54 cm). The average body weight of newborns was 3486.36 ± 564.15 g (2370 g – 4780 g). The Apgar score at 1 minute was 9.11 ± 1.25, and at 5 minutes it was 9.67 ± 0.73.

In relation to the nutritional status, the respondents were divided into two groups:

Table 1. Incidence of complications during pregnancy in all respondents
Tabela 1. *Učestalost komplikacija tokom trudnoće u celoj grupi ispitanica*

Parameters (N/*Br.* = 71)/*Parametri (*N/*Br. = 71)*	%
Arterial hypertension/*Arterijska hipertenzija*	11.27
Gestational diabetes/*Gestacijski dijabetes*	11.27
Obstetric cholestasis/*Opstetrička holestaza*	2.82
Cesarean delivery/*Porođaj carskim rezom*	43.94



Graph 1. Maternal complications among groups of respondents
Grafikon 1. *Maternalne komplikacije među grupama ispitanica*

Legend/*Legenda*: HTA – arterial hyperetension/*arterijska hipertenzija*; GDM – gestational diabetes mellitus/*gestacijski dijabetes melitus*; OCL – obstetrička holestaza

– Group I - BMI < 25 kg/m² - pregnant women with normal body weight
– Group II - BMI > 30 kg/m² - obese pregnant women.

Comparing the two examined groups, the average age in group I of pregnant women with normal nutritional status was 28.93 ± 5.11, while in group II of obese pregnant women it was 30.56 ± 6.15. There was no statistically significant age difference between group I and group II. The average age in group I was 39.21 ± 0.92 and 39.44 ± 1.08 in group II. The gestational age was not statistically different between the two groups (p = 0.36). The average body height in group I was 169.47 ± 5.64 cm, and 163.86 ± 7.24 cm in group II. The average body weight in group I was 68.86 ± 6.42 kg, and 91.67 ± 12.49 kg in group II. There was a highly statically significant difference in body weight between the examined groups (p < 0.0005). The pregnant women in group I had an average BMI of 23.92 ± 1.026 kg/m², while in the group II the average BMI was 34.13 ± 4.09 kg/m², showing a highly statically significant difference in BMI between the examined groups (p < 0.0005). Weight gain during pregnancy between the two groups was statistically significantly different (p < 0.05).

The comparison between the two examined groups showed a statistically significant difference in the incidence of arterial hypertension, while the difference between gestational diabetes and obstetric cholestasis was observed, but it was not statistically significant in our sample **(Graph 1)**. The frequency of cesarean section was statistically significantly more common in obese pregnant women.

The results of our study showed that infants of obese mothers had a higher birth weight and body length, but this difference was not statistically significant **(Table 2)**. Apgar scores were lower in neonates of obese mothers and the difference was statistically significant at 5 minutes **(Table 2)**.

Discussion

Obesity is a major socio-epidemiological problem today. Obesity in the preconception period and during the pregnancy itself is accompanied by many risks for

Table 2. Comparison of body length, body weight and Apgar score in newborns in relation to the maternal nutritional status
Tabela 2. *Komparacija telesne dužine, telesne mase i Apgar skora kod novorođenčadi u odnosu na stepen telesne uhranjenosti majki*

Parameters *Parametri*	Pregnant women with normal nutritional status ($\overline{X}$ ± SD) *Normalno uhranjene trudnice ($\overline{X}$ ± SD)*	Obese pregnant women ($\overline{X}$ ± SD) *Gojazne trudnice ($\overline{X}$± SD)*	P
Newborn body length (cm) *Telesna dužina novorođenčeta (cm)*	49.7 ± 2.35	50.18 ± 2.02	0.383
Newborn body weight (g) *Telesna masa novorođenčeta (g)*	3327.4 ± 502.36	3596.4 ± 584.26	0.056
Apgar score at 1 minute *Apgar skor u 1. minutu*	9.44 ± 0.751	8.87 ± 1.47	0.068
Apgar score at 5 minutes *Apgar skor u 5. minutu*	9.89 ± 0.32	9.51 ± 0.89	0.038

the development of both maternal and fetal complications [1]. Pathophysiologically, due to the accumulation of adipose tissue in the central part of the body of obese pregnant women, due to changes in the secretion of adipocytokines, the tendency towards insulin resistance and development of gestational diabetes increases. As a consequence of gestational diabetes, the incidence of fetal macrosomia, polyhydramnios, premature birth of infants of diabetic mothers, higher rate of cesarean delivery, higher incidence of congenital fetal malformations, especially cardiovascular defects, has increased. In our study, an increased incidence of gestational diabetes was observed in obese pregnant women, but this difference was not statistically significant. In addition to the degree of obesity, weight gain during pregnancy is now in the focus of interest of experts as a special risk factor for numerous complications during pregnancy primarily affecting the increased amount of central adipose tissue of the fetus, and later for the development of obese children with increased adipose tissue [15]. Obese children have an increased tendency to develop type 2 diabetes during childhood and early adolescence, and their risk of developing cardiovascular disease is increased [16]. Pregnancy is characterized by an increased vascular volume, which, in addition to reduced vascular resistance typical for pregnancy, leads to arterial hypertension in predisposed pregnant women. Also, glomerular endotheliosis in preeclampsia is the pathophysiological basis for the development of hypertensive syndrome in pregnancy. The consequences of maternal arterial hypertension are preeclampsia, eclampsia, increased susceptibility to peripartum cardiomyopathy, thromboembolic incidents, while in the fetus the consequences can be premature birth, reduced body weight and fetal death. In our study, as in many others, a statistically significant higher incidence of hypertension was observed in obese pregnant women. Obstetric cholestasis is characterized by the appearance of pruritus, increased serum levels of bile acids and transaminases in the second and third trimesters of pregnancy [17]. The disease occurs in the second half of pregnancy when the level of estrogen reaches its maximum [18]. Similar to the literature data, a higher incidence of obstetric cholestasis was observed in obese pregnant women, but in our study this difference was not statistically significant. As in many other studies, our study also showed a significantly higher incidence of surgical delivery in obese pregnant women [19]. Unfortunately, there is a lot of discussion today regarding non-medical reasons for surgical termination of pregnancy. Interviews with obstetricians highlighted non-medical factors implicated in the high rate of CSs, including a convenience incentive, lack of supervision and training in public hospitals, as well as absence or lack of adherence with clinical guidelines.

According to the Statement on Caesarean Section (CS) Rates released by the World Health Organization, population-based CS rates higher than 10% are not optimal [20]. Although WHO has indicated that countries should not strive to achieve a specific rate, the rationale for the 10% recommendation is based on a systematic review and ecological analysis which have shown that CS rates exceeding 10% do not correlate with reductions in maternal and newborn mortality [21]. Higher incidence of CS in obese pregnant women increases the risk of developing postpartum complications such as bleeding, infections and wound dehiscence, and slower maternal recovery [22]. In obese pregnant women, due to the increased risk of poor pregnancy outcome, the risk of early termination of pregnancy and consequent iatrogenic prematurity is also increased [23]. In our subjects, the newborns had a higher birth weight and the Apgar scores were lower in obese mothers, although only at the limit of statistical significance. A statistically significantly lower Apgar score at 5 minutes was observed in newborns of obese mothers. Our data are in line with the literature data that support the fact that obese mothers give birth to children of higher birth weight and lower Apgar score. Fetal growth is a complex biological process that is regulated by both maternal and fetal factors including genes and environment. Maternal obesity probably contributes to macrosomia via mechanisms including increased insulin resistance (even in women who do not have diabetes) resulting in higher fetal glucose and insulin levels [24]. Placental lipases metabolize triglycerides in maternal blood, allowing free fatty acids to be transferred in excess to the growing fetus [25]. Fetal macrosomia has been shown to be a risk factor for obesity, diabetes, and increased cardiovascular risk in childhood and adolescence [26, 27].

Conclusion

Our research shows that hypertension is statistically significantly more common in obese pregnant women. A high incidence of gestational diabetes and obstetric cholestasis was observed, but this difference was not statistically significant. In our subjects, childbirth was statistically significantly more often completed by cesarean section in obese pregnant women. Newborns of obese women had a higher body weight and a lower Apgar score at the border of statistical significance at 1 minute. A statistically significantly lower Apgar score at 5 minutes was recorded in infants of obese mothers.

This paper may be used as a pilot study to plan research on the impact of the nutritional status on the course and outcome of pregnancy on a larger sample of respondents.

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CORRELATION OF CARDIOVASCULAR AND RESPIRATORY COMORBIDITIES WITH MOTOR FUNCTIONAL INDEPENDENCE IN THE ELDERLY AFTER HIP FRACTURE

KORELACIJA KARDIOVASKULARNOG I RESPIRATORNOG KOMORBIDITETA SA MOTORNOM FUNKCIONALNOM NEZAVISNOŠĆU POSLE PRELOMA KUKA U POPULACIJI STARIJIH

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Summary

Introduction. The aim of the study was to evaluate the correlation between different levels of examined comorbidities using the Cumulative Illness Rating Scale for Geriatrics and motor Functional Independence Measure test in the elderly after hip fracture. **Material and Methods.** The study included 203 geriatric patients, 65 years of age and older, who were referred to a rehabilitation program at the Institute for Rehabilitation after hip fracture. The following comorbidities were analyzed: cardiac, vascular, and respiratory. The motor component of Functional Independence Measure was used to assess functional recovery. The Cumulative Illness Rating Scale for Geriatrics was used to calculate the comorbidity index. The patients were assessed on 4 different occasions: on admission, on discharge, 3 months after discharge, and 6 months after discharge. The short-term and long-term efficiency of rehabilitation treatment was measured. **Results.** There is a significant difference in motor Functional Independence Measure scores between different levels of vascular ($p = 0.010$) and respiratory ($p = 0.047$) comorbidities only on admission, while at other times of observation no significant difference ($p > 0.05$) was found. The highest level of correlation was found in level 3 comorbidity severity index for cardiac comorbidity (discharge/3 months) (Pearson's correlation - $R = 0.938$) and vascular comorbidity (discharge/3 months) ($R = 0.912$), and level 2 comorbidity severity index for respiratory comorbidity (discharge/3 months) ($R = 0.941$). **Conclusion.** Rehabilitation treatment of the elderly after hip fracture plays a significant role both in short-term and long-term recovery, particularly in the functional domains even in persons with significant comorbidities. Early inclusion and an individually designed rehabilitation program with continuous monitoring of the elderly after hip fractures results in functional improvement and better quality of life.

Key words: Hip Fractures; Comorbidity; Motor Skills; Disability Evaluation; Recovery of Function; Geriatrics; Rehabilitation; Aged

Sažetak

Uvod. Cilj rada bio je procena korelacije između različitih stepena ispitivanih komorbiditeta i motoričke funkcionalne nezavisnosti koje su merene testom funkcionalne nezavisnosti kod starijih osoba nakon preloma kuka. **Materijali i metode.** Studija je obuhvatila 203 pacijenta starijih od 65 godina koji su upućeni u rehabilitacionu ustanovu nakon preloma kuka na dalje lečenje u Institut za rehabilitaciju. Analizirani su sledeći komorbiditeti: kardiološki, vaskularni i respiratorni. Za procenu funkcionalnog oporavka korišćena je motorička komponenta testa funkcionalne nezavisnosti. Za indeks težine komorbiditeta je korišćena Gerijatrijska skala komorbiditeta (*Cumulative Illnes Raiting Scale*). Pacijenti su procenjivani u četiri različite situacije: pri prijemu, pri otpustu, tri meseca nakon otpusta i šest meseci nakon otpusta. Merena je kratkoročna i dugoročna efikasnost rehabilitacionog tretmana. **Rezultati.** Postoji značajna razlika u vrednostima rezultata motoričkog skora testa funkcionalne nezavisnosti među različitim stepenima vaskularnih ($p = 0,010$) i respiratornih ($p = 0,047$) komorbiditeta samo na prijemu, dok za ostala vremena posmatranja nismo pronašli značajnu razliku ($p > 0,05$). Najviši nivo korelacije primećen je za stepen 3 indeksa težine komorbiditeta za kardiološki komorbiditet (otpust/3 meseca) ($R = 0,938$) i vaskularni komorbiditet (otpust/3 meseca) ($R = 0,912$) i stepen 2 indeksa težine komorbiditeta za respiratorni komorbiditet (otpust/3 meseca) ($R = 0,941$). **Zaključak.** Rehabilitacioni tretman starijih osoba nakon preloma kuka ima značajnu ulogu u kratkoročnom i dugoročnom oporavku, posebno u funkcionalnim domenima čak i kod osoba sa značajnim komorbiditetima. Pravovremeno uključivanje i individualno dizajnirani program rehabilitacije sa kontinuiranim praćenjem starije populacije nakon preloma kuka rezultira funkcionalnim poboljšanjem i boljim kvalitetom života.

Ključne reči: prelom kuka; komorbiditet; motorička funkcionalna nezavisnost; stari

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Abbreviations

CIRS-G – Cumulative Illness Rating Scale for Geriatrics
FIM – Functional Independence Measure
R – Pearson's correlation coefficient
ANOVA – analysis of variance
BMD – bone mineral density

Introduction

Previous studies have indicated the impact of numerous comorbidities on the course of primary and secondary rehabilitation in patients after hip fracture [1, 2]. It was pointed out that different conditions and their severity may affect the short-term and long-term functional recovery after hip fracture. The elderly patients may have multiple comorbidities at the same time [3–5]. Therefore, there is a great need for early identification of these patients and timely inclusion into adequate rehabilitation treatment in order to provide maximum functional recovery, and thus achieve better quality of life**.** The significant role of comorbidities during the recovery period after hip fracture in the elderly has already been emphasized and it was noticed that certain comorbidities and their severity may have an important role in achieving improvements [5, 6].

Given the facts above, we hypothesized that high incidence of different comorbidities may have different impacts on the functional recovery and improvement of the motor function. Thus, we aimed to evaluate the correlation between different levels of examined comorbidities and motor functional independence by Functional Independence Measure (FIM) test in the elderly after hip fracture.

Material and Methods

The study included 203 eligible participants aged 65 years and over who were referred to the rehabilitation facility after hip fracture for further treatment. Prior to the inclusion in the study, patients were informed about the study protocol and informed consents were obtained. The study followed the principles of good clinical practice and was approved by the Institutional Review Board. The following comorbidities were analyzed: cardiac, vascular, and respiratory. The severity of comorbidities from the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) was defined as follows: 0 – no problems; 1 – mild problems at present or significant problems in the past; 2 – moderate morbidity; 3 – severe problems, uncontrollable chronic problems; and 4 – extremely severe health conditions requiring emergency treatment [7].

The FIM test was used to assess the motor functional independence. It is a reliable tool for estimation of certain changes of the functional status over observed periods of time and it consists of 18 categories graded from 1 – 7 each [8].

The patients were assessed on 4 different occasions: on admission (Group A), on discharge (Group B), 3 months after discharge (Group C) and 6 months after discharge (Group D).

The results were presented as mean values (MV) with standard deviation (SD). The one-way analysis of variance (ANOVA) test was used for the evaluation of statistical differences among groups with different levels of comorbidities and among groups examined at different times. To evaluate the correlation between different examination times for the same CIRS-G groups we calculated the Pearson's correlation coefficient (R). For evaluation and quantification of variability that can be explained between different times of evaluation for the same level of CIRS-G severity of musculoskeletal impairment and the scores of motor functioning FIM test, we used η^2 = sum of squares (between groups)/sum of squares (Total) x 100, where sums of squares were gained from the one-way ANOVA test and results were presented as percentage (%) [5]. Statistical significance was set at $p < 0.05$.

Results

Different comorbidities showed different severity levels, with highest incidence of level 2 CIRS-G for cardiac and vascular comorbidities, and level 0 CIRS-G for respiratory comorbidities. In the group of patients with different levels of cardiac comorbidity there was a significant difference in FIM scores at the same points of examination ($p < 0.001$) **(Table 1)**.

Regarding vascular and respiratory comorbidity, there was a significant difference in FIM scores among different levels of vascular ($p = 0.010$) and respiratory ($p = 0.047$) comorbidities only on admission, while at other times of examination no significant difference was found ($p > 0.05$) **(Table 1)**.

In the group of patients with different levels of cardiac comorbidity, there was a positive correlation at different points of examination **(Table 2)**. The highest level of correlation was found in level 3 CIRS-G (discharge/3 months) ($R = 0.938$), while the lowest levels of correlation were found in level 1 CIRS-G (admission/3 months and admission/6 months) ($R = 0.577$ and $R = 0.577$) **(Table 2)**.

Regarding different levels of vascular comorbidity, there was a positive correlation at different times of examination in the evaluated group of patients **(Table 2)**. The highest level of correlation was found in level 3 CIRS-G (discharge/3 months) ($R = 0.912$), while the lowest level of correlation was found in level 0 CIRS-G (admission/6 months) ($R = 0.679$) **(Table 2)**.

In the group of patients with different levels of respiratory comorbidity, there was a positive correlation at different times of examination **(Table 2)**. The highest level of correlation was found in level 2 CIRS-G (discharge/3 months) ($R = 0.941$), while the lowest level of correlation was found in level 3 CIRS-G (admission/3 months) ($R = 0.488$) **(Table 2)**.

A significant improvement in FIM scores was found in every level of CIRS-G, regardless of the type of comorbidity (cardiac, vascular, or respiratory; $p < 0.001$) **(Table 3)**.

Table 1. Functional independence measure scores in different comorbidities
Tabela 1. *Vrednosti mera funkcionalne nezavisnosti kod različitih komorbiditeta*

Systems *Sistemi*	CIRS-G/*GSK*	Group A/*Grupa A*	Group B/*Grupa B*	Group C/*Grupa C*	Group D/*Grupa D*
		MV ± SD/*SV ± SD*	MV ± SD/*SV ± SD*	MV ± SD/*SV ± SD*	MV ± SD/*SV ± SD*
Cardio *Kardio*	0 (N = 56)	43.91 ± 8.27	64.66 ± 8.76	73.80 ± 12.63	76.32 ± 12.81
	1 (N = 33)	44.82 ± 4.42	65.97 ± 6.52	74.85 ± 8.85	77.70 ± 8.74
	2 (N = 78)	40.88 ± 7.20	59.44 ± 10.72	66.51 ± 15.38	69.10 ± 16.53
	3 (N = 35)	38.03 ± 8.26	56.57 ± 9.84	61.63 ± 13.52	63.51 ± 15.44
	4 (N = 1)	–	–	–	–
	p value*	<0.001	<0.001	<0.001	<0.001
Vascular *Vaskularni*	0 (N = 19)	42.58 ± 8.04	61.95 ± 12.40	70.00 ± 16.77	72.11 ± 18.49
	1 (N = 29)	45.41 ± 5.56	64.07 ± 7.01	71.79 ± 10.75	74.76 ± 10.89
	2 (N = 120)	41.71 ± 7.53	61.78 ± 10.37	69.64 ± 14.90	72.09 ± 15.81
	3 (N = 35)	39.06 ± 8.36	58.03 ± 8.70	64.26 ± 11.78	66.49 ± 12.63
	4 (N = 0)	–	–	–	–
	p value*	0.010	0.098	0.145	0.142
Respiratory *Respiratorni*	0 (N = 161)	42.41 ± 7.59	62.06 ± 9.72	69.89 ± 13.83	72.46 ± 14.70
	1 (N = 11)	47.00 ± 9.90	68.50 ± 10.61	78.00 ± 15.56	77.00 ± 9.90
	2 (N = 19)	37.95 ± 8.76	56.74 ± 13.52	61.89 ± 18.86	63.37 ± 20.30
	3 (N = 11)	39.36 ± 3.72	59.36 ± 3.72	67.45 ± 4.63	69.91 ± 5.99
	4 (N = 1)	–	–	–	–
	p value*	0.047	0.097	0.094	0.086

Legend: *One-way ANOVA test; CIRS-G - Cumulative Illness Rating Scale for Geriatrics; MV – mean value; SD – standard deviation
Legenda: **Jednosmerni ANOVA test; GSK – Gerijatrijska skala komorbiditeta; SV – srednja vrednost; SD – standardna devijacija*

Table 2. Correlation of functional independence at different times of follow-up
Tabela 2. *Korelacija funkcionalne nezavisnosti u različitim vremenima praćenja*

Systems *Sistemi*	CIRS-G *GSK*	Group A/Group B/ *Grupa A/Grupa B*	Group A/Group C *Grupa A/Grupa C*	Group A/Group D *Grupa A/Grupa D*	Group B/Group C *Grupa B/Grupa C*	Group B/Group D *Grupa B/Grupa D*
		R	R	R	R	R
Cardio *Kardio*	0	0.729	0.661	0.640	0.852	0.787
	1	0.589	0.577	0.577	0.742	0.717
	2	0.858	0.815	0.807	0.908	0.880
	3	0.711	0.740	0.693	0.938	0.839
	4	–	–	–	–	–
Vascular *Vaskularni*	0	0.888	0.782	0.679	0.820	0.698
	1	0.817	0.752	0.837	0.892	0.887
	2	0.784	0.751	0.713	0.873	0.820
	3	0.712	0.728	0.731	0.912	0.853
	4	–	–	–	–	–
Respiratory *Respiratorni*	0	0.790	0.757	0.753	0.882	0.825
	1	–	–	–	–	–
	2	0.839	0.852	0.810	0.941	0.927
	3	0.680	0.488	0.564	0.707	0.789
	4	–	–	–	–	–

Legend: R – Pearson's Correlation Coefficient; CIRS-G - Cumulative Illness Rating Scale for Geriatrics
Legenda: *R – Pirsonov korelacioni koeficijent; GSK – Gerijatrijska skala komorbiditeta*

The impact of different examination periods of every CIRS-G severity level of cardiac, vascular, and respiratory comorbidity on FIM scores was high. The highest values were found in cardiac comorbidity in level 1 CIRS-G (η^2 = 75.95%), in vascular comorbidity in level 1 CIRS-G (η^2 = 63.25%), and in respiratory comorbidity in level 3 CIRS-G (η^2 = 88.18%) **(Table 3)**.

