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Sadržaj / Table of Contents

The use of emergency department services for non-emergency conditions	3
<i>Ali Arhami Dolatabadi, Marzieh Maleki, Elham Memary, Hamid Kariman, Majid Shojaee, Alireza Baratloo</i>	
Human Capital in Healthcare Institutions: the Case of Slovenia.....	10
<i>Jasmina Starc, Irena Stopar</i>	
Factor validity and consistency of the Maslach burnout inventory - general survey among Lithuanian general practitioners, community nurses and social workers	18
<i>Raila Gediminas, Jaruseviciene Lina</i>	
Outcomes of IVF procedures based on the number of oocytes in COS with short antagonist protocol in woman with unexplained infertility.....	30
<i>Sanja Sibincic, Elmira Hajder, Nenad Lucic, Brankica Djukic-Kukolj, Nenad Babic, Djordje Cekrlija, Sanja Lukac, Mirjana Ostojic, Milica Gvero, Sasa Vujnic</i>	
Chronic inflammatory syndrome – markers in the study of the metabolic syndrome in primary health care	36
<i>Elena Popa, Agnes Bacusca, Adorata Elena Coman</i>	
Letrozole plus lower dose of Human menopausal Gonadotropins plus GnRH Antagonists Protocol for Women with Poor Ovarian Response Undergoing IUI Treatment Cycles: Randomized Controlled Trial.....	45
<i>Elmira Hajder, Sanja Sibincic, Mithad Hajder, Ensar Hajder</i>	
Instructions for the authors.....	52

The use of emergency department services for non-emergency conditions

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Abstract

Introduction: Emergency Departments (ED) are designed to provide health services to patients who are physiologically unstable and need continuous examination and treatment based on the progression of their disease. Naturally, a major part of critical care is performed in this department. Nevertheless, a number of patients visiting this department do not truly require emergency services. The present study was conducted to examine the reasons for the use of ED services for non-emergency conditions at Imam Hossein Hospital.

Methods: This cross-sectional study was conducted at the Emergency Department (ED) of Imam Hossein Hospital in Tehran, Iran. The study samples were selected through census sampling and the patients visiting the ED. A trained nurse collected the data using a checklist consisted of items on the patients' basic details and on their recent visit, including the time, date and reason for the visit. The inaccessibility of the physician in attendance, prescription renewal due to running out of medications, prescription renewal due to prescription flaws, clinics or private doctors' offices being closed, presenting test results requested by other physicians and presenting radiographs requested by other physicians were considered as non-emergency cases. The data obtained were analyzed in SPSS-22. Descriptive statistics were used to report the results as mean \pm standard deviation or as frequency + percentage.

Results: This study was performed on 1500 patients with a mean age of 40.0 ± 17.34 years (54.47% female). Overall, 601 (40.1%) of the patients had visited the ED for non-emergency conditions based on the definitions provided in

this study. Table 2 presents the reasons for non-emergency ED visits. Prescription renewal due to prescription flaws (16.7%) and the inaccessibility of the physician in attendance (14.07%) were the most frequent reasons for non-emergency ED visits. Table 3 presents the relationship between non-emergency ED visits and basic details in the examined patients.

Conclusion: Based on the present findings, about 40% of the ED visits to the examined hospital appear to have been due to non-emergency conditions. Prescription renewal due to prescription flaws and the inaccessibility of the physician in attendance were the most frequent reasons for non-emergency ED visits. Gender and previous history of disease were variables affecting non-emergency visits.