Table 3. Statistical analysis of the functional independence measure scores during the rehabilitation treatment for the same level of CIRS-G
Tabela 3. *Statistička interpretacija funkcionalne nezavisnosti tokom rehabilitacionog tretmana za isti stepen GSK*

CIRS-G/*GSK*	Cardio/*Kardio*		Vascular/*Vaskularni*		Respiratory/*Respiratorni*	
Group A/D/*Grupa A/D*	p value*/*p vrednost**	η^2 (%)	p value*/*p vrednost**	η^2 (%)	p value*/*p vrednost**	η^2 (%)
0	< 0.001	58.54	< 0.001	40.51	< 0.001	49.96
1	< 0.001	75.95	< 0.001	63.25	< 0.001	55.39
2	< 0.001	42.17	< 0.001	47.46	< 0.001	29.70
3	< 0.001	41.67	< 0.001	51.92	< 0.001	88.18
4	–	–	–	–	–	–

Legend: *One-way ANOVA; CIRS-G - Cumulative Illness Rating Scale for Geriatrics
Legenda: **Jednosmerni ANOVA; GSK – Gerijatrijska skala komorbiditeta*

Discussion

Differences in the distribution of comorbidity severity levels of evaluated parameters suggest that every patient should be assessed individually, along with an individually planned rehabilitation program and continuous monitoring in order to achieve the best treatment outcome. It should be kept in mind that part of treatment in the elderly after hip fracture is oriented to fall prevention [9]. Previous studies have reported that cardiovascular diseases may be associated with increased risk of non-spine fractures through the mechanisms that can lead to the reduction in hip bone mass or bone mineral density (BMD) [10, 11]. Along with well-known risk factors for cardiovascular disease that may be associated with reduced BMD (advanced age, physical inactivity, etc.), there are numerous biological and inflammatory markers which may play a certain role in bone mass reduction [12–14].

The significant difference in motor FIM scores at all examination time points regarding the cardiac comorbidity lead to the assumption that rehabilitation program has no great impact on the recovery in participants with higher CIRS-G scores. Contrary to this observation, absence of statistical difference in the motor FIM scores regarding CIRS-G in the group of patients with vascular and respiratory comorbidities after rehabilitation program suggest how effective rehabilitation treatment is, particularly, in these groups. Even after discharge, vascular and respiratory comorbidities persisted regarding CIRS-G, indicating not only positive short-term effects of rehabilitation but the necessity for long-term rehabilitation and follow-up as well.

The positive effects of rehabilitation program are also justified through the analysis of correlation coefficients in our study. We have demonstrated that such values differed with regards to the level of CIRS-G and time of examination. However, higher correlation between different CIRS-G levels and follow-ups for evaluated comorbidities, suggests a necessity for inclusion of the elderly after hip fracture into rehabilitation program. These findings are in accordance with previous reports [15, 16]. The positive long-term effects of rehabilitation analyzed by motor FIM scores in our study are confirmed by higher correlation with CIRS-G levels after discharge. It should be emphasized that variations in correlation levels, particularly in the groups of patients with cardiac and vascular comorbidities, resemble recovery capacities that are influenced by the level of CIRS-G. They are more pronounced in patients with cardiac comorbidities and in those with severe CIRS-G levels. A possible explanation for such findings is that patients with more severe cardiac comorbidities, apart from limitations in the capacity of functional recovery, implement rehabilitation treatment better even after discharge and follow the recommendations for active living more frequently than those with lower CIRS-G levels.

Additionally, we have obtained higher effects at different times of observation regarding different CIRS-G severity levels on FIM scores in all types of evaluated comorbidities. However, variations in these effects were noticed between different comorbidities implicating that a certain level may explain the heterogeneous effects of rehabilitation treatment on functional independence in the elderly after hip fracture with regards to the type of comorbidity.

Conclusion

Different levels and types of comorbidities in the elderly after hip fracture point to the necessity of individual approach to every patient. Rehabilitation treatment of the elderly after hip fracture has a significant role in both short-term and long-term recovery, particularly in functional domains. Therefore, timely inclusion and individually designed rehabilitation programs with continuous monitoring of the elderly after hip fracture results in functional improvement and better quality of life.

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ASSOCIATION BETWEEN INFANT AND YOUNG CHILD FEEDING PATTERNS AND SPEECH AND LANGUAGE DISORDERS

POVEZANOST OBRAZACA HRANJENJA DOJENČADI I DECE UZRASTA OD TRI DO ŠEST GODINA I POREMEĆAJA GOVORA I JEZIKA

Vesela MILANKOV[1], Nada OGNJENOVIĆ[2], Mila VESELINOVIĆ[1] and Vanja VELIČKOVIĆ[1]

Summary

Introduction. Feeding patterns include manners in which a child is fed during infancy and early childhood in order to provide him with appropriate nutrients that will enable his proper growth and development. The purpose of the present study was to determine the association between the dominant feeding patterns in early childhood and the manifestation of speech and language disorders in children aged 3 to 6 years. **Material and Methods.** A cross-sectional study was conducted during 2020 - 2021 and it included 100 children of typical development, aged 3 to 6 years. The research used the Child Development Inventory, as a developmental screening instrument. The questionnaire on feeding patterns was designed for the purpose of this research. For data entry and processing, the Statistical Package for the Social Sciences 20.0 software was used. **Results.** There were no significant differences between the age categories of children in terms of deviations in the development of expressive and receptive speech. Most of the examined children (55%) were bottle-fed, whereas the remaining 45% were breastfed. A significantly higher percentage of bottle-fed children showed a deviation in the development of expressive and receptive speech compared to children who were breastfed for at least the first 6 months (74.5% versus 8.9%). **Conclusion.** Bottle-fed children showed a greater number of deviations in the development of both expressive and receptive speech, compared to breastfed children. Deviations in speech and language development were registered at each examined age, which means that speech and language disorders are not detected and treated in a timely manner.

Key words: Feeding Behavior; Speech Disorders; Language Disorders; Speech-Language Pathology; Breast Feeding; Bottle Feeding; Infant; Child, Preschool

Sažetak

Uvod. Obrasci hranjenja podrazumevaju načine na koje dete može biti hranjeno i koji obezbeđuju za dete odgovarajuće nutritivne elemente koji će omogućiti njegov pravilan rast i razvoj. Cilj istraživanja bio je da utvrdimo povezanost dominantnih obrazaca hranjenja u ranom detinjstvu sa ispoljavanjem poremećaja govora i jezika kod dece u uzrastu od tri do šest godina. **Materijal i metode.** Istraživanje je sprovedeno kao studija preseka tokom 2020/21. godine. Istraživanjem je obuhvaćeno stotinu dece tipičnog razvoja, uzrasta od tri do šest godina. U istraživanju je korišćen instrument *Child Development Inventory* − Inventar dečjeg razvoja. Upitnik o obrascima hranjenja konstruisan je za svrhu ovog istraživanja. Za unos i obradu podataka korišćen je programski paket SPSS 20.0. **Rezultati.** Ne postoje značajne razlike između uzrasnih kategorija dece po pitanju odstupanja u razvijenosti ekspresivnog i receptivnog govora. Najčešći obrazac hranjenja ispitivane dece na ranom uzrastu bio je pomoću flašice, njih 55%, dok je preostalih 45% dece dojeno. Znatno veći procenat dece hranjene pomoću flašice pokazuje odstupanje u razvoju ekspresivnog i receptivnog govora u odnosu na decu koja su dojena minimalno prvih šest meseci (74,5% naspram, 8,9%). **Zaključak.** Deca hranjena na flašicu pokazuju veći broj odstupanja u razvijenosti kako ekspresivnog tako i receptivnog govora, u odnosu na decu koja su dojena. Odstupanja u razvoju govora i jezika registrovana su u svakom ispitivanom uzrastu, što znači da se govorno-jezičke smetnje ne detektuju i ne tretiraju pravovremeno.

Ključne reči: obrasci hranjenja; poremećaji govora; poremećaji jezika; govorno-jezički poremećaji; dojenje; hranjenje na flašicu; odojče; predškolsko dete

Introduction

The most common infant feeding patterns include breastfeeding, bottle feeding, and gastric tube feeding. All feeding patterns should ensure appropriate intake of nutrients that are needed for a child's proper growth and development [1].

Breastfeeding is one of the healthiest and most effective ways to ensure all the essential nutrients that infants and young children need. Certainly, these are not the only benefits associated with breastfeeding, as one of the feeding patterns. In addition to meeting the infant's nutritional needs, it has been associated with mother-infant bonding via the provision of regular intimate interaction between mother and child and stimulation of all senses that improve the child's psychomotor, intellectual and language development [2]. Equally, breastfeeding reduces the severity of respiratory diseases during infancy, otological diseases and gastrointestinal infections, malnutrition and the de-

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Abbreviations
CDI – Child Development Inventory
SD – standard deviation
UNICEF – United Nations Children's Fund

velopment of obesity, while it also affects the overall development of speech and language and motor skills [3–5].

The World Health Organization, pediatricians across the globe, as well as numerous Breastfeeding Associations recommend breastfeeding as the healthiest, easiest, and the least expensive way to feed a baby [6]. Breastfeeding is recommended as the primary method of feeding by 6 months of age due to its long-term benefits for the overall child development, including speech and language development [7].

In maternity hospitals around the world, as well as in our country, newborns are placed directly on their mother's chest immediately after birth to ensure the first contact with the newborn child. Also, it is important to establish an effective breastfeeding technique for newborns including both how mothers should get their babies latched on properly at the breast and find a comfortable position when they are breastfeeding [8].

On the other hand, bottle-feeding is one of the feeding patterns used as breast milk replacement. It requires the use of an artificial nipple, either by bottle or pacifier and formula feeding [9]. Nowadays, the majority of mothers are familiar with both breast and bottle-feeding patterns.

With regard to mouth movements during breastfeeding, the newborns open their mouth wide enough to catch their mother's nipple, while when bottle-feeding, babies do not have to open their mouth wide to latch onto the artificial nipple, or pacifier. During breastfeeding, the baby's top and bottom lips are curled outward, more relaxed and closer to each other. Additionally, breastfeeding and bottle-feeding differ with respect to the infant's jaw movements toward the inside of the mouth. Although a reduction in jaw movements was observed during breastfeeding, the activity of the perioral muscles during breastfeeding is higher than during bottle-feeding. Inadequate muscle tone gradually leads to the disturbed dynamic of muscle balance in the tongue, lips and cheeks. Pacifiers are made of a thicker material and they have different shape than the breast tissue and thus they lead to a non-physiological pressure in the oral cavity and limit the normal growth and development of the palate and occurrence of malocclusion [10, 11]. This type of infant feeding pattern can cause difficulties associated with the dental bite development due to the reduced muscular activity, resulting in altered dentition, as well as increased risk of developing speech and language disorders, with articulation and phonological disorders as the most common. Deviations in speech and language from developmental norms are more common in infants who are bottle-fed due to inadequate stimulation of oral muscles, which is not the case with breastfeeding [12, 13].

In addition, tube feeding is used as an alternative to breastfeeding and bottle feeding. It is often used to feed prematurely born babies, either fed via an orogastric or a nasogastric tube. Preterm babies are often prone to experience feeding difficulties that are related to the coordination of breathing, sucking and swallowing as compared to babies born at term. Correspondingly, premature babies are fed via a feeding tube, thus enabling them to receive adequate nutrition support for their proper growth and development in an alternative way. The use of gastric feeding tubes does not require the activation of speech organs and speech motor areas, leading to delayed stimulation of speech organs and muscle activation [14–16]. A number of s studies have shown that bottle-fed infants have speech difficulties, changes in jaw development, as well as teeth alignment problems and a poor bite. Therefore, this issue has been receiving increased attention in recent years. In addition to more frequent deviations in speech and language development in bottle-fed infants, it was noted that children produce their first words later than breastfed children, often causing delayed or slower speech and language development. It is considered that additional and timely educational supports for parents, especially mothers, is needed, in order to raise awareness of negative aspects and effects on bottle feeding [17–19].

The effects of different feeding patterns are factors that can contribute to a child's speech and language development, as well as a child's ability to speak properly, but also to deviations in speech that require appropriate intervention by speech and language specialists. Moreover, breastfeeding has been shown to be a protective factor for proper speech and language development, as well as the overall development of children [1, 16, 20–23].

The purpose of the present study was to determine the relationship between dominant feeding patterns and speech and language disorders diagnosed in children aged 3 to 6 years. We hypothesized that children, who were breastfed until at least 6 months of age, had a lower incidence of speech and language disorders.

Material and Methods

The research was conducted as a cross-sectional study in 2020 - 2021 in kindergartens within the Primary School "Braća Novakov" in Silbaš, Despotovo and Parage, which are the surrounding villages of the municipality of Bačka Palanka.

The research included 100 typically developing children, aged between 3 and 6 years. Inclusion criteria for participation in the present study were parent or guardian informed consent, children aged from 3 to 6 years without developmental disabilities. As for the breastfeeding pattern, infants were breastfed for at least the first 6 months. Only children whose parents signed the consent for their child's research participation were included in the sample. Thereupon, the research was approved by the Ethics Committee of the Faculty of Medicine in Novi Sad.

After obtaining a written consent from a school principal, the parents were given participant information sheets and consent forms. Then, the parents were given questionnaires with detailed instructions on how to fill them out. The average time required to fill out the questionnaire was about 20 minutes.

The Child Development Inventory (CDI), created by Dr. Harold Ireton in 1992, was used as a developmental screening instrument in this research [24]. The CDI is a standardized screening tool with high sensitivity (over 80%) while the validity of the test was confirmed by a sample of 1278 children aged 15 to 72 months in France. The CDI is a screening instrument comprising eight domains of child development and the General Development Scale. The instrument consists of 270 items that describe child's behavior from 15 to 72 months of age. The questionnaire is easy to use and does not require much time to complete. Parents complete the test by circling YES/NO next to each statement. The subscales found in this questionnaire measure the child's present development in eight areas: social, self-help, gross motor, fine motor, expressive language, language comprehension, letters, and numbers. The General Development Scale summarizes achievements on 8 subscales. For the purpose of the present research, two subscales were used for testing expressive and receptive language. The expressive language subscale contains 50 questions ranging from a simple gesture to a complex language structure, short story retelling, past and future events, proper use of grammar forms such as tenses. On the other hand, the receptive language subscale comprises 50 questions and describes language comprehension including items that range from understanding simple orders (responding to name, showing age-related body parts) to multi-level orders [24].

When scoring the test, only the YES response options were collected for each scale. Following the instructions given in the manual, the child's age-related development was calculated for each area. Children whose performance was 2 standard deviations (SDs) below the mean in at least one area of development were eligible for early intervention services due to developmental delay.

The Feeding Practices Questionnaire was developed for the purpose of this research. It was designed for parents or guardians in order to gather information about their children's feeding patterns, the manner in which the child was fed, the age at which solid foods were introduced, as well as the age at which the child spoke his first words.

The Statistical Package for the Social Sciences 20.0 software was used for data entry and processing. For the purpose of structural and descriptive analysis of the sample according to the relevant variables, frequency distribution and percentages were used, in order to show the representation of a certain category or response. The characteristics of the numerical data were processed using standard procedures of descriptive and comparative statistics for the analysis of numerical features. As part of descriptive statistics, data are presented in the form of arithmetic mean, SD, as well as frequency and percentage. In the context of comparative statistics, the Pearson's coefficient of linear correlation and chi-square test were used. In the tests applied, the threshold probability (p) value corresponded to the significance level of 95% ($p < 0.05$) and 99% ($p < 0.01$).

Results

The sample included 100 respondents, 43% of girls and 57% of boys aged from 3 to 6 years. As shown in **Table 1**, 20% of children were from 3 to 4 years of age, 25% were 5 years of age, while a slightly higher number of respondents were in the age category of 6 years (35%). The age range included children between 36 and 72 months with a mean age of

Table 1. Socio-demographic characteristics of the tested sample
Tabela 1. *Socio-demografske karakteristike ispitivanog uzorka*

Age/*Uzrast*	Categories (n/*br.*, %)/*Kategorije*
3 years/*3 godine*	20 (20%)
4 years/*4 godine*	20 (20%)
5 years/*5 godina*	25 (25%)
6 years/*6 godina*	35 (35%)
Age range/*Raspon*	36 - 72 months/*meseci*
Mean Age (months)/*Prosečna starost (meseci)*	60.6 (12.9%)
Gender (n/*br.*, %)/*Pol*	
Boys/*Dečaci*	57 (57%)
Girls/*Devojčice*	43 (43%)
Parents' level of education/*Stručna sprema roditelja*	
Primary school/*Osnovna škola*	27 (27%)
Secondary school/*Srednja škola*	55 (55%)
College of Vocational Education/*Visoka strukovna škola*	9 (9%)
Higher Education/*Visoka škola*	9 (9%)

Table 2. Differences in the expressive language development with regard to the age
Tabela 2*. Razlike u razvijenosti ekspresivnog govora u odnosu na uzrast*

	Age/*Uzrast*				
Expressive language skills *Ekspresivni govor*	3 Years/*Godine*	4 Years/*Godine*	5 Years/*Godina*	6 Years/*Godina*	χ^2 p/*p*
There are no deviations *Nema odstupanja*	9 (45%)	11 (55%)	17 (68%)	18 (51.4%)	2.696 df = 3
There are deviations *Ima odstupanja*	11 (55%)	9 (45%)	8 (32%)	17 (48.6%)	p = 0.441

Table 3. Differences in the development of receptive speech with regard to the age
Tabela 3. *Razlike u razvijenosti receptivnog govora u odnosu na uzrast*

	Age/Uzrast				
Receptive speech *Receptivni govor*	3 Years/*Godine*	4 Years/*Godine*	5 Years/*Godina*	6 Years/*Godina*	χ^2 p/*p*
There are no deviations *Nema odstupanja*	13 (65%)	14 (70%)	19 (76%)	29 (82.9%)	2.499 df = 3
There are deviations *Ima odstupanja*	7 (35%)	6 (30%)	6 (24%)	6 (17.1%)	p = 0.475

Table 4. The significance of correlation coefficients
Tabela 4. *Koeficijenti korelacije i nivo značajnosti*

	Age/*Uzrast*
Expressive language skills/*Ekspresivni govor*	-0.066
(p/*p*)	0.515
Receptive speech/*Receptivni govor*	-0.139
(p/*p*)	0.168

60.6 (12.9%) months. As for the parents' educational level **(Table 1)**, the largest percentage of parents had a secondary education (55%), while the next most frequent were parents with a primary education. In the examined sample, 18% of parents had a degree in vocational college and higher education.