Key words: Emergency department; emergencies; health services misuse

Introduction

Emergency Departments (EDs) are designed to provide health services to patients who are physiologically unstable and need continuous examination and treatment based on the progression of their disease (1, 2). Naturally, a major part of critical care is performed in this department. Nevertheless, a number of patients visiting this department do not truly require emergency services (3). Various studies have shown that 10-30% of all visits to EDs in the US are made by patients with non-emergency conditions (4-6). It is worth noting that visits to EDs instead of outpatient clinics for non-emergency conditions may result in unnecessary tests and therapeutic procedures in addition to interfering with the duties of physicians offering primary

health care services (7, 8). The data provided on health economics in the US shows that examining and treating non-emergency cases in outpatient clinics leads to annual savings of approximately 4400 million dollars in this sector (9). The number of patients visiting EDs for non-emergency conditions may further increase in the near future along with the increased public demands and the shortage of physicians offering primary health care services (10). Many health care system planners are therefore trying to develop a program to reduce the frequency of non-emergency visits to EDs. It should be noted, however, that some hospitals adopt financial policies that lead to an increase in non-emergency visits but boost their own income (11), while health care systems are constantly seeking to train patients to understand which conditions require emergency services, to create financial barriers such as increasing charges for patients in EDs and to encourage primary healthcare physicians to work in night shifts and during the holidays as well so as to help reduce ED visits for non-emergency conditions (12, 13). Despite all these attempts, ED visits for non-emergency conditions are increasing by day. One reason for this increase may be the counter reaction to the financial policies adopted and the reduced franchise for emergency patients, which still have not been able to prevent unnecessary patient visits to EDs (11). Given the lack of studies on the reasons for patients' visits to EDs in Iran, the present study was conducted to examine the reasons for the use of ED services for non-emergency conditions at Imam Hossein Hospital.

Materials and Methods

Study Design

This cross-sectional study was conducted at the Emergency Department (ED) of Imam Hossein Hospital in Tehran, Iran, from July 2014 to July 2015. Sampling started after obtaining the approval of the Ethics Committee of Shahid Beheshti University of Medical Sciences and all the researchers adhered to the Declaration of Helsinki throughout the study.

Participants

The study samples were selected through census sampling and the patients visiting the ED of Imam

Hossein Hospital from late July 2014 to late July 2015 were included in the study. All the patients admitted to the ED of the select hospital were divided into cases needing emergency services and other cases, based on the New York University Emergency Department Algorithm. The patients whose initial examination led to therapeutic procedures at the ED or direct referral to operating rooms were recognized as true emergency patients. Other patients whose reason for visiting the ED was a type of disease not requiring emergency care according to their examinations and who were at triage level four or five were also included in the study after confirmation by the physician. The patients completed a pre-developed checklist.

Data Collection

A trained nurse collected the data using a checklist. The checklist consisted of items on the patients' basic details (gender, age, nationality, level of education, medical history, history of drug abuse and type of insurance) and on their recent visit, including the time, date and reason for the visit. The inaccessibility of the physician in attendance, prescription renewal due to running out of medications, prescription renewal due to prescription flaws, clinics or private doctors' offices being closed, presenting test results requested by other physicians and presenting radiographs requested by other physicians were considered as non-emergency cases.

Statistical Data Analysis

The data obtained were analyzed in SPSS-22. Descriptive statistics were used to report the results as mean \pm standard deviation or as frequency + percentage. Fisher's exact test and Mann-Whitney U test tests were used to compare the study variables. The level of statistical significance was set at $P < 0.05$.

Results

Basic Details of the Patients

This study was performed on 1500 patients with a mean age of 40.0 ± 17.34 years (a minimum age of 1 and a maximum of 95); 54.47% of the patients were female. Table 1 presents a summary of the patients' basic details. A total of 1230 patients (82.01%) were aged 18-64 years, and 1449

(97.58%) were of Iranian nationality. The most frequent level of education observed among the patients (27.43%) was associate's degree.