Using the χ^2 test, the association between the speech and language disorders and belonging to the same age-group was assessed. The results are shown in **Tables 2** and **3**.

As shown in **Table 2**, using the χ^2 test, no statistically significant differences were found between different age groups (3, 4, 5 and 6 years), in terms of deviations in the development of receptive speech.

As it can be seen in **Table 3**, by using the χ^2 test, no statistically significant differences were found between different age groups of children in terms of receptive speech.

Using the Pearson's correlation coefficient, the linear relationship between children's age in months and presence of speech and language disorders was assessed. The results are shown in **Table 4**.

As shown in **Table 4**, assessing the association between children's age and speech and language disorders, there is no evidence of a statistically significant relationship between children's age and the expressive speech development, as well as between the children's age and the development of receptive speech.

With respect to the correlation of feeding frequency for breastfed and bottle-fed children by the time they are 6 months old, a slightly higher percentage (55%) of examined children were botte-fed compared to those who were breastfed (45%).

Using the χ^2 test, the relationship between different feeding patterns and the presence of speech-language disorders was assesed. The results are shown in **Tables 5** and **6**.

The results of the χ^2 test showed that there was a significant relationship between feeding patterns and expressive language development at $\chi^2 = 43.11$; $p < 0.001$. It can be seen that a significantly higher percentage of bottle-fed children showed a deviation in the development of expressive speech compared to children who were breastfed for at least the first 6 months (74.5% vs. 8.9%) **(Table 5)**. In other words, 91.1% of breastfed children showed no disorders in the domain of expressive language, i.e., language production, compared to 25.5% of children who were bottle-fed.

As seen in **Table 6**, the results of the χ^2 test showed a significant relationship between feeding patterns and receptive language development at $\chi^2 = 22.64$; $p < 0.001$. It can be noticed that a higher percentage of bottle-fed children showed deviations in the development of receptive language skills, i.e., deviations in speech comprehension, compared to breastfed children (43.6% vs. 2.2%). In other words,

Table 5. The association between feeding patterns and the development of expressive language
Tabela 5. *Povezanost obrazaca hranjenja i razvijenosti ekspresivnog govora*

Feeding pattern/*Obrasci hranjenja*			
	Breast feeding *Dojenje*	Bottle feeding *Hranjenje pomoću flašice*	χ^2 p/*p*
Expressive language/*Espresivni govor*			43.108
There are no deviations/*Nema odstupanja*	41 (91.1%)	14 (25.5%)	df = 1
There are deviations/*Ima odstupanja*	4 (8.9%)	41 (74.5%)	p < 0.001

Table 6. The association between feeding patterns and the development of receptive language skills
Tabela 6. *Povezanost obrazaca hranjenja i razvijenosti receptivnog govora*

Feeding pattern/*Obrasci hranjenja*			
	Breast feeding *Dojenje*	Bottle feeding *Hranjenje pomoću flašice*	χ^2 p/*p*
Receptive language/*Receptivni govor*			22.640
There are no deviations/*Nema odstupanja*	44 (97.8%)	31 (56.4%)	Df = 1
There are deviations/*Ima odstupanja*	1 (2.2%)	24 (43.6%)	p < 0.001

97.8% of children who were breastfed until they were 6 months old did not show disorders in the domain of receptive language skills compared to 56.4% of children who were bottle-fed.

Discussion

The World Health Organization, United Nations Children's Fund (UNICEF), pediatricians throughout the world, as well as numerous associations recommend guidelines on breastfeeding as the healthiest, most appropriate feeding option available, and the least expensive due to its stimulating and protective effect on the overall child's growth and development [7]. Statistics show that the percentage of breastfed children has increased and that in 2000, 36% of children were breastfed, and in 2015, as many as 43%. In 1997, Sweden ranked highest with 97% (26.27) of infants who were breastfed until 6 months of age [25, 26].

A study by Asara et al. [27] indicates a high percentage of breastfeeding as a feeding pattern (77.3%), while the percentage of bottle-fed children was 22.7%. A study conducted in Mexico showed that the percentage of breastfeeding as a feeding pattern until 6 months of age accounted for 31%, while the percentage of adapted formula-fed infants in the same age group was 69%. In Indonesia, the percentage of breastfed infants was 42%, while 58% of infants were bottle-fed [28].

The UNICEF data show that there are only 13% of women in Serbia who breastfeed their children until 6 months of age, which is a small percentage, thus requiring interventions to increase their awareness of the benefits of breastfeeding [25].

The research data that have been obtained for the purpose of this study show that 45% of infants are breastfed compared to those bottle-fed, which is slightly higher and amounts to 55%. These data are in-line with the findings of other studies [28, 29], which suggests that the percentage of breastfed children is lower compared to the percentage of bottle-fed children. There are different reasons why women choose bottle-feeding instead of breastfeeding. The most frequently cited reasons to stop breastfeeding in the study conducted in the United Kingdom were related to the fact that many mothers experience discomfort or pain or they do not see benefits of breastfeeding as a feeding practice. As stated in the previous research, one of the benefits of bottle feeding arises from the fact that in this way other family members are more likely to be actively involved in feeding babies and bonding experience, as well as that mothers have the opportunity to be away from home longer and return to work before the end of their maternity leave [6]. Results of a longitudinal study that followed the impact of breastfeeding on a number of areas of children's development, from birth to the age of three, showed that in terms of language development breastfeeding reduces the risk of speech disorders by 50 – 60% compared to children who are being fed otherwise [30]. As pointed out earlier, different feeding patterns can also affect early speech and language development in children [15, 16, 20, 22, 23].

In our research, we identified speech and language disorders among children 3 to 6 years of age. The obtained data indicate that there is no statistically significant difference between different age categories in relation to the presence of deviations both in speech production and speech-language comprehension. As already shown in studies by Campbell et al. and Schriber et al. [31, 32] the prevalence of speech and language disorders in children varies with their age. It is increasing from 15 – 16% at the age of 3, while decreasing to 4% at the age of 6 years. A smaller percentage of speech and language disorders in children aged 6 is explained by timely detection of the child with speech delay and early onset of speech and language therapy at the youngest possible age.

Our results are not in line with previous research findings, indicating that there is no difference in deviations in speech-language development based on ages and thus speech and language disorders can be found at any age. Hence, we can assume that children from the examined groups were not referred for assessment in a timely manner for speech and language disorders. In a research [13, 15, 16, 19, 20] examining the impact of different feeding patterns on children's speech and language development, the assessment of the effects of breastfeeding and bottle feeding was carried out; the results suggest that a larger number of deviations in speech and language development have been found in bottle-fed than in breastfed children. Breastfed children scored higher on tests that assessed speech comprehension, the number of words produced correctly and better articulation of sounds compared to bottle-fed children. The research confirms and suggests protective effects of breastfeeding on the overall child development [20].

Given that a significantly higher percentage of bottle-fed children demonstrated deviations precisely in these areas of speech-language development, our research findings are in line with the data provided by these authors.

Therefore, we investigated speech and language development through expressive language development acquisition, i.e., speech production skills. The data we obtained indicate that as many as 74.5% of bottle-fed infants show deviations in speech production compared to 8.9% of breastfed infants. A research by Vieira et al. [33] indicates that bottle-fed children do not show statistically significant deviations in speech production, although bottle-feeding contributes to the reduction of orofacial region muscles, which significantly affects the occurrence of articulation disorders. Further Brisque Neiva et al. [34] suggest that deviations in expressive language, i.e., language production, are lower if the child is breastfed due to effects of stimulation to the motility of oral cavity. Accordingly, Barbosa [16] in her research examined the influence of bottle feeding and breastfeeding as a feeding pattern on the development of expressive speech. Out of a total of 128 children, 42.6% of bottle-fed children showed deviations in expressive speech, and the study revealed that among the barriers cited were the inactivation of oral muscles, poor and altered dentition, as well as changes in dental bite that were recorded during the study [12, 34].

In our research, we have also assessed the influence of breastfeeding and bottle feeding on the development of receptive language skills, i.e., language comprehension in children. The data that we obtained are in favor of the fact that bottle-fed children, in 43.6% of cases show a deviation in the development of receptive speech compared to children who are breastfed [2.2%]. In both cases, the development of expressive and receptive speech showed greater deviations from developmental norms in bottle-fed children, therefore we can conclude that the assumption we made at the very start of the present study proved to be true.

Conclusion

A large number of studies have confirmed that disorders in children's speech and language development have a number of possible causes and infant feeding patterns have been reported as one of the possible causes.

Deviations in speech and language development were registered within every age group of the sample, which means that a number of speech and language disorders were not detected and treated in a timely manner.

The incidence in deviations of expressive and receptive speech is higher in bottle-fed children as compared to breastfed children.

The present study underlines the need for further more detailed research in order to determine specific deviations in children's speech and language development as early as possible by using more precise instruments and screening tests, and thus comparing the effects of different feeding patterns on the test achievements.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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GROVER'S DISEASE IN A PATIENT WITH ATOPIC DERMATITIS – A CASE REPORT

GROVEROVA BOLEST KOD PACIJENTA SA ATOPIJSKIM DERMATITISOM – PRIKAZ SLUČAJA

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Summary

Introduction. Grover's disease is characterized by pruriginous polymorphic rash with a variable course and duration. Although the etiology is still unknown, the disease is often associated with other dermatoses, malignant diseases, use of certain medications, as well as immunosuppression. **Case Report.** We report a case of a 70-year-old male patient who was referred for examination to the Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, due to a rash that lasted for nine months. The first lesions on the skin appeared around the nipples as exudative eczematous plaques. A few months later, identical lesions appeared on the lower legs. During treatment with systemic antihistamines and topical corticosteroids, there were episodes of transient improvements and re-exacerbations. In the meantime, erythematous brownish, round and oval papules appeared on the abdomen and the back, accompanied by intense itch. Laboratory findings revealed eosinophilia and elevated serum immunoglobulin E levels. A skin biopsy of the back lesion was performed and the histopathological examination confirmed the diagnosis of Grover's disease. After the systemic treatment using corticosteroids and antihistamines, with gradual dose reduction and application of topical corticosteroids and emollients, complete regression of the skin lesions was achieved. **Conclusion.** Since the clinical manifestations of the disease may be nonspecific and discrete, dermatopathological analysis is of crucial importance in making the correct diagnosis. In patients with atopy, the treatment with systemic corticosteroids, antihistamines and topical agents may lead to regression of skin lesions with a significant improvement in the quality of life.

Key words: Dermatitis, Atopic; Acantholysis; Skin Diseases; Signs and Symptoms; Diagnosis; Morphological and Microscopic Findings; Glucocorticoids; Histamine Antagonists

Sažetak

Uvod. Groverovu bolest karakteriše pojava polimorfne pruriginozne ospe različitog toka i dužine trajanja. Iako nepoznate etiologije, bolest može često biti udružena sa drugim dermatozama, malignitetima, primenom određenih lekova, kao i kod imunosuprimiranih bolesnika. **Prikaz slučaja.** Prikazujemo pacijenta starosti 70 godina koji se javio na pregled na Kliniku za kožno-venerične bolesti Kliničkog centra Vojvodine, zbog ospe koja je trajala devet meseci. Prve promene na koži javile su se u predelu oko mamila u vidu ekcematoidnih plakova sa vlaženjem. Nekoliko meseci kasnije javili su se identični plakovi i na potkolenicama. Tokom lečenja sistemskim antihistaminicima i lokalno kortikosteroidima, dolazilo je do prolaznog poboljšanja i ponovne egzacerbacije. U međuvremenu su se javile promene u vidu eritematozno-braonkastih okruglih i ovalnih papula na koži leđa i prednjeg trbušnog zida koje su bile praćene intenzivnim osećajem svraba. Laboratorijski nalazi su pokazali prisustvo eozinofilije i povišenih vrednosti serumskih imunoglobulina E. Urađena je biopsija promene na koži leđa i histopatološkom analizom je potvrđena dijagnoza Groverove bolesti. Nakon sprovedene sistemske terapije kortikosteroidima i antihistaminicima sa postepenim snižavanjem doze, uz aplikaciju topikalnih kortikosteroida i emolijenasa, postignuta je potpuna regresija promena na koži. **Zaključak.** S obzirom na to da klinička manifestacija bolesti može biti nespecifična i diskretna, dermatopatološka analiza je od posebnog značaja u pravilnom postavljanju dijagnoze. Kod pacijenata sa atopijom, sprovođenje sistemske terapije kortikosteriodima i antihistaminicima, uz primenu lokalne terapije, može dovesti do regresije kožnih promena uz značajno poboljšanje kvaliteta života.

Ključne reči: atopijski dermatitis; akantoliza; kožne bolesti; znaci i simptomi; dijagnoza; morfološki i mikroskopski nalazi; kortikosteroidi; antihistaminici

Introduction

Grover's disease is a benign dermatosis of unknown etiology with a variable duration. It is characterized by polymorphous papulovesicular rash followed by intense itch. The disease is predominantly seen in Caucasian middle-aged men. Although it may be self-limiting, in some cases treatment is necessary, with varying degrees of success, especially in patients suffering from other derma-

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toses or in transplant and immunosuppressed patients [1–4].

The aim of this paper was to emphasize the importance of proper diagnosis of Grover's disease, as well as to indicate the possibility of its association with atopy, which may lead to certain therapeutic challenges.

Case Report

We present a 70-year-old male patient who was referred for examination to the Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, due to a pruriginous rash that lasted for nine months. The medical history data showed that the first skin lesions appeared on the chest bilaterally, and a few months later identical plaques appeared on the lower legs as well. During the treatment with systemic antihistamines and topical corticosteroids, there were episodes of transient improvement followed by exacerbations. After the skin lesions spread to the abdomen and the back, accompanied by intense itch, the patient was referred to our clinic. At the time of admission, the patient was afebrile, in a good general condition, with noticeable eczematous exudative plaques in the perimammilar region and on the lower legs, with erythematous-brownish round and oval papules on the skin of the abdomen and the back **(Figures 1 and 2)**. Laboratory findings revealed eosinophilia (11.5%) and elevated serum immunoglobulin E levels, while the inflammatory and biochemical parameters were within the reference range. The mycological and microbiological analysis of the affected perimammilar skin was negative. Having revised previous histopathological biopsy findings of the perimammilar area, a nonspecific chronic dermatitis was described, while Paget's disease was excluded. Due to inconclusive findings, another skin biopsy of the skin lesion on the back was performed. The dermatopathological analysis confirmed the diagnosis of Grover's disease. There was an epidermis of uneven thickness with diffuse hyperkeratosis and focal parakeratosis, with irregularly elongated rete ridges. A perivascular patchy focally denser inflammatory infiltrate composed of lymphocytes and a smaller number of eosinophilic granulocytes was visible in the upper dermis. The infiltrate partially invaded the epidermis with focal acantholysis and spongiosis. Skin adnexa were reduced, atrophic in appearance, while sweat glands had proper features **(Figure 3)**.

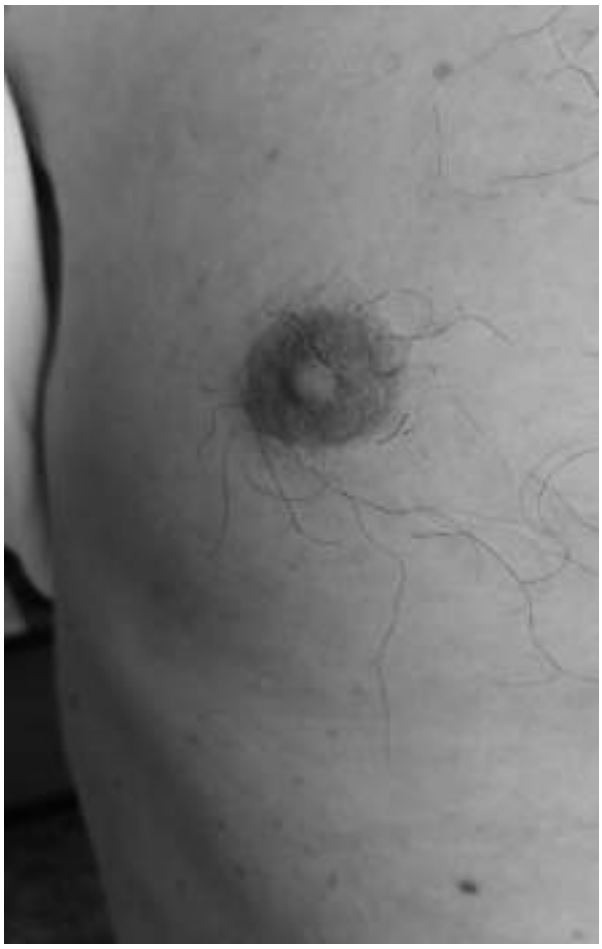

Figure 1. Erythematous-brownish round and oval papules on the trunk
Slika 1. *Eritematozno-braonkaste, okrugle i ovalne papule na trupu*

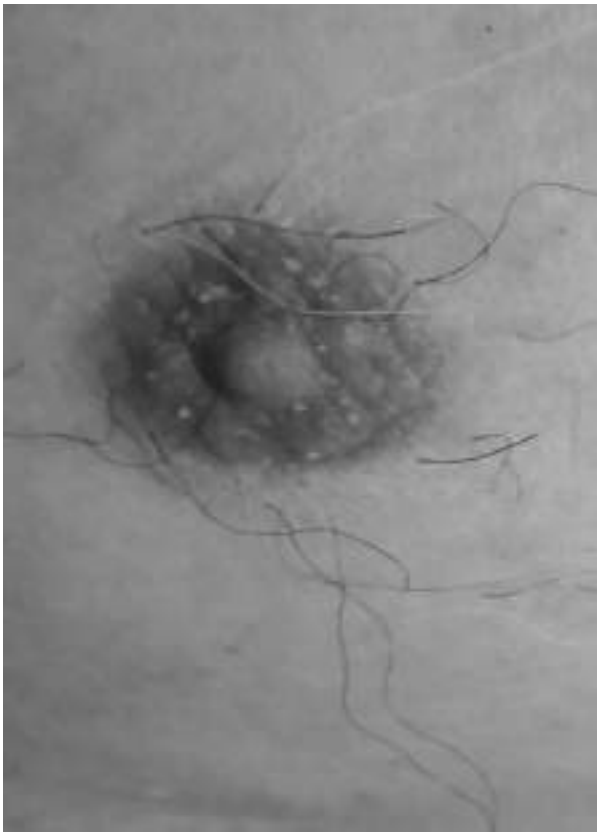

Figure 2. Exudative eczematous plaques in the perimammilar area
Slika 2. *Ekcematoidni plakovi sa eksudacijom perimamilarno*

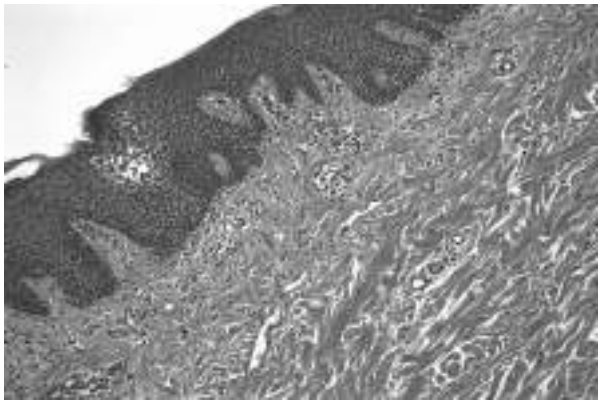

Figure 3. Grover's disease: There are a few acantholytic cells surrounded by focal spongiosis. The infiltrate composed of lymphocytes and eosinophils is visible in the upper dermis
Slika 3. *Groverova bolest: Prisutno je nekoliko akantolitičnih ćelija okruženih fokalnom spongiozom. U gornjem dermisu vidljiv je infiltrat koji se sastoji od limfocita i eozinofila*

The patient complained about skin dryness and itching. He presented with pruritic erythematous plaques on the eyelids, in cubital and popliteal regions, that indicated atopic dermatitis. A standard inhalant allergy test was done and sensitization to grass pollen was determined, which confirmed the atopic constitution in our patient. Considering long duration of skin lesions and unsatisfactory response to topical therapy, a systemic therapy with levocetirizine and methylprednisolone at a dose of 40 mg with gradual dose reduction was administered. Additionally, a fluocinolone acetonide ointment was used twice a day, as well as appropriate skin care with emollients. After finishing the treatment, a complete regression of skin lesions was achieved.

Discussion

The disease was first described in 1970 by Grover who reported about six patients with a nonspecific papulovesicular rash with histological features similar to Darier's disease as well as Hailey-Hailey disease, but the clinical manifestations indicated a separate entity [5]. After that, Chalet gave a more detailed presentation of the clinical picture and potential four types of acantholysis: Darier-like, pemphigus-like, spongiotic and Hailey-Hailey-like, which has been confirmed in recent publications. Fernandez-Figueras et al. reported an extended description of the histological findings of this dermatosis. Based on the fact that Grover's disease is histologically characterized by acantholysis, which is often associated with visible dyskeratosis and eczematous lesions as in our patient, these authors identified other possible histological patterns such as porokeratotic, lentiginous, vesicular, lichenoid and dysmaturative. Moreover, they also pointed to the appearance of neutrophil granulocytes in dermal infiltrates, apart from lymphocytes and eosinophils. According to this study, a vascular degeneration in the form of endothelial tumefaction due to cytoplasmic edema and erythrocyte extravasation can often be found [6]. Other researchers showed that early histological lesions in Grover's disease are represented by elongation of rete ridges, mild focal acantholysis and occurrence of eosinophils, which can be helpful in dermatopathological analysis of discrete nonspecific lesions if the clinical correlation is feasible [7].

The etiology is still unknown. Triggering factors such as increased sweating, heat and sun exposure were described, which would indicate that the disease has a seasonal character and occurs more often in summer, but according to other authors, Grover's disease appears more frequently in winter months because of skin dryness and impaired epidermal integrity [1–4, 8]. A potential mechanism for the development of skin lesions could be damage to the epidermis by the toxic effects of sweat uric acid after occlusion of the gland ducts, although this has not been completely proven [1, 4]. Furthermore, Phillips et al. examined the autoimmune mechanism of Grover's disease, but even this study did not provide a clear insight into the etiology of the disease [9].

Although it was originally regarded as a transient acantholytic dermatosis, a more appropriate term would be just Grover's disease, on the account of the fact that it has a variable course and duration. Quirk and Heenan defined three variants of the disease: transient eruptive with a sudden onset of pruriginous rash that recedes within a few weeks; persistent pruritic with a slightly less pronounced itch than in the previous variant, but with a prolonged duration and poor response to the therapy; and a chronic asymptomatic with persistent papules on the trunk and in the submammary region mimicking folliculitis that cannot be histologically confirmed [10]. Skin lesions are typically polymorphous in the form of papulovesicles or smooth light erythematous or brownish papules, with crusts or keratotic surface, in nummular, herpetiform or zosteriform distribution or may confluent into plaques [4]. The skin lesions mainly affect the trunk and the back, upper extremities and thighs, but may also have an atypical extensive presentation especially in patients suffering from malignancy, during the course of oncologic treatment or in transplants [11–20]. Given that Grover's disease has been shown to be associated with hematological or visceral malignancies, it is of the utmost importance to examine the patient in that direction as well [4].

From the dermatological point of view, in relation to Grover's disease, folliculitis, miliaria, dermatitis herpetiformis, insect stings, herpes viral infections, benign familiar pemphigus (Hailey-Hailey disease), pemphigus foliaceus and pemphigus vulgaris, Darier's disease as well as Galli-Galli disease should be considered in the differential diagnosis [1–4]. In accordance with the literature data reporting cases of coexistence of Grover's disease and pemphigus foliaceus, as well as pityriasis rubra pilaris-like Grover's disease, a thorough dermatopathological analysis is crucial in making an accurate diagnosis [21–23]. Furthermore,

recent literature data have revealed that Grover's disease may occur in patients with COVID-19 disease, but it is still unknown what the exact role of a new coronavirus is in the etiology of Grover's disease [24]. In our case report, it is of special significance to point to the possibility of association of Grover's disease and atopic dermatitis, which is consistent with the literature data [25, 26]. Our patient had eosinophilia, elevated serum immunoglobulin E levels of 700 IU/ml and pruritic erythematous plaques on the eyelids, in cubital and popliteal region with a marked skin xerosis of the whole body. The standard allergy test to inhalant allergens confirmed the sensitization to grass pollen, and with all previously mentioned, it indicated an atopic constitution in our patient.

In patients suffering from both atopy and Grover's disease, the treatment can be particularly challenging. Apart from avoidance of provoking factors and skin care with emollients, topical corticosteroids such as triamcinolone acetonide or fluticasone propionate applied twice daily, are recommended as first line therapy [27, 28]. In resistant cases, instead of topical corticosteroids, application of D vitamin analogues can be beneficial due to anti-inflammatory effects and impact on keratinization. Persistent forms may have a satisfying response to low doses of systemic retinoids or corticosteroids, regardless of the topical therapy. It has also been shown that phototherapy may be beneficial in cases with a severe clinical form. Novel studies highlight subcutaneous administration of etanercept, tumor necrosis-alpha blocker, in achieving a complete resolution while pointing at the same time to the potential mechanism of the disease, as well as a potential of photodynamic therapy with aminolevulinic acid in chronic cases. In addition to all of the above, the use of systemic antihistamines is highly recommended in order to relieve itching [28].

Conclusion

Grover's disease is a relatively common skin disorder that is often unrecognized. Given that the clinical picture may be nonspecific and discrete, a dermatopathological analysis is of utmost importance in making the correct diagnosis and exclusion of other acantholytic dermatoses. Although of unknown etiology, Grover's disease may often occur in patients with skin xerosis and atopic dermatitis, which may result in a prolonged treatment with systemic corticosteroids and antihistamines.

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ULTRASONOGRAPHIC FINDINGS OF EPIDIDYMAL TORSION IN ADULTS – A RARE CAUSE OF ACUTE SCROTUM

ULTRAZVUČNI NALAZ TORZIJE EPIDIDIMISA KOD ODRASLIH – REDAK UZROK AKUTNOG SKROTUMA

Daniela DONAT[1], Slobodan TORBICA[1, 3], Sandra TRIVUNIĆ DAJKO[2, 3] and Viktor TILL[1, 3]

Summary

Introduction. Epididymal torsion is a rare cause of acute scrotum. Only a few cases have been described in the literature, and preoperative ultrasound diagnosis was done only in two cases. So far, according to our data, cases of epididymal torsion in adults have not previously been reported in the literature. **Case Report.** We report the case of a 39-year-old man, who was admitted to the hospital for pain in the left hemiscrotum lasting for three days. The physical examination revealed a swelling limited to the left hemiscrotum, so the patient was referred for an ultrasound examination with the diagnosis of epididymitis. The ultrasonography showed that the left epididymis was significantly enlarged in the head area with and heterogeneous structure of the parenchyma on a gray-scale, without a significant Color Doppler signal. At the level of the neck and the body of the epididymis, there was a "whirlpool sign" with a reactive hydrocele and edema of the left scrotum soft tissue that was highly suspicious for torsion of the epididymis. The patient underwent emergency surgery and epididymal torsion of about 540 degrees was confirmed intraoperatively. **Conclusion.** The torsion of the epididymis should be kept in mind in the differential diagnosis of acute scrotal pain in adults.

Key words: Ultrasonography; Ultrasonography, Doppler, Color; Scrotum; Epididymis; Torsion Abnormality; Adult; Acute Pain; Signs and Symptoms; Genital Diseases, Male

Sažetak

Uvod. Torzija epididimisa je vrlo redak uzrok akutnog skrotuma. Samo je nekoliko slučajeva torzije epididimisa opisano u literaturi, a samo dva slučaja imaju preoperativnu ultrazvučnu dijagnozu. Do sada, u literaturi prema našim podacima nije opisana torzija epididimisa kod odraslih. **Prikaz slučaja.** Predstavljamo slučaj 39-godišnjeg muškarca koji je primljen u bolnicu zbog bolova u levom hemiskrotumu, koji traju tri dana. Na fizikalnom pregledu otkriven je otok ograničen na levi hemiskrotum, pa je pacijent upućen na ultrazvučni pregled sa dijagnozom epididimitisa. Ultrasonografski levi epididimis je značajno uvećan u predelu glave i heterogene strukture parenhima na sivoj skali, bez signifikantnog kolor dopler signala. Na prelasku vrata u telo epididimisa videli smo znak „vrtloga" sa reaktivnom hidrokelom i edemom mekog tkiva levog skrotuma, što je bilo visoko suspektno za torziju epididimisa. Pacijent je odmah operisan i intraoperativno je potvrđeno postojanje torzije epididimisa za oko 540 stepeni. **Zaključak.** Torziju epididimisa treba imati na umu u diferencijalnoj dijagnozi akutnog skrotuma kod odraslih.

Ključne reči: ultrasonografija; kolor dopler sonografija; skrotum; epididimis; torzija; odrasli; akutni bol; znaci i simptomi; muška genitalna oboljenja

Introduction

Epididymal torsion is a rare cause of acute scrotum. Only a few cases have been described in the literature and preoperative ultrasound diagnosis was made only in two cases. So far, cases of torsion of the epididymis in adults have not previously been reported in the literature.

Case Report

We report the case of a 39-year-old man, who was admitted to the hospital due to intense pain and swelling of the left hemiscrotum. The pain started 72 hours before admission and was increasing in severity. In his medical history, the patient denied earlier testicular problems. The physical examination revealed a swelling limited to the left hemiscrotum and scrotal skin erythema. The right hemiscrotum was normal on physical examination. The patient was referred for an ultrasound examination with the diagnosis of epididymitis. The ultrasonography showed a significantly enlarged left epididymis in the head area with spermatocele **(Figure 1)**, 4 x 3 cm in diameter and heterogeneous structure on gray-scale without significant Color Doppler signal **(Figure 2)**. At the level of the neck and the body of the epididymis, there was a "whirlpool sign" **(Figure 3)** with a reactive hydrocele and edema of the left scrotum soft tissue that was highly suspi-

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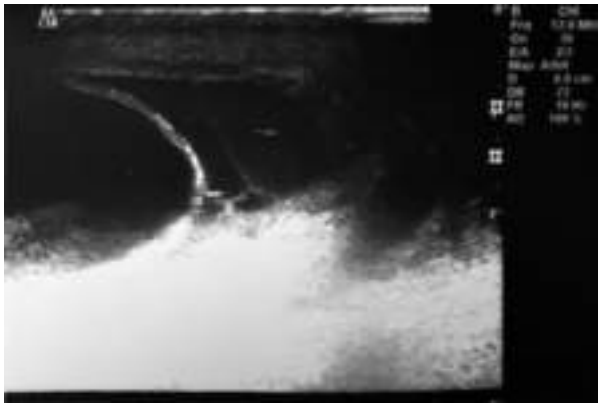

Figure 1. Reactive spermatocele
Slika 1. *Reaktivna spermatokela*

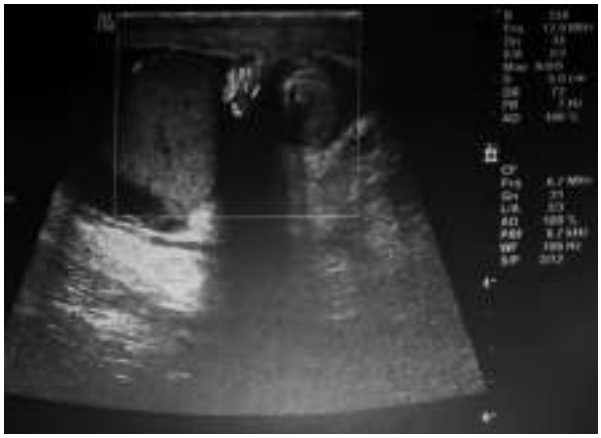

Figure 2. Epididymal head heterogeneous echogenicity on gray-scale without color Doppler signal
Slika 2. *Heterogena tekstura glave epididimisa na sivoj skali bez prisustva kolor dopler signala*

cious for torsion of the epididymis. Also, edema of the left scrotal soft tissue was noticed **(Figure 4)**. The left testicle had a normal echo-structure, and the right scrotum was normal. The patient underwent emergency surgery and epididymal torsion of about 540

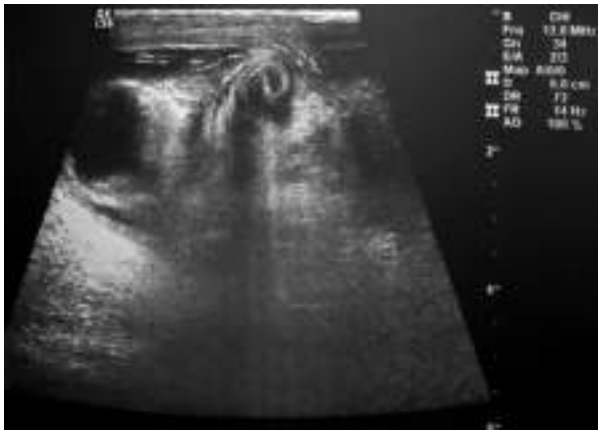

Figure 3. "Whirpool sign"
Slika 3. *Znak vrtloga*

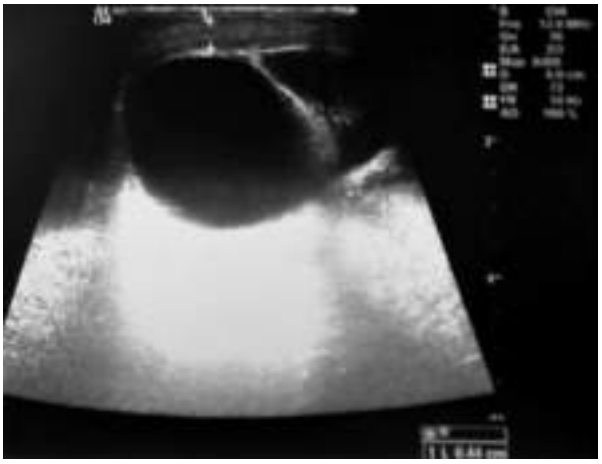

Figure 4. Scrotal soft tissue edema
Slika 4. *Otok skrotalne vreće*

degrees was confirmed intraoperatively. The removed part of epididymal head was sent for histopathologic analysis which confirmed hemorrhagic infarction of the resected epididymis **(Figure 5)**.

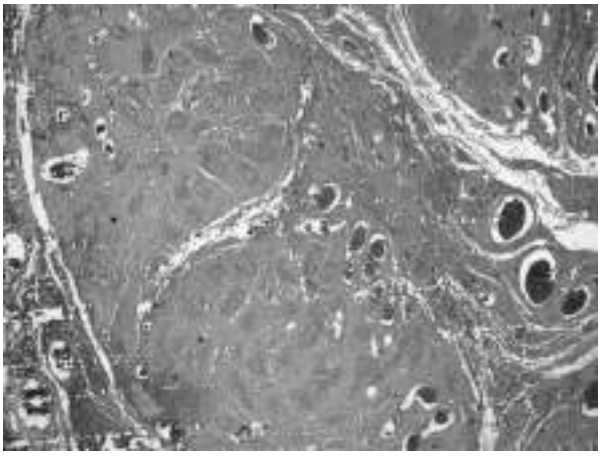

Figure 5. Hemorrhagic infarction of epididymis, histopathological finding (standard hematoxylin-eosin staining, magnification x 2.5)
Slika 5. *Hemoragična infarkcija epididdimisa, patohistološki nalaz (standardno* ***hematoksilin-eozin bojenje, uveličanje x 2,5)***

Discussion

Isolated torsion of the epididymal head is an uncommon cause of acute scrotal pain [1–6]. The most frequently used diagnostic techniques in patients with acute scrotum include B mode ultrasonography imaging and color Doppler with point spectral analysis of the intratesticular waveforms; they showed extremely high sensitivity in the diagnosis of testicular and epididymal torsion as well as in the differential diagnosis of torsion and acute inflammatory conditions. The diagnosis of epididymal torsion is based on the detection of echotexture abnormalities of the involved epidi-

dymis as well as on demonstration of absence of flow. In our patient, ultrasonographic findings included a normal testis with normal vascular signals and a markedly enlarged, heterogeneous epididymal head with a "whirlpool sign". The shape of the vessels at the epididymal head suggested a twist. Changes detected on ultrasonography were confirmed at surgery when isolated torsion of the epididymal head was diagnosed. Abnormal attachment of the epididymis is rare in patients with normally descended testicles [2]. In a surgical series, the epididymis was found either completely attached to the testis or attached at the level of the body and tail in 96.4% of cases, whereas attachment only at the level of head was seen in 2.7%, and nonfusion was seen in 0.9%; furthermore, attachment at the level of the epididymal head or at the tail only was found in 2.4% of cases in a group of fetuses who died from causes unrelated to the genital tract [3].

Conclusion

The isolated torsion of the epididymis should be kept in mind in the differential diagnosis of acute scrotal pain in adults.

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INFLAMMATORY MYOFIBROBLASTIC TUMOR OF THE URINARY BLADDER: TREATMENT AND A TWO-YEAR MONITORING – CASE REPORT

INFLAMATORNI MIOFIBROBLASTNI TUMOR MOKRAĆNE BEŠIKE – TERAPIJA I DVOGODIŠNJI MONITORING – PRIKAZ SLUČAJA

Stevan STOJANOVIĆ[1, 2], Žarko DIMITRIĆ[1], Ivan LEVAKOV[1, 2], Mladen POPOV[1, 2], Sandra TRIVUNIĆ DAJKO[2,3] and Slobodan TORBICA[2,4]

Summary

Introduction. Inflammatory myofibroblastic tumor of the bladder or inflammatory pseudotumor is benign in nature. It is also known as a pseudotumor, because it macroscopically mimics infiltrative tumors of the bladder. The first inflammatory pseudotumor ever described was found in the lungs. In the 80s of the last century, it was first described in the urinary bladder. Its etiology is unknown and the incidence is extremely rare. **Case Report.** We present a case of a 46-year-old man who came to the Emergency Center for the first time due to an unpleasant feeling when urinating, painless hematuria and appearance of blood clots during urination. An urgent diagnosis revealed a tumor mass in the bladder. Additional diagnostics and surgical treatment was performed by transurethral electroresection of the urinary bladder. After the histopathological examination, an inflammatory myofibroblastic tumor of the bladder was diagnosed. The patient was discharged on the third day of admission. On control examinations, the patient underwent only cystoscopy and ultrasonography. No recurrences were observed. **Conclusion.** A review of the available literature showed that in such cases, after transurethral resection of bladder tumor, most urologists opted for more radical surgical procedures. After a two-year follow-up, we proved that a tumor of the bladder can be kept under control after transurethral resection of bladder tumor, without recurrence, by regular monitoring using ultrasonography and cystoscopy.