Table 1. The basic details of the studied patients

Variable	Number (%)
Gender	
Female	817(54.47)
Male	683(45.53)
Age	
<18	16(1.06)
18-64	1230(82.01)
>64	254(16.93)
Nationality	
Iranian	1449(97.58)
Afghan	34(2.29)
Other	2(0.13)
Level of Education	
PhD	30(2.01)
Master's Degree	153(10.19)
Bachelor's Degree	65(4.36)
Associate's Degree	411(27.43)
High School Diploma	343(22.87)
Junior High School Diploma	305(20.32)
Illiterate	188(12.54)
Other	5(0.28)
Medical History	
Hypertension	196(13.07)
Diabetes	152(10.13)
Asthma	12(0.80)
Stroke	10(0.67)
Myocardial Infarction	9(0.60)
Seizures	5(0.33)
Chronic Kidney Failure	3(0.20)
Other	267(17.80)
Drug Abuse	
Cigarettes	201(13.4)
Alcohol	5(0.33)
Narcotics	43(2.87)
Other	14(0.93)
Insurance	
Social Security	864(57.60)
Iran Health Insurance Organization	376(25.07)
Treatment Services	45(3.00)
Armed Forces	29(1.93)
Rural	26(1.73)
Imam Khomeini Relief Foundation	1(0.07)
Other	107(7.13)
No Insurance	52(3.47)

The analysis of the patient's medical history showed hypertension to have the highest frequency (n=196, 13.07%). A total of 201 patients (13.4%) smoked cigarettes and 60 (4.0%) reported at least one type of drug abuse. A total of 864 patients (57.6%) were covered by social security insurance. As for the time of the ED visit, 83.86% of the patients had visited this department on working days and 80.18% between 8am and 2pm.

Factors Related to the Patients' Current Condition

Overall, 601 (40.1%) of the patients had visited the ED for non-emergency conditions based on the definitions provided in this study. Table 2 presents the reasons for non-emergency ED visits. Prescription renewal due to prescription flaws (16.7%) and the inaccessibility of the physician in attendance (14.07%) were the most frequent reasons for non-emergency ED visits. Table 3 presents the relationship between non-emergency ED visits and basic details in the examined patients.

Table 2. The frequency distribution of the reasons for non-emergency visits to the Emergency Department

Reason of visit	Number (%)
Prescription renewal due to prescription flaws	269(16.7)
The inaccessibility of the physician in attendance	211(14.1)
Presenting test results requested by other physicians	64(4.0)
Prescription renewal due to running out of medications	34(2.3)
Presenting radiographs requested by other physicians	17(1.1)
Clinics or private doctors' offices being closed	14(0.9)
Other	50(3.1)

Table 3. The relationship between non-emergency visits to the Emergency Department and basic details in the studied patients

Variable	Non-Emergency	Emergency	P-Value
	Number (%)	Number (%)	
Gender			
Male	202(33.6)	486(53.5)	<0.001
Female	399(66.4)	418(46.5)	
Age			
0-15	29(4.9)	41(4.6)	0.327
15-30	137(23.1)	244(27.3)	
30-45	190(32)	292(32.6)	
45-60	146(24.6)	191(21.3)	
>60	92(15.5)	127(14.2)	
Ethnicity			
Iranian	581(97.8)	868(97.4)	0.547
Afghan	11(1.9)	23(2.6)	
Other	2(0.3)	0(0.0)	
Level of Education			
Illiterate	81(13.6)	106(11.8)	0.86
Junior High School Diploma	119(20)	184(20.5)	
High School Diploma	134(22.6)	207(23.1)	
Associate's Degree	166(27.9)	243(27.1)	
Bachelor's Degree	23(3.9)	42(4.7)	
Master's Degree	97(10.8)	55(9.3)	
PhD	16(1.8)	14(2.4)	
Other	2(0.3)	2(0.2)	
Hour of Visit			
8-14	455(76.3)	730(82.8)	<0.001
14-20	81(13.6)	56(6.3)	
20-2	47(7.9)	78(8.8)	
2-8	13(2.5)	18(2)	
Time of Visit			
Weekdays	527(90.2)	694(79.6)	<0.001
Holidays	57(9.8)	178(20.4)	
Addiction			
None	585(97.3)	857(95.3)	0.03
Addicted	16(2.7)	42(4.7)	
History of Disease			
Yes	358(59.6)	650(72.3)	0.962
No	243(40.4)	249(27.7)	
Insurance Coverage			
With Insurance Coverage	580(96.5)	868(96.6)	0.962
Without Insurance Coverage	21(3.5)	31(3.4)	

Discussion

According to the present findings, it appears that almost 40% of the visits to the ED of the examined hospital are due to non-emergency conditions. Prescription renewal due to prescription

flaws and the inaccessibility of the physician in attendance were the most frequent reasons for non-emergency ED visits in this hospital. Gender and previous history of disease were variables affecting non-emergency visits.