Key words: Urinary Bladder Neoplasms; Myofibroma; Cystoscopy; Hematuria; Immunohistochemistry; Diagnosis; Urologic Surgical Procedures

Sažetak

Uvod. Inflamatorni miofibroblastni tumor mokraćne bešike ili pseudotumor benigne je etiologije. Naziv pseudotumor dobio je po tome što makroskopski gledano imitira infiltrativne tumore mokraćne bešike. Prvi ikada opisan pseudotumor viđen je na plućima. Osamdesetih godina prošlog veka je prvi put opisan u mokraćnoj bešici. Incidencija je izrazito retka. **Prikaz slučaja.** Prikazujemo slučaj muškarca starosti 46 godina. Radi se o pacijentu koji se javio prvi put u Urgentni centar zbog neprijatnog osećaja pri mokrenju, bezbolne hematurije i izbacivanja krvnih ugrušaka tokom mokrenja. Sprovedena je urgentna dijagnostika te je viđena tumorska promena u mokraćnoj bešici. Sprovedena je i dodatna dijagnostika i operativno lečenje, transuretralna elektroresekcija mokraćne bešike. Nakon patohistološke analize dobijen je nalaz inflamatornog miofibroblastnog tumora mokraćne bešike. Trećeg dana hospitalziacije pacijent je otpušten. Na dosadašnjim kontrolnim pregledima pacijent je samo ultrazvučno i cistoskopski praćen. Nisu uočeni recidivi. **Zaključak.** Uvidom u dostupnu literaturu uvideli smo da se kod većine ovakvih slučajeva, nakon transuretralne elektroresekcije mokraćne bešike, većina urologa opredeljivala za radikalnije operacije. Dvogodišnjim praćenjem pacijenta dokazali smo da se tumor mokraćne bešike može držati pod kontrolom, bez recidiva, redovnim praćenjem (ultrazvučno i cistoskopski) nakon inicijalno načinjene transuretralne elektroresekcije mokraćne bešike.

Ključne reči: karcinomi mokraćne bešike; miofibrom; cistoskopija; hematurija; imunohistohemija; dijagnoza; urološke hirurške procedure

Introduction

Inflammatory myofibroblastic tumor (IMT) of the urinary bladder is a rare benign condition of unknown etiology which macroscopically mimics infiltrative tumors of the urinary bladder. It has been reported only in a few cases and its malignant potential is being researched. The IMT may occur in other sites (lungs, retroperitoneum, uterus, etc.), but its appearance in the urinary bladder is rare. We will present the diagnosis, treatment, and monitoring of a case that was documented for the first time in our clinic. A male patient was referred to our Clinical Center due to dysuria and painless hematuria. He was examined by an urologist, underwent computerized tomography (CT) and cystoscopy that revealed a tumor lesion. The patient underwent transurethral electro-resection of a bladder tumor (TURBT), and the pathology report confirmed

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Abbreviations

IMT – inflammatory myofibroblastic tumor
CT – computerized tomography
US – ultrasonography
TURBT – transurethral resection of bladder tumor
HE – hematoxylin and eosin

the diagnosis of IMT. On the third day of hospitalization the patient was discharged in a very good condition, without hematuria. After surgery, the patient was monitored using cystoscopy, ultrasonography (US), and CT. After the initial TURBT, the patient was regularly monitored and his treatment did not require further interventions.

Case Report

A 46-year-old male was examined at the Clinical Center of Vojvodina with a slight burning sensation during urination, painless hematuria, and blood clots in the urine. He was treated for hypertension for 4 years and was a smoker for 20 years. Emergency diagnosis included laboratory tests, US, and urine test. The laboratory test results were within normal reference ranges. The urine sediment showed a macroscopic hematuria, while the emergency US scan showed a hypoechoic mass, clearly bordered and around 25 x 20 mm in size in the right side of the bladder dome, with a minimal color Doppler signal. The parenchyma of the other organs showed no pathological changes. A conservative home treatment was recommended including hydration and antibiotic treatment. After the end of the treatment

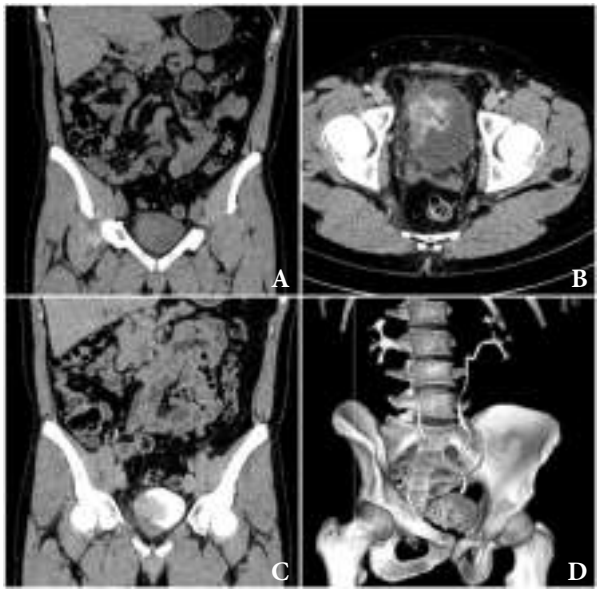

Figure 1. Abdominal and minor pelvis CT: A - native phase coronal section; B - axial section venous phase; C - delayed venous phase; D - 3D reconstruction of the urinary bladder
Slika 1. *Kompjuterizovana tomografija abdomena i male karlice: A – koronalni presek nativno, B – venska faza aksijalni presek, C – odložena venska faza, D – 3D rekonstrukcija mokraćne bešike*

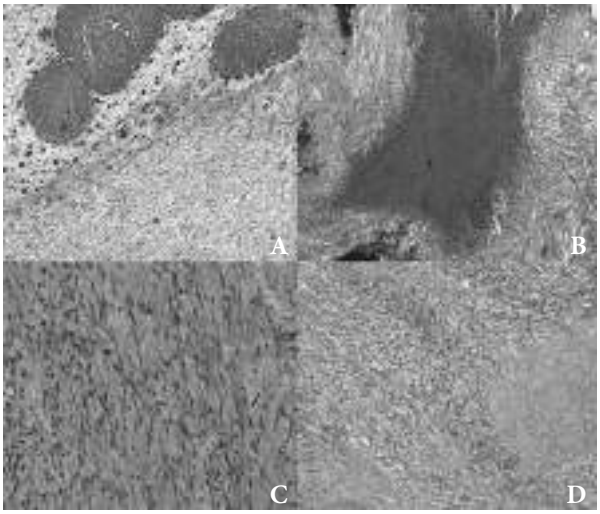

Figure 2. Histological view of the IMT by standard HE staining: A - tumor cells infiltrating the lamina propria of the mucosa with preserved urothelium, enhancement x 5; B - necrotic area inside the tumor, enhancement x 5; C - spindle fibroblastic tumor cells and inflammatory cells, enhancement x 20; D - tumor infiltrating the strands of tunica muscularis of the urinary bladder, enhancement x10)
Slika 2. *Histološki izgled inflamatornog miofibroblastnog tumora na standardnom hematoksilin-eozin bojenju: A (ćelije tumora infiltruju vezivo lamine proprije sluznice, čiji je urotel očuvan, uveličanje x 5; B (područje nekroze unutar tumora, uveličanje x 5), C (vretenaste fibroblastne ćelije tumora i zapaljenske ćelije, uveličanje x 20), D (tumor infiltruje snopove tunicae muscularis zida mokraćne bešike, uveličanje x 10)*

and a negative urine culture test, a cystoscopy was performed, which showed a wide tumorous lesion, around 5 mm in size, on the right lateral wall, with infiltrative characteristics. A CT scan of the abdomen was performed, showing a soft tissue lesion on the thickened right lateral wall of the urinary bladder, 37 x 42 x 34 mm in size, with swollen inguinal lymph nodes around 11 mm in size. Other organs showed no signs of the disease **(Figure 1)**. The patient underwent a TURBT of the entire tumor; a sample was taken from the base of the tumor and sent for histopathological analysis. The material was fixated in 4% buffered formalin and embedded into paraffin blocks, after which the samples were cut and stained using the standard hematoxylin and eosin (HE) method. Immunohistochemistry for the following antibodies was done: SMA, ALK1, Desmin, AE1-AE3, cytokeratine-CK8/18, Vimentin, DOG1, CD117, EMA, Myogenin, p53, H-caldesmin, HMB45, s-100, GFAP, Synaptophysin, CD34, CD31, CD68, and ki-67. Forty-four histological samples showed that both mucosa and tunica muscularis were wrapped by the regular and slightly hyperplastic urothelium, without irregularities. The mucosa and outer muscle layer contained soft-tissues spindle cell lesions with cytoplasmic extensions, oval nuclei embedded into edematous and myxoid stroma permeated by inflammatory infiltration and areas of necro-

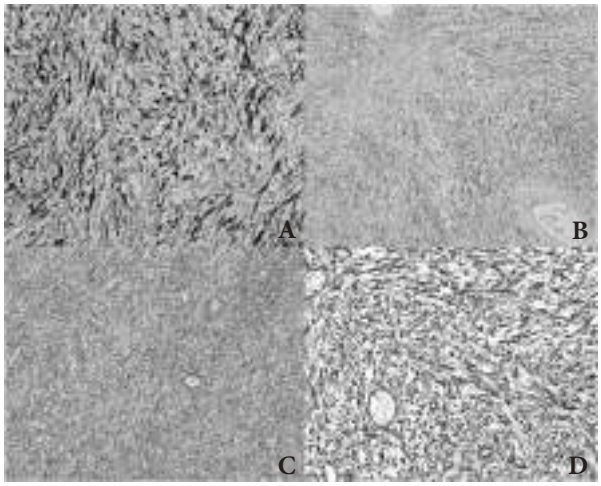

Figure 3. Positive immunohistochemical staining for IMT: A - CK 8-18 +++, enhancement x 10; B - ALK-1 ++, enhancement x 10; C - SMA ++, enhancement x 10; D - vimentin +++, enhancement x 10

Slika 3. *Pozitivna imunohistohemijska bojenja za opisan slučaj inflamatornog miofibroblastnog tumora: A (CK 8-18+++, uveličanje x 10), B (ALK-1 ++, uveličanje x 10), C (SMA ++, uveličanje x 10), D (vimentin +++, uveličanje x 10)*

sis. The immunohistochemical profile of the first sample showed positivity for SMA, ALK1, AE1/AE3, CK8/18, Vimentin, p53, CD68 and ki-67 > 5%.

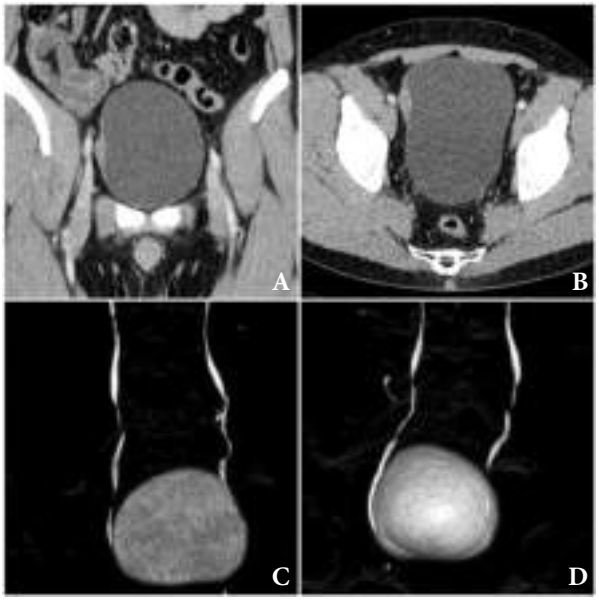

Figure 4. Minor pelvis CT: A - coronal section, venous phase; B - axial section, venous phase; C - 3D reconstruction, front of the urinary bladder; D - 3D reconstruction, back of the urinary bladder

Slika 4. *Kompjuterizovana tomografija male karlice: A – koronalni presek venska faza, B – venska faza aksijalni presek, C – 3D rekonstrukcija - prednja strana mokraćne bešike, D – 3D rekonstrukcija- zadnja strana mokraćne bešike*

Negative stains were: Desmin, DOG1, CD117, EMA, Myogenin, Hcaldesmon, HMB45, S100, GFAP, Synaptophysin, CD34 and CD31. Morphological and certain immunohistochemical characteristics of IMT are shown in **Figures 2** and **3**.

The second sample (from the base of the tumor) had the same morphological characteristics as the first one. The patient was discharged for home treatment on the third day after surgery. A cystoscopy was performed two weeks after surgery and showed normal scarring. A month after surgery, a CT of the minor pelvis was performed showing distended urinary bladder, post contrast partially filled with contrast; irregular segmentary thickening of the right lateral wall up to 10 mm in size, and post contrast without significant imbibed contrast; minimally swollen lymph nodes **(Figure 4)**. The patient was monitored by cystoscopy and US every three months (no abnormality detected) and every six months starting this year.

Discussion

First reported by Brunn in 1937, IMT, is an extremely rare, soft tissue benign disease with an incidence of 0.04 – 0.07% [1]. The tumor lesion consists of spindle cells with cytoplasmic extensions, wrapped in myxoid stroma, and permeated by inflammatory infiltrate and areas of necrosis [2, 3]. According to the World Health Organization, IMT is an intermediate tumor that affects children and young adults [4]. Typically it is located in the liver and biliary tract (32%), lungs (27%) and gastrointestinal tract (10%), but in the urogenital system, IMT most frequently occurs in the bladder and kidneys [5, 6]. The urinary bladder IMT was first described by Roth et al. in 1980s [7]. Prior knowledge of similar tumors is necessary in order to differentiate it from similar spindle cell tumors (e.g. leiomyosarcoma) [8, 9]. Bladder cancer is the 9th most common cancer worldwide and the 7th most common worldwide in men [10]. The IMT is described in literature by different names (nodular fasciitis, inflammatory pseudotumor, pseudo-malignant spindle cell proliferation, etc.) [11–13]. It may occur in many organs, including the urinary bladder, where it is rare, but it has the same morphological characteristics in all locations [14]. This type is mostly benign, with as of yet unexplained malignant potential [2, 11]. It is not sex- (women are somewhat more susceptible than men) or age-specific [15]. In almost all cases it is characterized by hematuria. Besides the listed, cystoscopy should not be omitted, as it is the gold standard of diagnostics for these cases and the basis for further diagnosis and treatment. In most cases there is positive staining for SMA (90%), CK (> 50%), Desmin (50%) and ALK1 (20 – 89%). The CT is necessary for a detailed evaluation of the disease. The characteristic of this disease is a ring formation made of contrast which forms around the polypoid nodules within the urinary bladder, and this can enable easier diagnosis [15]. This disease has a relatively good prognosis and a low metastatic potential.

Conclusion

In most cases, inflammatory myofibroblastic tumor is treated by partial cystectomy [13], but some authors consider it to be overtreatment. Based on the two-year experience of treating this patient, cystoscopy (initially every three months, followed by every six months) and ultrasonography of the urinary system, we assert that it is possible to consider a less invasive operative procedure, transurethral resection of bladder tumor, with frequent follow ups.

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EFFECTS OF POSITIVE END-EXPIRATORY PRESSURE, CARBON DIOXIDE AND BODY POSITION ON INTRACRANIAL PRESSURE MEASURED BY ULTRASOUND ASSESSMENT OF OPTIC NERVE SHEATH DIAMETER

UTICAJ POZITIVNOG END-EKSPIRATORNOG PRITISKA, UGLJEN-DIOKSIDA I POLOŽAJA TELA NA INTRAKRANIJALNI PRITISAK MERENOG ULTRAZVUČNOM PROCENOM PREČNIKA OMOTAČA OPTIČKOG NERVA

Adrijana BOJIČIĆ[1], Gordana JOVANOVIĆ[1, 2], Filip PAJIČIĆ[2, 3] and Milanka TATIĆ[2, 4]

Summary

Introduction. The optic nerve is surrounded by layers of meninges and cerebrospinal fluid, which is why intracranial pressure affects the optic nerve sheath. Noninvasive measurement of the optic nerve sheath diameter is simple, accurate, repeatable and with minimal side effects. **Effects of positive end-expiratory pressure on intracranial pressure.** The application of positive end-expiratory pressure plays a significant role in improving gas exchange, but it leads to an increase in intrathoracic and central venous pressure, cerebral blood volume, reduces arterial and cerebral perfusion pressure and thus futher increases intracranial pressure. The effect of positive end-expiratory pressure depends on basal intracranial pressure and respiratory system compliance. **Effects of carbon dioxide on intracranial pressure.** Hypercapnia leads to cerebral vasodilatation and increases cerebral blood flow and intracranial pressure. Hypocapnia reduces intracranial pressure, but its prolonged effect may lead to cerebral ischemia. **Effects of body position on intracranial pressure.** Body position affects intracranial pressure, primarily by affecting cerebral venous drainage. **Conclusion.** Body position, application of positive end-expiratory pressure, and changes in carbon dioxide can affect intracranial pressure, which is why its monitoring is of importance. Numerous studies show that their effects on intracranial pressure can be easily monitored by ultrasound assessment of optic nerve sheath diameter.

Key words: Intracranial Pressure; Optic Nerve; Ultrasonography; Positive-Pressure Respiration; Posture; Carbon Dioxide; Myelin Sheath; Intracranial Hypertension; Diagnosis

Sažetak

Uvod. Optički nerv je okružen moždanim opnama i cerebrospinalnom tečnošću, zbog čega intrakranijalni pritisak utiče na omotače optičkog nerva. Neinvazivno merenje prečnika omotača optičkog nerva je jednostavno, tačno, ponovljivo i sa minimalnim neželjenim efektima. **Uticaj pozitivnog end-ekspiratornog pritiska na intrakranijalni pritisak.** Primena pozitivnog end-ekspiratornog pritiska ima značajnu ulogu u poboljšanju gasne razmene, ali dovodi do porasta intratorakalnog i centralnog venskog pritiska, cerebralnog volumena krvi, smanjuje arterijski i cerebralni perfuzioni pritisak a time dalje povećava intrakranijalni pritisak. Uticaj pozitivnog end-ekspiratornog pritiska zavisi od bazalnog intrakranijalnog pritiska i respiratorne komplijanse. **Uticaj ugljen-dioksida na intrakranijalni pritisak.** U hiperkapniji dolazi do cerebralne vazodilatacije, porasta cerebralnog protoka krvi i intrakranijalnog pritiska. Hipokapnija dovodi do snižavanja intrakranijalnog pritiska, ali njen produžen efekat može dovesti do ishemije mozga. **Dejstvo položaja tela na intrakranijalni pritisak.** Položaj tela utiče na intrakranijalni pritisak, prevashodno uticajem na cerebralnu vensku drenažu. **Zaključak.** Položaj tela, primena pozitivnog end-ekspiratornog pritiska i promene ugljen-dioksida mogu uticati na intrakranijalni pritisak, zbog čega je korisno njegovo praćenje. Brojne studije pokazuju da se njihov uticaj na intrakranijalni pritisak lako može pratiti ultrazvučnim merenjem prečnika omotača optičkog nerva.

Ključne reči: intrakranijalni pritisak; optički nerv; ultrasonografija; pozitivni end-ekspiratorni pritisak; položaj tela; ugljen dioksid; mijelinski omotač; intrakranijalna hipertenzija; dijagnoza

Introduction

Intracranial pressure (ICP) monitoring is important because many intra- and extracranial causes may lead to intracranial hypertension, which induces secondary brain injury [1, 2]. Intraventricular catheters and intraparenchymal probes remain the gold standard for ICP monitoring, but these invasive

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Abbreviations

ONSD – optic nerve sheath diameter
ALI – acute lung injury
ARDS – acute respiratory distress syndrome
PEEP – positive end-expiratory pressure
CPP – cerebral perfusion pressure
MAP – mean arterial pressure
ICP – intracranial pressure
CVP – central venous pressure
PaCO2 – partial carbon-dioxide pressure
EtCO2 – end-tidal carbon-dioxide
CSF – cerebrospinal fluid

methods may cause infection, bleeding, they are expensive and require special education [3–5]. Non-invasive methods have been proposed recently, especially ultrasound optic nerve sheath diameter (ONSD) measurement, because it is simple, accurate, repeatable and has minimal side effects. The optic nerve is surrounded by layers of meninges and cerebrospinal fluid, so ICP changes directly affect the ONSD. Many studies showed that ONSD changes measured by ultrasound happen in real-time, just like changes measured via invasive methods [2, 4].

The ONSD measurements are performed in a supine position, with eyes closed and head elevated to 30°. A linear probe is used, and it shows the retrobulbar hypoechoic area which represents the optic nerve. The sheath diameter is measured 3 mm behind the posterior pole of the eye, because there is the greatest enlargement in this zone due to the distribution and density of arachnoid trabeculae [2, 5]. In 1996, Helmke and Hansen used ultrasound to measure ONSD on cadavers when gelatin was applied in subarachnoid space and they found that at 3 mm behind the optic disc it was larger by 60%, and at 10 mm retrobulbarly only by 35% [6].

Many factors in patients' treatment can affect ICP and it can easily be measured by ultrasound, not only in neurosurgical patients. Patients with brain lesions often require intubation and mechanical ventilation because of altered consciousness, anticipated neurologic deterioration and intracranial hypertension [7]. Thirty percent of these patients develop respiratory failure, pneumonia, pulmonary edema, embolism, acute lung injury (ALI) and acute distress syndrome (ARDS), so they require mechanical ventilation [7–9]. Hypoxemia and hypercapnia can cause secondary brain injury, so in order to prevent it, they should be avoided in patients with positive-pressure ventilation [7].

Effects of positive end-expiratory pressure on intracranial pressure

Mechanical ventilation with positive end-expiratory pressure (PEEP) is important in the treatment of ALI and ARDS because it improves oxygenation, alveolar recruitment, functional residual capacity, and reduces risks of atelectrauma, pulmonary shunting, ventilator-induced lung injuries and pneumonia [9, 10]. However, PEEP increases intrathoracic pressure, which decreases venous return to the right atrium, increases jugular venous pressure and cerebral blood volume and then intracranial pressure [8, 10, 11]. Cerebral perfusion pressure (CPP) corresponds to the difference between mean arterial pressure (MAP) and ICP [1, 4]. Decreased venous return reduces cardiac output and MAP, therefore leading to compensatory cerebral vasodilatation, cerebral blood volume increase and ICP increase [7, 11, 12]. There is a positive correlation between PEEP and ICP, and negative between PEEP and CPP [8]. Boone et al. demonstrated that for every centimeter H_2O increase of PEEP, there was a 0.31 mmHg increase in ICP and a 0.85 mmHg decrease in CPP [13]. According to Shapiro and Marshal, administration 4 – 8 cmH_2O of PEEP increased ICP by 10 mmHg or more [12].

The PEEP application increases pleural pressure and central venous pressure (CVP), therefore reduces cerebral venous drainage and then increases ICP [14]. In 2017, Shojaee et al. reported about an increase in CVP by 2.5 cmH_2O after 5 cmH_2O of PEEP was applied [15]. Georgiadis et al. showed that after 8 cmH_2O and 12 cmH_2O of PEEP was applied, there was a decrease in MAP [10]. Some studies do not demonstrate a correlation between MAP and ONSD, maybe because of intact cerebral autoregulation, which maintains CPP within 50 – 150 mmHg of MAP [16]. Maintaining constant cerebral blood flow depends on cerebral autoregulation, which is often impaired in brain lesions and then it is passively changing due to CPP [13, 17]. Complications of high PEEP and low MAP do not happen in patients with preserved cerebral autoregulation. In patients with impaired autoregulation, due to traumatic brain injury or intracranial hemorrhage, complications of decreased MAP are observed [18].

According to the Starling resistor model, if the intrathoracic pressure exceeds baseline ICP under the influence of PEEP, the ICP increases. When the baseline ICP is higher than the applied PEEP, the ICP will not change. A study conducted between 2016 and 2019, demonstrated ICP increase after PEEP application only when the baseline ICP was approximate to CVP, and patients with lower ICP had a positive response to PEEP application [19]. Chen et al. investigated the effect of 10 and 15 cmH_2O of PEEP on ICP and they found there was consequent intracranial hypertension only when the baseline ICP was lower than PEEP. It shows that PEEP can be safely applied when it is lower than ICP. Intracranial hypertension can diminish transmission of intrathoracic pressure intracranially by compressing cerebral venous system [9, 20].

Effects of PEEP on ICP depend on respiratory compliance. Studies demonstrate that there is a smaller transmission of PEEP to the intracranial compartment in patients with low respiratory compliance. Caricato found that application of 0 – 12 cmH_2O PEEP in patients with normal respiratory compliance can decrease MAP and CPP. There was no decrease in patients with low respiratory compliance [11]. In non-recruitable patients, PEEP application can induce alveolar hyperinflation, increase in pulmonary elastance and dead space, and therefore increase of partial carbon-dioxide pressure ($PaCO_2$).

Hypercapnia, often present in ARDS, can increase ICP. If the application of PEEP causes alveolar recruitment, pulmonary elastance and dead space will reduce, and there will be better oxygenation and decreased $PaCO_2$ [14, 21]. Flexman et al. found that recruitment manoeuvres increase ICP, decrease MAP and CPP [22]. A prospective study published in 2015 examined application of PEEP up to 15 cmH_2O in patients with traumatic brain injury and ARDS. There was no impact on ICP and CPP, and brain oxygenation was better. The PEEP can safely be applied in patients with ARDS and traumatic brain injury, although there are no significant effects on ICP and CPP, and it can even have a useful impact on brain metabolism [13, 21].

The study by Renu Bala et al. investigated the effect of PEEP on noninvasive ICP predictor – ONSD. During application of 0 cmH_2O PEEP, ONSD was 0.44 ± 0.06 cm. When PEEP increased to 8 cmH_2O, ONSD was 0.45 ± 0.07 cm, then 0.47 ± 0.07 while applying PEEP of 12 cmH_2O, and 0.49 ± 0.07 cm when PEEP was 15 cmH_2O [16]. In 2018, Khandelwal applied PEEP of 0, 3, and 5 cmH_2O and studied its effect on ONSD in pediatric patients. When PEEP increased from 0 to 3 cmH_2O there was no significant change in ONSD, but when PEEP increased to 5 cmH_2O there was a significant difference [9].

Effects of carbon-dioxide on intracranial pressure

Carbon-dioxide affects vascular tonus and changes its diameter, therefore affects cerebral blood flow and ICP. It is well known that hypercapnia causes vasodilatation and increases cerebral blood flow, in contrast to hypocapnia [23]. Klinzing measured ONSD in hypo- and hyperventilation in patients with traumatic brain injury. The greatest effect on ONSD in hyperventilation was after 50 minutes and moderate hyperventilation induced a significant decrease in ICP. In normoventilation ($PaCO_2$ 4.99 kPa) ONSD was 5.79 mm, after 10 minutes of hyperventilation ($PaCO_2$ 4.44 kPa) ONSD was 5.62 mm, and after 50 minutes ($PaCO_2$ 4.04 kPa) it was 5.6 mm. After 10 minutes of hypoventilation ($PaCO_2$ 5.5 kPa) ONSD was 5.95 mm, and after 50 minutes ($PaCO_2$ 5.7 kPa) ONSD was 6.1 mm [24]. In intracranial hypertension ONSD ranges from 0.48 to 0.57 cm as described in the literature [25].

Kim et al. measured ONSD in patients without intracranial lesions during cervical discectomy under general anesthesia. After 1 and 5 minutes following reaching end-tidal carbon-dioxide ($etCO_2$) of 40 mmHg, ONSD values were 5.0 ± 0.5 and 5.0 ± 0.4 mm, then 1 and 5 minutes after achieving $etCO_2$ of 30 mmHg, ONSD was 3.8 ± 0.6 and 4.0 ± 0.4 mm. This study found that ONSD decrease can happen in 10 minutes in hyperventilation, even in patients without intracranial lesions and with normal cerebral compliance. Expiratory CO_2 has good correlation with $PaCO_2$, but there is a greater difference between these two in patients with low cardiac output and respiratory diseases. The real value of systemic CO_2 is better shown with $PaCO_2$. The benefit is that $etCO_2$ can be continuously monitored, while $PaCO_2$ measurement requires multiple blood sampling [26].

Kapoor et al. measured ONSD in general anesthesia during brachial plexus surgery in hypo- and hypercapnia. Five minutes after achieving $etCO_2$ 30, 40 and 50 mmHg, ONSD was 0.29, 0.34 and 0.40 cm. There is a significant difference in ONSD at different $etCO_2$ values, and this research was conducted in patients without brain lesions with good intracranial compliance [25]. In a 2019 study, decrease of ONSD was 10% (0.02 cm) when $etCO_2$ decreased from 39.74 ± 1.23 to 35.98 ± 1.29 mmHg. As $etCO_2$ decreased to 33.02 ± 0.74 and 29.29 ± 1.18 mm Hg, ONSD was reduced by 17% (0.03 cm) and 25% (0.04 cm), respectively [16].

It is known that hypercapnia can cause damage in patients with traumatic brain injuries, but prolonged hyperventilation can also have unfavourable effects. Hyperventilation and hypocapnia lead to vasoconstriction and cerebral blood flow reduction and then a decrease of ICP, but prolonged hyperventilation can cause brain ischemia [8]. In traumatic brain injuries there can be ischemia and hyperemia at the same time, because of the disruption of perfusion and oxygen use. Although hyperventilation improves CPP and ICP, in injuries it increases the brain volume with low perfusion [27]. Spontaneous central neurogenic hyperventilation is described in patients with brain injuries and tumors. In a 2009 study, hypoxia of brain parenchyma occurred in 16% of patients with $etCO_2$ 35 – 44 mmHg, and when $etCO_2$ was 24 mmHg, it increased to 34%. It is recommended that $PaCO_2$ should not be below 29 mmHg in patients with brain trauma in the first 24 hours [28].

Effects of body position on intracranial pressure

Examination of cerebral blood flow and cerebrospinal fluid (CSF) was performed with magnetic resonance imaging in a supine position and the upright sitting position. In a supine position cerebral venous blood was predominantly drained by jugular veins, while in sitting position there was a partial or complete collapse of jugular veins, and 50% of drainage was via vertebral, epidural or deep cervical veins. While sitting, there was a smaller total cerebral blood volume, smaller oscillatory CSF volume and better intracranial compliance, which is equal to volume and pressure difference, with reduction of ICP. Also, a greater flow of CSF to the spinal canal is described in sitting position [29].

When the head is elevated to an angle of 30° in a supine position, jugular outflow is reduced, and drainage by vertebral veins is better and independent of intrathoracic pressure. Prone position can make drainage through jugular veins difficult. There are also valves in jugular veins at thoracic inlet, that prevent blood flow cranially and protect the brain from sudden pressure increase (e. g. while coughing) [10, 11, 14]. Robba et al. measured ONSD changes in a supine

and prone position during PEEP application. There was greater ONSD increase in the prone than in the supine position, and ONSD additionally increased when PEEP was applied in the prone position. Values of ONSD were 0.40 ± 0.01 in the supine and 0.48 ± 0.01 mm in the prone position. When PEEP was applied in the prone position, ONSD was 0.49 ± 0.01, and when the patient returned to the supine position and PEEP was still being applied, ONSD was 0.42 ± 0.01 mm [30].

In a study published in 2020, ONSD was measured in pediatric patients with cleft palate during palatoplasty with a head angle extended to 70°. The ONSD was measured in the supine position after anesthesia induction (4.19 ± 0.26 mm), 10 minutes after neck extension (5.20 ± 0.29 mm), at the end of the procedure with the neck still extended (4.38 ± 0.36 mm) and 10 minutes after return to the supine position (4.35 ± 0.30 mm). The largest ONSD was 10 minutes after neck extension, but ONSD values did not return to baseline even at the end of the intervention. Neck extension increases ICP due to a potential collapse of jugular veins which reduces cerebral venous outflow. The ONSD reduction is seen during the procedure and indicates good adaptability on ICP changes [31]. Head-down position with neck extension increases ICP, but it is different in Trendelenburg position in which the whole body is in the supine position without neck movement. The Trendelenburg position also can increase intrathoracic pressure and ICP [32].

Blecha et al. measured ONSD during laparoscopic prostatectomy 20 minutes after induction of anesthesia (5.88 ± 0.44 mm), after gas insufflation in the supine position and achieving 15 mmHg of intraabdominal pressure (6.08 ± 0.52 mm), after 30 minutes in steep Trendelenburg position (6.07 ±0.49 mm), during Santorini's plexus preparation when intraabdominal pressure was 25 mmHg (6.04 ±0.50 mm) and before waking the patients in the supine position (5.96 ± 0.49 mm). In younger patients ONSD reduced with time and that is an indicator of better ICP adaptability [33]. Patients in Trendelenburg position with pneumoperitoneum have reduced respiratory compliance and pressure is not transmitted to the intracranial compartment [34]. Nausea and headache are described after laparoscopic surgery, which can be a consequence of high ICP. There is an increase of $PaCO_2$ during pneumoperitoneum, which can cause cerebral vasodilation and increase in ICP [35]. Increase of cerebral blood flow in Trendelenburg position in healthy patients, by Monro-Kellie doctrine, can be easily regulated with CSF decrease, which is not the case in brain injuries. In Kim's study there was no significant difference in ONSD in Trendelenburg and reverse Trendelenburg position because of preserved compensatory mechanisms [36].

Conclusion

A noninvasive method of intracranial pressure measurement by ultrasound estimation of optic nerve sheath diameter is easy, accurate, repeatable and with minimal side-effects. Optic nerve sheath diameter measurement can be used in everyday practice to monitor the effects of mechanical ventilation and patient's position on intracranial pressure. Application of positive end-expiratory pressure increases intracranial pressure, but there are no side effects in patients with preserved cerebral autoregulation. It can be safely used when it does not exceed the baseline intracranial pressure. In patients with low respiratory compliance, application of positive end-expiratory pressure does not increase intracranial pressure. Carbon-dioxide affects intracranial pressure by changing the diameter and tonus of blood vessels and cerebral blood flow. Hypercapnia increases intracranial pressure, while hypocapnia decreases it, but it can lead to brain ischemia. In the first 24 h since brain trauma, hyperventilation below carbon-dioxide partial pressure of 29 mmHg is not recommended. Body position leads to intracranial pressure changes by affecting cerebral venous drainage. It is useful to measure optic nerve sheath diameter in different positions to avoid brain damage.

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ROBOTICS IN PHYSICAL MEDICINE AND NEUROREHABILITATION

ROBOTIKA U FIZIKALNOJ MEDICINI I NEUROREHABILTACIJI

Vesna PAUŠIĆ[1], Grigorije JOVANOVIĆ[2] and Svetlana SIMIĆ[1]

Summary

Introduction. Robots have been used for rehabilitation purposes since the 1960s. The aim of this paper is to present the application of robotics in physical medicine and rehabilitation with special reference to robotic devices used in rehabilitation. **Material and Methods.** The paper uses literature related to the application of robotics in medicine and rehabilitation. The literature review was conducted using the following databases: Serbian Library Consortium for Coordinated Acquisition, Medical Literature Analysis and Retrieval System, Google Scholar, Science Citation Index, and portal of Croatian scientific journals "Hrčak". **Development of robotics in rehabilitation.** Nowadays, there are a great number of different robotic systems for rehabilitation. Robotics in rehabilitation is of utter importance because it works on the principle of neuroplasticity. **Robots for lower limb rehabilitation.** These robotic systems are most often in the form of exoskeletons. **Robots for upper limb rehabilitation.** Upper limb rehabilitation robots are therapeutic devices that help or provide support for arm or hand movements. **Robot for upper body rehabilitation.** Robot "Tymo". **Conclusion.** By using robots in physical medicine and neurorehabilitation, a faster and more complete functional recovery of the patient can be achieved.

Key words: Physical and Rehabilitation Medicine; Robotics; Neurological Rehabilitation; Neuronal Plasticity; Exoskeleton Device; Upper Extremity; Lower Extremity; Torso; Movement Disorders

Sažetak

Uvod. Primena robota u rehabilitaciji datira još od 1960-ih godina. Ovaj rad ima za cilj da prikaže primenu robotike u fizikalnoj medicini i rehabilitaciji, sa posebnim osvrtom na robotske uređaje koji se koriste u rehabilitaciji. **Materijal i metode.** U radu je korišćena literatura koja se odnosi na primenu robotike u medicini i rehabilitaciji. Citirane baze po kojima se radio pregled literature bile su *Kobson*, *Medline*, *Google Schoolar*, *Science Citation Index* i *Hrvatski znanstveni portal Hrčak*. **Razvoj robotike u rehabilitaciji.** Postoji veliki broj različitih robotskih sistema za rehabilitaciju. Robotika u rehabilitaciji je od izuzetnog značaja zbog toga što funkcioniše na principu neuroplastičnosti. **Roboti za rehabilitaciju donjih ekstremiteta.** Ovi robotski sistemi najčešće su realizovani u formi egzoskeleta. **Roboti za rehabilitaciju gornjih ekstremiteta.** Roboti za rehabilitaciju gornjih ekstremiteta su terapeutski uređaji koji pomažu ili pružaju podršku pokretima ruke ili šake. **Robot za rehabilitaciju trupa.** Robot *Tymo*. **Zaključak.** Primenom robota u fizikalnoj medicini i neurorehabilitaciji može se postići brži i potpuniji funkcionalni oporavak pacijenta.

Ključne reči: fizikalna medicina i rehabilitacija; robotika, neurološka rehabilitacija; neuronska plastičnost; egzoskelet; gornji ekstremiteti; donji ekstremiteti; torzo; poremećaji kretanja

Introduction

Robots have been used for rehabilitation purposes since the 1960s [1]. Application of robots in rehabilitation was initially focused on replacing lost functions in individuals with physical disabilities through the use of devices such as robotic orthoses, robotic workstations, feeding devices, and robotic wheelchairs [2]. The application of robots in medicine (diagnostics, surgery, health care, rehabilitation etc.) has not been included in practice to a great extent, but nowadays, it is one of the most perspective fields for investing significant financial assets and scientific resources and therefore relevant results are expected to be achieved [3]. Over the last two decades, there has been an increasing amount of research into the use of robots in physical medicine [4–7]. Application of robots in medical rehabilitation is expanding and includes numerous ideas, solutions and prototypes which may help in certain, although not all stages of rehabilitation [8]. The word robotics has a Slavic root and the word robot originates from the Czech word "robotnik" which may be translated as a slave, worker. It was first used by the Czech author Karel Čapek in his play Rossum's Universal Robots (R. U. R.) [9]. In 1960, Joseph F. Engelberger and George C. Devol developed the first industrial robot for the General Motors car factory, and the first robotics institute was founded in 1965 [10]. The objective of this paper was to show how robotics is applied in physical medicine, specifically focusing on robotic devices of newest generation which are used in orthopedic and neurorehabilitation of the torso, upper and lower extremities.