A similar study conducted in the US reported non-emergency ED visits as 37%, which is almost consistent with the results obtained in the present study (11). Younger age, easier access to EDs compared to their alternatives, patients' referral by physicians and negative perceptions of the centers providing primary medical services are reported as the reasons for non-emergency ED visits (2). In this study, prescription renewal due to prescription flaws, the inaccessibility of the physician in attendance and presenting para-clinical tests requested by other physicians were the most frequent reasons for non-emergency ED visits.

In one study, Sarver et al. argued that patients who are dissatisfied with the primary medical services provided by their family physician or who have difficulty booking an appointment with a specialist are more likely to use ED services for non-emergency conditions (14).

Rust et al. examined the barriers to the use of regular medical services and the alternative use of emergency services in the US. A total of 23413 respondents who had access to regular medical services participated in this survey. One out of every five respondents who reportedly had no barriers to using regular medical services had used ED services over the past year, while one out of each three respondents who reported at least one barrier to using regular medical services had used ED services over the past year. The reasons for non-emergency visits to the ED in the cited study included the lack of access to medical services over the phone, the lack of quick access to non-emergency medical service providers, long waiting times in outpatient clinics, outpatient clinics being closed when the patient has time to visit and problems with the access to public transportation. Interventions for improving the access to medical services, such as adjusting work hours, appear to help improve patients' satisfaction with medical services and to preserve health economic resources and to thus also prevent overcrowded EDs (15).

Several studies have examined the role of insurance in the frequency of non-emergency ED visits. Cheung et al. studied the barriers to the timely provision of primary medical services and the use of ED services for patients using federal insurance compared to patients using private insurances. They found that patients using federal insurance

are faced with greater barriers to a timely access to primary medical services and therefore visit EDs more frequently than patients using private insurances (16). Weber et al. studied the effect of the lack of access to insurance services and primary medical services on the increase in ED visits and found that patients who use ED services do not differ from others in terms of insurance and access to medical services; however, they are more likely to suffer from a poor health status and be faced with some difficulties in seeking outpatient medical services. Their study also showed that improving outpatient services helps reduce ED visits (17). In another study, Weber et al. examined the effect of insurance on the frequency of ED visits and showed that the increase in the number of ED visits between 1996 and 2003 cannot be linked to the lack of access to insurance services. They argued that the non-poor and those covered by the services of a family physician seem to have several improper reasons for visiting EDs (18). As for insurance coverage or the lack thereof, it is generally the case that people without insurance coverage visit EDs more frequently and people with insurance coverage have more frequent non-emergency visits (19). In the present study, less than 4% of the patients with non-emergency conditions had no insurance coverage, and insurance coverage or the lack thereof did not affect the rate of non-emergency ED visits.

In a study conducted to examine the reasons for non-emergency visits to EDs, Liu et al. studied the data obtained from 135723 ED visits between 1992 and 1996 and found that non-emergency visits are definitely correlated with socio-demographic factors (20); similarly, the present study found age to be an influential factor in non-emergency ED visits.

Learning about the precise statistics of this issue leads to a better understanding of the existing needs and can help authorities plan in line with these needs. Given the limited facilities of EDs, which often over-admit patients, and the consequent reduced emergency preparedness for unexpected accidents and crises, it is upon the authorities to prioritize emergency departments in their health care plans and to devise strategies for preventing their overcrowding. Access to more accurate and comprehensive data on the patients

visiting EDs helps adopt more practical strategies for reducing overcrowding in these departments.

Limitations

This study was performed in just one center and during one month. It would be better to perform such studies in multi centers and prolong period to evaluate more effective factors and more applicable results.