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Abbreviations

R. U. R.	– Rossum's Universal Robots
MEDLINE	– Medical Literature Analysis and Retrieval System
KOBSON	– Serbian Library Consortium for Coordinated Acquisition
SCI	– Science Citation Index
Hrčak	– Croatian scientific journals
COVID-19	– coronavirus disease 2019
VR	– virtual reality

Material and Methods

This paper deals with the application of robotics in physical medicine and rehabilitation. Papers in Serbian, English and Croatian were studied. The literature review was conducted using the following databases: Serbian Library Consortium for Coordinated Acquisition (KOBSON), Medical Literature Analysis and Retrieval System (MEDLINE), Google Scholar, Science Citation Index (SCI), and a central portal of Croatian scientific journals "Hrčak". The key words used in the search were robotics, medicine, rehabilitation, neurorehabilitation.

Development of robotics in physical medicine and rehabilitation

Nowadays, there is a vast number of diverse robotic systems for rehabilitation. In the age of coronavirus disease 2019 (COVID-19) pandemic, a variety of potential implementations have been proposed to utilize robots in healthcare [11]. Robotics in rehabilitation is of utter importance, because it works on principle of neuroplasticity, i.e. the brain's ability to change, reorganize, and establish new synapses and enable the development of new types of rehabilitation treatment [12]. The application of specially designed virtual games using robots can provide an entertaining therapy experience, promoting the patient to put in effort into the exercises [13].

Robots for lower limb rehabilitation

The existing robots designed for physical therapy are commonly involved with neuromotor training of patients suffering from neurological diseases [14]. Verticalization of the patient and maximum independence are priorities in rehabilitation. The main problem in rehabilitation of lower limbs is the fact that patients are not able to maintain balance and walk on their own [15]. Robotic systems provide stability and mass compensation to the patients [16 - 17]. Apart from this, these systems actively move lower extremities of a patient through an integrated software system that coordinates with the sensors, thus mimicking the therapist. These robotic systems are most commonly in the form of exoskeletons [18].

The Lokomat robotic device, produced by Hocoma, is an advanced robot made to restore the function of lower limbs in adults and children with partial or complete loss of function in lower extremities [19]. The device consists of a treadmill integrated with a dynamic support system, robotic orthoses and a control system [20]. In an amusing and interactive way, by using video games, Lokomat encourages the patient to make a certain move several times, which improves the patient's recovery. It moves the patient's legs in walking cycles in sagittal axis [21]. Additional motivation for the patient is the biofeedback, i.e. precise measure of efforts through sensors located on knees and hips. In this way, the patient has a clear insight into his/her functional recovery [19].

The Andago robot provides stability and feeling of security while walking, quality posture and in this manner, it eliminates the fear of free walking [22]. The Andago is the safest robotic device [23]. It provides constant control of functional recovery which enables patients to walk safely without fear of falling after rehabilitation on this device. The device automatically displays the graphical functional recovery which may be stored in the patient's digital card [24].

The C-Mill and virtual reality (VR) is a robotic device that combines virtual technology with a treadmill developed to train and assess patient gait and balance for safe daily walking. It comes in three models: C-Mill, C-Mill VR and C-Mill VR +. Although the C-Mill VR and C-Mill VR + models use elements of virtual technology to stimulate patients, their ultimate goal is different. The C-Mill VR robotic device is used for training automated movements while the C-Mill VR + is a comprehensive rehabilitation solution with support for balance and body weight [25].

Robots for upper limb rehabilitation

Robots for upper limb rehabilitation are therapeutic devices which assist or support arm or hand movements.

The Armeo Spring is a robotic device for hand rehabilitation which, with the help of exoskeletons with integrating springs, facilitates active movements of the upper limbs [26]. Software video games allow the patient to move his arms in different directions and perform more precise movements as well as squeeze [27]. The therapist adjusts the patient's working space depending on his functional ability, and the exoskeleton supports natural movements in the flexion of the shoulders, elbows and fingers [28]. Training on the Armeo device encourages interaction between the patient and the device which leads to a greater independence in moving the arm and greater self-confidence at the same time.

The Myro robotic device is actually a therapeutic multifunctional and interactive work board which can be controlled in three ways by real objects, force (pushing and pulling) and touch. The special feature and uniqueness of the sensory device is oriented to neurorehabilitation and built-in sensors provide training the patent's cognitive abilities, concentration, selective attention, visual and spatial orientation and fine and gross motor skills from everyday life with things and objects on a large interactive surface (such as holding a pencil, a coin, a ball or cup and etc.) [29].

Robotic devices for upper body rehabilitation

The Tymo is the thinnest rehabilitation platform in the world that improves balance and posture control. It is used for the rehabilitation of the arms, torso and lower extremities [30]. It can be used unilaterally, bilaterally, statically or dynamically. The design of the Tymo device allows therapy in a wheelchair, next to the bed, on the table to train the upper extremities and in a standing position [31]. Being flexible, with the possibility of choosing several different positions, it allows practicing balance, torso and extremities in a simple and interesting way. A special extension may be placed beneath the platform and Tymo becomes mobile and may be used for analysis and training of balance. The software and accompanying interactive programs insights motivate the patients [32].

Robotics is beneficial for the rehabilitation of all disorders with symptoms that manifest in the musculoskeletal system. The aim of using robots is to decrease impairments, and also, primarily, to improve functional abilities. Mehrholz et al. [33] carried out a systematic review of 17 trials with 837 participants and found that electromechanical and robot-assisted gait training may support recovery of independent walking in post-stroke patients. Another systematic review by the same authors of 19 randomized controlled trials including 666 participants showed that electromechanical and robot-assisted arm training gave some benefit to the participants in terms of improving activities of daily living and arm functions, whereas it did not increase muscle strength [34]. Nevertheless, further research is necessary to clarify the therapeutic modes, types of exercises, post-stroke phases, and the intensity at which they are most useful.

Contraindications to the use of Lokomat and other robotic devices in the rehabilitation of patients may be osteoporosis or osteopenia, instability of the hip and knee joints, inability to control the head, joint contracture or range of motion due to spasticity, any health condition that prevents active rehabilitation such as respiratory diseases, osteomyelitis, infections, and inflammatory processes [35].

Conclusion

Robots have proved to be an important part of rehabilitation especially in therapy including a lot of repetitions or as additional stimulus for patients doing a certain activity in a quality and proper manner [36]. Although opinions on using contemporary technologies in medicine (rehabilitation) are divided, nowadays they are believed to be of great help if used properly and in compliance with ethical norms. Robotic rehabilitation should be a link between different physiotherapy techniques and relevant fields of rehabilitation which are increasingly accepted, as shown by positive results of numerous studies [37]. The perspective of robotic rehabilitation, which is supported by the results of some studies, includes standardization of therapeutic protocols, simultaneous application of different devices to individualize the therapeutic procedure, and the expected fall in prices as a result of lowering development costs. Previous neurorehabilitation techniques with good therapeutic effects should not be discarded with a new era of robotics, but it is necessary to continue their application in combination with new automated techniques in order to achieve the best therapeutic effect, leading to faster training and reduced treatment costs. By using robots in physical medicine and neurorehabilitation, a faster and more complete functional recovery of patients can be achieved.

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CONSERVATIVE APPROACH IN THE MANAGEMENT OF ECTOPIC PREGNANCY

KONZERVATVNI PRISTUP U LEČENJU EKTOPIČNE TRUDNOĆE

Jelena NIŠEVIĆ[1], Jelena VUKOVIĆ[2, 3], Stevan MILATOVIĆ[2, 3] and Srđan ĐURĐEVIĆ[1]

Summary

Introduction. Ectopic pregnancy is defined as the implantation of a fertilized ovum outside the uterine cavity and it is one of the leading causes of maternal morbidity and mortality. **Localization and risk factors.** The most common localization of ectopic pregnancy is within the fallopian tube, while other localizations include abdominal organs, ovaries, scars after previous cesarean sections, and cervix. Risk factors for ectopic pregnancy include previous fallopian tube injuries, infertility including multiple embryo transfers, use of contraceptives, smoking, older age, prior history of ectopic pregnancy, intentional abortions. **Diagnostic procedures.** Measurement of serum beta-human chorionic gonadotropin levels along with certain ultrasonography signs, i.e. extrauterine gestational sac, with a present yolk sac and/or embryo, with or without a cardiac activity, have the highest degree of reliability in making the diagnosis, whereas uncertain signs, such as “blob” and “bagel” signs, also have a high positive predictive value. **Therapeutic modalities.** Ectopic pregnancy can be treated by surgical, medical or expectant management. Expectant and medical management are reserved for hemodynamically stable patients who are adequately informed and where monitoring and control are possible. **Conservative treatment**. Before the initiation of treatment with methotrexate, it is necessary to rule out a vital intrauterine pregnancy, and consider the contraindications for methotrexate therapy, based on detailed medical history and laboratory tests. The Clinic of Obstetrics and Gynecology of the Clinical Center of Vojvodina uses a two-dose protocol by which methotrexate is administered intramuscularly and which has proven to be highly successful with few side effects. **Surgical treatment modalities.** Candidates for emergency laparoscopy or laparotomy are women who are hemodynamically unstable and who should not receive methotrexate. **Conclusion.** In properly selected patients, the success rate of methotrexate therapy is around 93%.

Key words: Pregnancy, Ectopic; Conservative Treatment; Methotrexate; Fallopian Tubes; Risk Factors; Signs and Symptoms; Clinical Protocols; Diagnosis

Sažetak

Uvod. Ektopična trudnoća podrazumeva implantaciju oplođene jajne ćelije izvan materične duplje i predstavlja jedan od vodećih uzroka maternalnog mortaliteta i morbiditeta čija je pojava u stalnom porastu. **Lokalizacija i faktori rizika.** Najčešća lokalizacija ektopične trudnoće je u jajovodu, dok druge lokalizacije uključuju trbušne organe, jajnike, ožiljke nakon prethodnih carskih rezova i grlić materice. Faktori rizika za vanmateričnu trudnoću uključuju prethodne povrede jajovoda, neplodnost, uključujući višestruke transfere embriona, upotrebu kontraceptivnih sredstava, pušenje, starije godine, istoriju ektopične trudnoće u prošlosti, namerni pobačaj. **Dijagnostičke procedure.** Dok određivanje serumske koncentracije beta humanog horionskog gonadotropina u prisustvu sigurnog sonografskog znaka, odnosno gestacijskog meška izvan materice sa prisutnom žumančanom vrećom i/ili embrionom, sa srčanom akcijom ili bez nje, ima najviši stepen pouzdanosti u postavljanju dijagnoze, uočavanje nesigurnih znakova poput „blob“ i „bagel“ znaka, takođe ima visoku pozitivnu prediktivnu vrednost. **Terapijski modaliteti**. Ektopična trudnoća može da se leči hirurški, medikamentno i ekspektativno. Ekspektativni i medikamentni tretman su rezervisani za hemodinamčki stabilne pacijentkinje koje su adekvatno informisane i sa mogućnošću monitoringa i kontrole. **Konzervativna terapija.** Da bi se započeo tretman metotreksatom, neophodno je isključiti prisustvo vitalne intrauterine trudnoće, kao i prisustvo kontraindikacija za primenu leka, a na osnovu detaljne anamneze i laboratorijskih pretraga. Na Klinici za ginekologiju i akušerstvo Kliničkog centra Vojvodine koristi se dvodozni protokol kojim se metotreksat aplikuje intramuskularno i koji se pokazao visoko uspešnim uz nizak stepen neželjenih dejstava. **Hirurški terapijski modaliteti.** Kandidatkinje za hitnu laparoskopiju ili laparotomiju jesu one žene koje su hemodinamički nestabilne i nisu pogodne za upotrebu metotreksata. **Zaključak.** Kod pravilno odabranih pacijentkinja, stopa uspešnosti terapije metotreksatom je oko 93%.

Ključne reči: ektopična trudnoća; konzervativni tretman; metotreksat; jajovodi; faktori rizika; znaci i simptomi; klinički protokoli; dijagnoza

Introduction

Ectopic pregnancy is defined as the implantation of a fertilized ovum outside the uterine cavity and it is one of the leading causes of maternal morbidity and mortality [1]. In addition to extrauterine localizations (abdominal cavity, ovaries, fallopian tubes), the term ectopic pregnancy also refers to localization inside the uterus but outside the endometrium, such as the interstitial and cervical pregnancies. It is a common life-threatening emergency, and the incidence of ectopic pregnancy is high in the developing world and

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Abbreviations
MTX – methotrexate
Beta-hCG – beta-human chorionic gonadotropin

is steadily rising. The estimated maternal mortality rate in 2009 in the United Kingdom was around 3.4% [2]. The term "pregnancy of unknown location" is used when the biochemical test for pregnancy in the blood is positive, but the gestational sac is not seen on ultrasound [3]. This happens in about 8 – 31% of women, which largely depends on the experience of the physician making the diagnosis. The simultaneous existence of pregnancy inside and outside the uterine cavity is called heterotopic pregnancy and it occurs in about 0.09% of pregnancies, more often after assisted reproduction technologies [4].

Localization and risk factors for ectopic pregnancy

The most common localization of ectopic pregnancy is in the fallopian tubes (about 95%) while other localizations include abdominal organs (1%), ovaries (1 – 3%), scars after previous cesarean section (1 – 3%) and cervix (1%) [5] **(Figure 1)**. In the region of the fallopian tube, the most common place of implantation of ectopic pregnancy is in the ampullary (42%), then in the isthmic part of the fallopian tube (28%), in the interstitium (13%) and about 7% in the infundibular part of the fallopian tubes **(Figure 2)**. Ectopic pregnancies outside the fallopian tubes are often overlooked or late diagnosed and are associated with higher maternal morbidity and mortality [6]. A very rare localization is the rudimentary horn of the uterus, while Litwicka et al. reported that there is an increase in the prevalence of ectopic pregnancies located in cesarean section scars, which is expected given the increase in the incidence of surgical termination of labor [7]. Risk factors for ectopic pregnancy include previous fallopian tube injuries (infections and pelvic inflammatory diseases, previous surgeries, ovarian cystectomy, etc.), infertility and assisted reproduction techniques, including multiple embryo transfers, use of contraceptives, smoking, older age (over 35 years), previous occurrence of ectopic pregnancy, and spontaneous or intentional abortions. About 50% of ectopic pregnancies are without established risk factors. Some authors believe that assisted reproduction techniques could account for as much as 2 – 5% of ectopic pregnancies, and that this risk is higher than the risk of ectopic pregnancy in preexisting diseases of the fallopian tubes [8, 9].

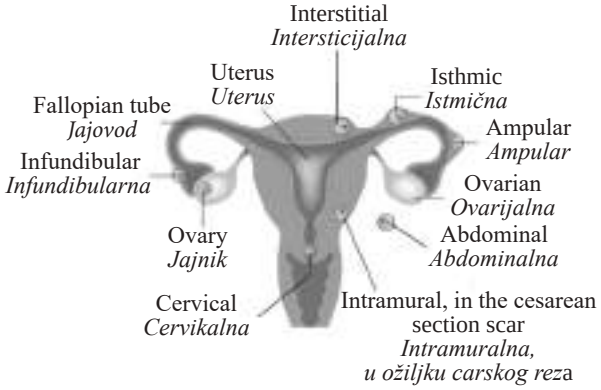

Figure 1. The most common sites of an ectopic pregnancy (downloaded from eww.drgadgilsclinic.comectopic-removal.html)
Slika 1. *Lokalizacije ektopične trudnoće (preuzeto sa www.drgadgilsclinic.comectopic-removal.html)*

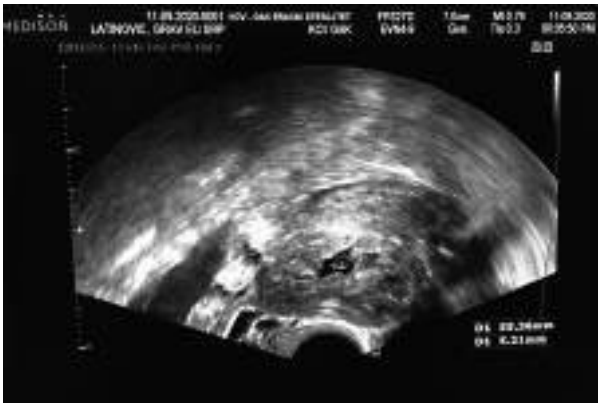

Figure 2. Ultrasonographic scan of ectopic pregnancy in the fallopian tube
Slika 2. *Ultrasonografski snimak ektopične trudnoće u jajovodu*

Symptoms and diagnostic procedures

The diagnosis of ectopic pregnancy includes a detailed medical history, physical examination, beta-human chorionic gonadotropin (beta-hCG) blood test, ultrasound examination and culdocentesis. The most common symptoms of an ectopic pregnancy are absence of menstruation and irregular vaginal bleeding and abdominal pain with a feeling of "discomfort" in the pelvis. All sexually active women of reproductive age who develop acute abdominal pain or uterine bleeding should be tested for pregnancy [10]. For a long time, culdocentesis or transvaginal aspiration of the Douglas pouch was used as the most important diagnostic procedure [11]. Nowadays, diagnostic laparoscopy is considered to be the gold standard in the diagnosis of ectopic pregnancy, but less invasive and equally reliable diagnostic procedures, such as ultrasound, are increasingly used. Hemodynamically unstable women and those with an acute abdomen must be urgently evaluated and treated. In such cases, emergency laparoscopy and laparotomy are used for diagnosis, but also for resolving a ruptured ectopic pregnancy with administration of lost fluid and blood derivatives if needed.

Ultrasonographic signs of ectopic pregnancy are very diverse. It would be ideal to visualize the fetus outside the uterine cavity. However, this happens in about 8 – 26% of cases of all ectopic pregnancies [12]. If this is not possible, it is necessary to identify some other ultrasonographic signs of ectopic preg-

nancy, such as empty uterine cavity, presence of free fluid in Douglas space, appearance of "adnexal tumor mass", altered appearance of the cervix (so-called "barrel shaped"), and gestational or pseudogestational sac [13]. In the middle of the 6th gestational week of pregnancy, a gestational sac should be seen on the endovaginal ultrasound examination. The pseudogestational sac often represents a diagnostic sonographic problem and should be distinguished from the true gestational sac [14]. It should always be borne in mind that gestational sac in the uterine cavity present on ultrasonography does not exclude simultaneous existence of a tubal pregnancy in heterotopic pregnancies. In the conducted meta-analysis, Richardson et al. reported that in case of impossibility of clear visualization of ectopic pregnancy, other mentioned indicators have low sensitivity and good specificity for the identification of tubal pregnancy [13]. However, Kirk et al. explained that during 5,318 performed ultrasound examinations in women with symptomatic and asymptomatic ectopic pregnancies, the sensitivity of endovaginal ultrasound examination was 98.3% and the specificity 99.9% [15]. A certain sonographic sign of an ectopic pregnancy is gestational sac outside the uterus, with the yolk sac and/or embryo, with or without a recorded cardiac action. In contrast, the uncertain sign of the presence of an ectopic pregnancy in the fallopian tube is the characteristic inhomogeneous mass in the area of the adnexa (the so-called "blob sign") or the extrauterine presence of a bag-like structure ("bagel sign") [16]. Nadim et al. concluded that these signs ("blob sign and bagel sign"), although they are uncertain signs of ectopic pregnancy, have a positive predictive value of over 95%. In the presence of pregnancy in a cesarean scar, the ultrasound examination shows an empty uterine cavity, empty and closed cervical canal, a thin myometrium, or absence of a myometrium between the uterine cavity and the bladder and a gestational sac in the anterior lower segment of the uterus at the site of the previous cesarean scar [17]. Endovaginal sonographic examination has found its significance and place in the diagnosis of the so-called "cervical" pregnancies. Ultrasound criteria include empty uterine cavity, barrel-shaped cervix, gestational sac below the level of the inner cervical ostium, and increased peri-trophoblastic vascularization on the color Doppler [17].