Conclusion

Based on the present findings, about 40% of the ED visits to the examined hospital appear to have been due to non-emergency conditions. Prescription renewal due to prescription flaws and the inaccessibility of the physician in attendance were the most frequent reasons for non-emergency ED visits. Gender and previous history of disease were variables affecting non-emergency visits.

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Authorship Contribution

All authors followed the recommendations of the International Committee of Medical Journal Editors (ICMJE).

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Human Capital in Healthcare Institutions: the Case of Slovenia

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Abstract

Background: Human capital in healthcare institutions is all the healthcare professionals that help the healthcare institution to create new value by means of their attitudes, intellectual flexibility and abilities.

Materials and Methods: A quantitative research study with an online survey was conducted on a sample of 410 nurses employed at healthcare institutions. Cronbach's alpha coefficient 0.896. The data was processed using SPSS 19.0. The t-test for independent samples was used.

Results: Differences have been observed between the opinions of nurses employed at healthcare institutions in Central Slovenia and those employed at healthcare institutions in Eastern Slovenia regarding human capital valuation. The greatest differences are seen in the opinions of nurses regarding their salaries ($p=0.000$); the sense of security provided by their manager ($p=0.000$); the investment in human capital ($p=0.000$); the awareness of its importance for the organisation with regard to achieving goals ($p=0.000$); and regarding the planning of professional development ($p=0.000$).

Discussion: The growth and development of human capital in healthcare institutions can be reflected in the improved performance of nurses, which, in turn, is evident in the quality of the implementation of healthcare and nursing services; more efficient organisation of their work; their desire to receive professional training and further education, and take on new duties; in the satisfaction of patients; and in the more effective identification of their needs.

Key words: human capital, nurses, healthcare, healthcare institutions

Introduction

Human capital is a resource that contributes to the development of an organisation (1). The creative

element of every organisation is its employees, who possess knowledge, skills, experience, creativity and abilities. In professional and scientific literature, human capital is defined in many different ways, yet all those definitions agree that it concerns investments in the abilities of individuals who are creatively involved in the work process by using their knowledge and experiences, and who solve any problems they encounter. Furthermore, by investing in education, the company is increasing its added value, economic profitability and efficiency (2).

If the employees are motivated and satisfied, they present great potential, which can be redirected towards achieving the goals of the organisation, thus making it competitive on the market (3, 4, 5). Therefore, human capital is a set of all the skills, abilities, experiences and knowledge of an individual (6). However, until that knowledge becomes applicable within the scope of the organisation's goals and as long as the results do not strive towards new value, one cannot talk about human capital. Therefore, the task of top-level management is to identify this knowledge, skills and potential, which must be guided and encouraged through motivation; afterwards it must plan the investments in said knowledge and development, and in the skills that are required for the practical application of this knowledge. By doing so, the organisation gains qualified and motivated people who represent its valuable human capital. Different authors explain human capital in different ways. Zupan et al. (7) describe human capital as an internal dimension of intellectual capital, which encompasses the elements of education, competences, values, attitudes and experiences of individuals. Hudson (8) defines human capital as a combination of an individual's inherited abilities, competences gained through training and education that have been developed through experience, and a demonstrated attitude towards life and work. Ross (7) separates human capital into abilities, intellectual flexibility and attitude towards work, whereas

Spence (9) is of the opinion that the visible signs of human capital are rewarded, because they simultaneously signal other qualities of workers. Černetič (10) defines human capital as the first form of capital that we encounter in the socioeconomic system. The forms of intellectual and social capital appear later on (6). For this reason, the organisations of today are not satisfied with the end-of-year profit alone, but expect positive potential and performance projections in the future. Human capital is also described as an internal dimension of intellectual capital, which encompasses the elements of education, competences, values, attitudes and experiences of individuals (8).

Today, human capital is a synonym for knowledge that is of great importance and invaluable. Ivanuša-Bezdek (11) states that organisations are experiencing a constantly growing need for additional knowledge of employees and the need for higher quality and more professional implementation of tasks. Knowledge application provides a strategic advantage over other companies. Thus human capital denotes more than just formal education. Dalkir (12) labels human capital the collective organisational ability of management to utilise knowledge and make the organisation successful and competitive. If we were to expand the concept of human capital to all those abilities that might not be directly connected with work, we would perceive its breadth, namely that human capital is not owned by the organisation but borrowed by it on a daily basis; moreover, that the value of human capital can be increased through use, e.g. by gaining new experiences and knowledge. Every organisation is capable of making an information system and responsibilities framework that would ensure the utilisation of human potential in work organisation (13, 14, 15).

Dakhli and De Clerco (16) focus on the division of human capital into three layers:

- *firm-specific human capital*: refers to the skills and knowledge that are valuable only within a specific company. Even though firm-specific skills generate advantage for the company over its competitors, they cannot be transferred to other companies.
- *industry-specific human capital*: refers to the skills and knowledge derived from the experience of a specific industry. If this type of human capital is based on an exchange of quality knowledge among industry

participants, it can play an important part in generating innovations within the industry. When ideas for products or processes are, on the one hand, the result of good communication among partners and, on the other hand, of the presence of the so-called silent know-how in the existing technology, this type of human capital is of great importance in creating innovations. This silent nature of the said capital often makes this second type of human capital understandable only to specialists in a particular industry, which provides a defence mechanism that reduces the need for patent protection.

- *individual-specific human capital*: refers to knowledge that can be used in various companies and industries. It encompasses an individual's experience, formal education, professional training and length of service. Research of human capital has shown that the total level of human capital greatly influences economic performance.

It is therefore sensible to prioritise human resources, thus enabling employees to continuously gain new knowledge that stimulates their creativity and innovativeness, and increases their motivation for their own professional and career development, and for entrepreneurial thinking and acting. Hence, it is not enough that companies are aware of the growing importance of human capital; they should start designing efficient human resource management systems. In doing so, they must abide by three basic principles, which it would be sensible to evaluate within the scope of human resource management (17):

- Human resources is the most important asset of an organisation.
- The key to an organisation's success is efficient human resource management.
- This success is most easily achieved if the organisation's personnel policy and business procedures are closely interconnected and contribute the most to the attainment of common goals.

The authors researching the types of human capital have defined three different types of human capital:

From here on in, we will be focusing on the human capital in healthcare institutions. Slovenian healthcare is generally under great pressure from the public. Every day, one can hear about more or less bad news and experiences of individuals who are dissatisfied with their treatment. This raises the question as to what is in fact happening with human capital in healthcare institutions. The Slovenian healthcare industry often talks about quality and necessary changes, but these involve highly demanding processes in which the key dimension of success is the management's ability to truly manage the knowledge potential of each individual in the organisation. It is typical of healthcare that it is a specific field which cannot be easily influenced by any other professional field. However, numerous basic and applied research studies have shown that it can no longer be discussed merely from the aspect of medical science (18). Nevertheless, Starc and Ilič (1) point out the possibility of change, for they both see the future of healthcare in the professionalisation of healthcare professionals in the following aspects: fast, i.e. efficient decision-making in crisis situations is required; more efficient organisation of the operation of the healthcare industry and of the work of employees; career advancement; taking on new duties; quality of healthcare and nursing services; work-performing skills for achieving greater productivity; responsibility for the work performed; quality management and control of work processes; achieving compliance with standards; patient satisfaction; more efficient identification of the patient's needs; and passing the knowledge gained on to one's colleagues.

For the further successful development of the healthcare system it is important that we stop viewing healthcare as a system of isolated components, because in healthcare institutions people make up a system in which individuals and groups come together. This means nurses, doctors, system users, managers, etc. All of them have different views and interests. The success and efficiency of a healthcare organisation is not reflected in what an individual component of the system is doing, but in how the components are cooperating to achieve the common goals (18). The growth and development of human capital can be seen in the improved performance of individuals and of

the healthcare organisation, namely according to the following performance indicators (1): quality of healthcare services; more efficient work organisation; employee satisfaction; expansion of healthcare activities and improving the abilities of employees; affiliation to the organisation; workplace productivity; quality of interpersonal relationships; adapting; modified working conditions; easier and faster adoption of new technology; achieving optimal utilisation of resources; more efficient utilisation of material; more efficient utilisation of working hours.