Measurement of the serum beta-hCG levels significantly contributes to making an accurate diagnosis in women with suspected ectopic pregnancy. In 50 – 70% of all cases where the values of beta-hCG are elevated and the gestational sac is not sonographically visible, it should be thought about the possibility of ectopic pregnancy [18]. Of much greater importance is the serial measurement of beta-hCG concentration at 48 hour intervals. If the increase of beta-hCG level is less than 50% or if there is a plateau, it is clear that it is not a normal intrauterine pregnancy. Women with a decrease of serum beta-hCG levels should be monitored until the complete decrease in values, because cases of fallopian tube rupture have been described even at very low beta-hCG values. In women with early pregnancies, who bleed and report abdominal pain, progesterone values below 50 nmol/l suggest a tubal pregnancy. When the levels of progesterone in the blood are below 20 nmol/l, it is certain that the fetus is not alive, regardless of the location of the pregnancy [19].

If a reliable diagnosis cannot be made by ultrasound examination, one of the diagnostic options is the use of diagnostic curettage. The intrauterine pregnancy is confirmed by the presence of chorionic villi, while the presence of decidua or proliferative endometrium is an unreliable sign for the final diagnosis of ectopic pregnancy. The experience of clinicians is also important in diagnosing ectopic pregnancy and application of an optimal therapeutic option. Fernandez et al. have developed the "Fernandez score" which should facilitate an accurate diagnosis. The parameters to be monitored and scored are the level of serum beta-hCG and progesterone, abdominal pain, hematosalpinx diameter (cm) and hemoperitoneum volume (ml). A score of less than 12 indicates that expectant or drug treatment should be used with a single dose of methotrexate (MTX), while a score of 12 or more indicates the need for surgical option [20]. Other scores, such as Elito score and others, have been described in the literature [21].

Therapeutic modalities in the treatment of ectopic pregnancy

Ectopic pregnancy can be treated by surgical, medical or expectant management. Expectant management is reserved for patients who are hemodynamically stable and adequately counseled with the possibility of monitoring and control, and access to emergency surgical treatment if necessary [22]. At levels of beta-hCG < 200 mIU/ml, spontaneous resolution occurs in 88% of cases. In a study published by Van Mello et al., at serum beta-hCG levels < 2000 mIU/ml, success of successive treatment was recorded in 59% of patients [25].

Medical treatment with MTX is an option for hemodynamically stable women who are carefully selected.

Medical treatment of ectopic pregnancy using Methotrexate

The MTX is a cytotoxic drug and a folic acid antagonist. It is not primarily registered for ectopic pregnancy treatment, but due to its considerable effect on actively proliferating trophoblastic tissues, this type of treatment is effective and is a standard therapeutic procedure in adequately selected cases **(Figure 3)**. Side effects of MTX include bone marrow suppression, nausea, vomiting, diarrhea, liver damage, stomatitis, rash, alopecia, and so on. As an antidote for these adverse reactions, Leucovorin is given at a dose of 0.1 mg/kg. Although there are studies on the oral use of MTX in the treatment of ectopic pregnancy, it is still most often administered intramuscularly or locally [23].

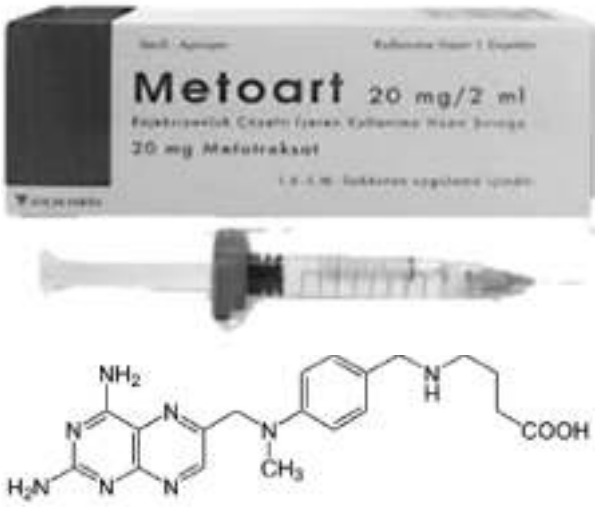

Figure 3. Methotrexate for intramuscular application; formula of methotrexate
Slika 3. *Metotreksat za intramuskularnu primenu; formula metotreksata*

Transvaginal ultrasound-guided topical application of MTX in ectopic pregnancy with localization in the fallopian tube is less effective than laparoscopic salpingotomy if fetal cardiac activity is present. It has also been shown to be more effective to inject MTX locally under ultrasound control rather than laparoscopically [24]. The application of MTX in situ is an option in the treatment of uncomplicated cervical, interstitial and pregnancy in a cesarean scar. In case of cervical pregnancy, MTX can be administered systemically or "in situ", however, patients should be informed in advance about the possible risks of bleeding and other complications [25]. Considering pregnancies in a cesarean scar, preference is given to local application over systemic, especially in case of present fetal cardiac activity. It should be combined with procedures that prevent secondary bleeding [26]. Nevertheless, cases of failed MTX therapy and subsequent surgical excision and reparation of the cesarean scar site have been described [27]. In case of ovarian pregnancy, MTX should not be the first choice therapy. Koch et al. studied a sample of 5,446 women and proved that in case of local application of MTX (cervical, interstitial and pregnancy in cesarean scar) there is a significantly longer period of decline of beta-hCG levels (29.2 days) than in case of systemic MTX application [28].

In order to start treatment with MTX, vital intrauterine pregnancy should first be ruled out. Then, it is necessary to objectively assess the woman's condition, as well as to exclude the possibility of elevated serum creatinine, liver transaminases or bone marrow dysfunction, severe anemia, leukopenia, or thrombocytopenia. It is necessary to perform laboratory tests: serum beta-hCG concentration, complete blood count, hemostasis, liver and kidney panel, blood group and Rh factor. Relative contraindications for using MTX include: presence of fetal cardiac action, sac size > 4 cm, transfusion rejection, inability to monitor and control, hematosalpinx, high basal progesterone levels, and beta-hCG levels > 5000 mIU/ml. Some studies have reported failure of MTX treatment in 57 – 62% of cases with beta-hCG levels above 5000 mIU/ml, while Menon et al. reported that at beta-hCG levels > 5000 mIU/ml, treatment failure is 14.3% versus only 3.7% of failure at values less than 5000 mIU/ml [29]. Potter et al. showed that the risk of failure is 5.5 times higher for beta-hCG levels above 5000 mIU/ml [30]. Absolute contraindications include vital intrauterine pregnancy, immunodeficiency, moderate to severe anemia, leukopenia or thrombocytopenia, sensitivity to MTX, active lung disease and ulcer disease, clinically significant liver dysfunction, renal dysfunction, breastfeeding, lactation and rupture. There is also evidence of failure of MTX therapy in women in whom there is a rapid increase of beta-hCG levels, i.e. an increase of more than 50% over a period of 48 hours [32].

If the criteria for the use of MTX are met, the MTX protocol is selected. Three protocols have been published: single-dose, two-dose and the multiple dose protocol [33–35]. Single-dose protocol involves intramuscular administration of MTX 50 mg/m^2 on day 1. After that, serum beta-hCG levels are measured on days 4 and 7. If the decrease of beta-hCG levels is less than 15% in the period of 4 – 7 days, it is necessary to repeat the dose of MTX (25% of patients). If the decrease of beta-hCG level is > 15%, the patient should be monitored at intervals of 7 days. If there is no significant decrease of beta-hCG levels after 2 doses, a surgical treatment is considered [33].

The two-dose protocol was first introduced in 2007 and it showed higher efficiency rate and fewer side effects. It includes intramuscular administration of 50 mg/m^2 MTX on days 1 and 4, and measuring beta-hCG levels on days 4 and 7. If the decrease of beta-hCG level is > 15%, the patient is monitored for 7 days, and if the decrease of beta-hCG is less than 15%, the dose should be repeated on day 7, and beta-hCG measurement should be done on day 11. If the decrease of beta-hCG levels is less than 15% from day 7 – 11, the dose of MTX should be repeated on day 11, and beta-hCG measurement should be repeated on day 14. If there is no significant decline even after the 4th dose of MTX, a surgical treatment is considered [36]. This protocol is also used at the Clinic of Obstetrics and Gynecology of the Clinical Center of Vojvodina in Novi Sad.

The third protocol, the so-called fixed multiple dose protocol, consists of intramuscular MTX 1 mg/kg on days 1, 3, 5 and 7 with folic acid 0.1 mg/kg on days 2, 4, 6 and 8 and/or Leucovorin. Beta-hCG levels are measured on days of MTX administration. If there is a drop over 15%, MTX is discontinued and monitoring is performed for 7 days, and if there is no significant drop after the 4th dose, surgical treatment is considered [37].

From the beginning of MTX application in the therapy of ectopic pregnancy until today, numerous researches have been conducted. Kasum et al. proved that the initial levels of beta-hCG and progesterone were inversely proportional to the success of drug treatment in a selected group of patients and that these two parameters are important predictors in the treatment

of ectopic pregnancy with MTX [38]. Li Jin Bo et al. explored the possibility of using MTX in the treatment of heterotopic pregnancy. They concluded that MTX cannot be applied in case of heterotopic pregnancy, either locally or systemically, because it has teratogenic effects on the vital intrauterine fetus [39].

A meta-analysis conducted by Alur-Gupta et al. showed that the two-dose MTX administration protocol is superior to the single-dose protocol in terms of treatment outcome, and they recommend it as the first-line treatment in women with high levels of beta-hCG and large tumorous adnexal masses. Also, they proved that the multiple dose protocol does not have a significant reduction in the number of failed MTX treatments, but has a higher incidence of side effects [40]. An important aspect of MTX therapy is the possibility of achieving a healthy pregnancy after treatment. The teratogenicity of MTX has been proven, as well as the retention of its derivatives in tissues. A 2016 study by Lagarce et al. showed that in the group of women treated with MTX, 6.7% of pregnancies ended in miscarriage and that two major malformations were described among children, one of which was the tetralogy of Fallot, which is consistent with previously described cases of MTX exposure during early pregnancy. It is recommended to avoid conception and pregnancy for 3 to 6 months after MTX administration [41].

Surgical procedures in the treatment of ectopic pregnancy

Candidates for surgical treatment are women who are hemodynamically unstable, who are not recommended to use MTX or in whom the treatment with MTX had no effect, as well as those with a heterotopic pregnancy. In women with tubal pregnancy who are in the reproductive period, salpingotomy is the method of choice. Also, salpingectomy is the method of choice in women who have repeated pregnancies in the fallopian tube, those who have a pregnancy larger than 5 cm, as well as in those who have completed childbearing [42]. If the contralateral fallopian tube is preserved, salpingotomy and/or salpingectomy have the same effect on pregnancy after the intervention. In 2015, Kutlešić et al. described a rare case of abdominal pregnancy, diagnosed at 6 weeks of gestation, located in the vesicouterine pouch, which was successfully treated by laparoscopy [45].

Conclusion

Ectopic pregnancy is the implantation of a fertilized ovum outside the uterine cavity. The most common localization is in the fallopian tube. Depending on whether it occurs in acute or subacute form, it has different symptoms. The use of endovaginal sonography and determination of serum beta-human chorionic gonadotropin levels have the highest degree of reliability in making the diagnosis. Ectopic pregnancy can be treated by surgical, medical or expectant management. Methotrexate, an antineoplastic drug, given topically or systemically, is used in drug treatment. In properly selected patients, the success rate is around 93%. Methotrexate can be administered in three ways: as a single-dose, a two-dose, and a multiple dose protocol, where the two-dose is described as the most effective with the fewest complications and side effects.

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Primaju se samo radovi koji su napisani na engleskom jeziku, uz sažetak rada i naslov rada koji treba da budu napisani na engleskom i srpskom jeziku.

Radove koji su pristigli u časopis *Medicinski pregled* pregleda jedan ili više članova Uređivačkog odbora Časopisa. Oni radovi koji su napisani prema pravilima Časopisa šalju se na anonimnu recenziju kod najmanje dva recenzenta, stručnjaka iz odgovarajuće oblasti biomedicine. Načinjene recenzije radova pregleda glavni urednik ili članovi Uređivačkog odbora i one nisu garancija da će rad biti prihvaćen za štampu. Materijal koji je pristigao u časopis ostaje poverljiv dok se rad nalazi na recenziji, a identitet autora i recenzenata su zaštićeni, osim u slučaju ako oni odluče drugačije.

U časopisu *Medicinski pregled* objavljuju se: uvodnici, originalni članci, prethodna ili kratka saopštenja, pregledni članci, stručni članci, prikazi slučajeva, članci iz istorije medicine i drugi članci.

1. Uvodnici – do 5 strana. Sadrže mišljenja ili diskusiju o posebno značajnoj temi za Časopis, kao i o podacima koji su štampani u ovom ili nekom drugom časopisu. Obično ih piše jedan autor po pozivu.

2. Originalni članci – do 12 strana. Predstavljaju rezultate istraživanja autora rada i njihovo tumačenje. Istraživanje treba da bude obrađeno i izloženo na način da se može ponoviti, a analiza rezultata i zaključci jasni da bi se mogli proveriti.

3. Pregledni članci – do 10 strana. Predstavljaju sistematsko, sveobuhvatno i kritičko izlaganje problema na osnovu analiziranih i diskutovanih podataka iz literature, a koji oslikavaju postojeću situaciju u određenom području istraživanja. Literatura koja se koristi u radu mora da sadrži najmanje 5 radova autora članka iz uže naučne oblasti koja je opisana u radu.

4. Prethodna ili kratka saopštenja – do 4 strane. Sadrže izuzetno važne naučne rezultate koje bi trebalo objaviti u što kraćem vremenu. Ne moraju da sadrže detaljan opis metodologije rada i rezultata, ali moraju da imaju sva poglavlja kao originalni članci u sažetoj formi.

5. Stručni članci – do 10 strana. Odnose se na proveru ili prikaz prethodnog istraživanja i predstavljaju koristan izvor za širenje znanja i prilagođavanja originalnog istraživanja potrebama postojeće nauke i prakse.

6. Prikazi slučajeva – do 6 strana. Opisuju retke slučajeve iz prakse. Slični su stručnim člancima. U ovim radovima prikazuju se neuobičajeni oblici i tokovi oboljenja, neočekivane reakcije na primenjenu terapiju, primene novih dijagnostičkih procedura ili retke i nove bolesti.

7. Članci iz istorije medicine – do 10 strana. Ovi članci opisuju događaje iz prošlosti sa ciljem da omoguće očuvanje medicinske i zdravstvene kulture. Imaju karakter stručnih članaka.

8. Ostali članci – U časopisu Medicinski pregled objavljuju se feljtoni, prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih organizacija, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novosti u medicini, pitanja i odgovori, stručne i staleške vesti i članci napisani u znak sećanja (*In memoriam).*

Priprema rukopisa

Kompletan rukopis, uključujući tekst rada, sve priloge i propratno pismo, treba poslati na elektronsku adresu koja je prethodno navedena.

Propratno pismo:

– mora da sadrži izjavu svih autora da se radi o originalnom radu koji prethodno nije objavljen niti prihvaćen za štampu u drugim časopisima;

– autori svojim potpisom preuzimaju odgovornost da rad ispunjava sve postavljene uslove i da ne postoji sukob interesa i

– autor mora navesti kategoriju članka (originalni rad, pregleni rad, prethodno saopštenje, stručni rad, prikaz slučaja, rad iz istorije medicine, itd.).

Rukopis

Opšta uputstva

Tekst rada treba da bude napisan u programu *Microsoft Word* za *Windows*, na A4 formatu stranice (sve četiri margine 2,5 cm), proreda 1,5 (isto važi i za tabele), fontom *Times New Roman*, veličinom slova 12 *pt*. Neophodno je koristiti međunarodni sistem mernih jedinica (*SI*), uz izuzetak temperature (° *C*) i krvnog pritiska (*mmHg*).

Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana

Naslovna strana treba da sadrži: kratak i sažet naslov rada, bez skraćenica, skraćeni naslov rada (do 40 karaktera), imena i prezimena autora (ne više od 6) i afilijacije svih autora. Na dnu strane treba da piše ime, prezime i titula autora zaduženog za korespondenciju, njena/njegova adresa, elektronska adresa, broj telefona i faksa.

2. Sažetak

Sažetak ne može da sadrži više od 250 reči niti skraćenice. Treba da bude strukturisan, kratak i sažet, sa jasnim pregledom problema istraživanja, ciljevima, metodama, značajnim rezultatima i zaključcima.

Sažetak originalnih i stručnih članaka treba da sadrži uvod (sa ciljevima istraživanja), materijale i metode, rezultate i zaključak.

Sažetak prikaza slučaja treba da sadrži uvod, prikaz slučaja i zaključak.

Sažetak preglednih članaka treba da sadrži Uvod, podnaslove koji odgovaraju istima u tekstu i Zaključak.

Navesti do 10 ključnih reči ispod sažetka. One su pomoć prilikom indeksiranja, ali autorove ključne reči mogu biti izmenjene u skladu sa odgovarajućim deskriptorima, odnosno terminima iz *Medical Subject Headings, MeSH.*

Sažetak treba da bude napisan na srpskom i engleskom jeziku. Sažetak na srpskom jeziku trebalo bi da predstavlja prevod sažetka na engleskom, što podrazumeva da sadrži jednake delove.

3. Tekst članka

Originalni rad treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima istraživanja), Materijal i metode, Rezultati, Diskusija, Zaključak, spisak skraćenica (ukoliko su

korišćene u tekstu). Nije neophodno da se u posebnom poglavlju rada napiše zahvalnica onima koji su pomogli da se istraživanje uradi, kao i da se rad napiše.

Prikaz slučaja treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima), Prikaz slučaja, Diskusija i Zaključak.

Uvod

U poglavlju Uvod potrebno je jasno definisati predmet istraživanja (prirodu i značaj istraživanja), navesti značajne navode literature i jasno definisati ciljeve istraživanja i hipoteze.

Materijal i metode

Materijal i metode rada treba da sadrže podatke o vrsti studije (prospektivna/retrospektivna, uslove za uključivanje i ograničenja studije, trajanje istraživanja, demografske podatke, period praćenja). Detaljno treba opisati statističke metode da bi čitaoci rada mogli da provere iznesene rezultate.

Rezultati

Rezultati predstavljaju detaljan prikaz podataka koji su dobijeni istraživanjem. Sve tabele, grafikoni, sheme i slike moraju biti citirani u tekstu rada i označeni brojevima po redosledu njihovog navođenja.

Diskusija

Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

Zaključak

Zaključci moraju proisteći isključivo iz rezultata istraživanja rada; treba izbegavati uopštene i nepotrebne zaključke. Zaključci koji su navedeni u tekstu rada moraju biti u saglasnosti sa zaključcima iz Sažetka.

4. Literatura

Potrebno je da se literatura numeriše arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (*http://www.nlm.nih.gov/tsd/serials/lji.html*). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al*.

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ Organizacija kao autor

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ Bez autora

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ Volumen sa suplementom

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ Sveska sa suplementom

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ Sažetak u časopisu

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije

∗ Jedan ili više autora

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ Urednik (urednici) kao autor (autori)

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ Poglavlje u knjizi

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ Zbornik radova sa kongresa

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ Disertacija

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ Monografija u elektronskom formatu

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ Kompjuterska datoteka

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG, GIF, TIFF, EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/user/register.

Manuscript submission should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/

A SUPPLEMENTARY FILE, WITH THE STATEMENT THAT THE PAPER HAS NOT BEEN SUBMITTED OR ACCEPTED FOR PUBLICATION ELSEWHERE AND A CONSENT SIGNED BY ALL AUTHORS, HAVE TO BE ENCLOSED WITH THE MANUSCRIPT.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.