Recognising the importance of lifelong learning in one's life and career contributes to asserting the scientific and professional human capital of healthcare professionals. The development of healthcare professionals is a process and as such requires expert knowledge in human resource planning, education and management (19).

In light of the frequent criticism of healthcare professionals and, above all, their media exposure, it would be sensible to ask what satisfies them in their working environment. Employee satisfaction is defined as the desired or positive emotional state that is the result of an individual's evaluation or perception of work and of his/her previous experience with work and in the workplace. Satisfaction is about the so-called individual effective reaction on the working environment, work and working conditions (6).

Materials and Methods

The purpose of the research was to establish whether differences exist in human capital valuation in healthcare institutions in Central and Eastern Slovenia.

The following hypothesis was proposed: Nurses employed at healthcare institutions in Central Slovenia place greater emphasis on the development of human capital than the nurses employed at healthcare institutions in Eastern Slovenia.

The research is based on the descriptive and causal non-experimental method of empirical research. The data collection technique consisted of a questionnaire for the measurement of human capital factors, which had been prepared based on the theoretical premises of various authors (5, 7, 11, 14, 19, 25).

The respondents rated the human capital factors according to an attitude scale model. The scale levels were arranged from 1 to 5, with 1 meaning "I strongly disagree", 2 "I disagree", 3 "Undecided", 4 "I agree", and 5 "I strongly agree".

The data was processed using the SPSS 19.0 statistical software package. The reliability of the attitude scale on the dimensions of human capital is confirmed by Cronbach's α with a value of 0.896 for the entire scale. According to George and Mallery (20), this scale has excellent reliability. The differences in the dimensions of human capital factors among employees in Central and Eastern Slovenia were verified with a t-test for independent samples.

The hypothesis was verified using a t-test for independent samples by comparing two groups and testing the null hypothesis that the two means are equal.

The survey encompassed 410 nurses employed at healthcare institutions in Slovenia, of whom, 210 nurses were from Central Slovenia (74% were women and 26% were men) and 200 nurses were from Eastern Slovenia (85% were women and 15% were men). 21% of the nurses surveyed are employed at the tertiary level, 24% at the secondary level, and 55% at the primary level of healthcare. At the time of the survey, 26% of the respondents were between 18 and 30 years of age, 50% between 31 and 40, 16% between 41 and 50, and 8% between 51 and 60. The majority (27%) had a length of service of up to 5 years, 34% from 6 to 10 years, 20% from 11 to 20 years, 10% from 21 to 30 years, and only 9% from 31 to 40 years. 56% of them are employed for an indefinite duration, 14% for a limited duration, and 30% part-time for an indefinite duration.

Results

Table 1 shows the claims with statistically significant differences between the two samples with the significance level of $p < 0.001$. These claims are: "My salary matches my knowledge and abilities." ($t = -10.13$, $p = 0.000$); "My manager gives me a sense of security." ($t = -9.34$, $p = 0.000$); "Investing in human capital is a long-term investment." ($t = 7.48$, $p = 0.000$); "I am aware that I am very important in the organisation." ($t = -5.55$, $p = 0.000$); "The manager and I have made a joint plan of my professional development." ($t = -5.29$, $p = 0.000$); "Without us employees, the company's goals would not be attainable." ($t = 4.78$, $p = 0.000$); "Employees are the foundation of every healthcare institution." ($t = 4.57$, $p = 0.000$); and "I have gained many new experiences in my working environment." ($t = 3.74$, $p = 0.000$).

The claims with statistically significant differences with the significance level of $p < 0.01$, are: "I can share emotional events with my co-workers." ($t = -3.50$, $p = 0.001$); "I enjoy following the achievements of the healthcare institution." ($t = -3.02$, $p = 0.003$); "At work, I have the opportunity to suggest improvements." ($t = -2.74$, $p = 0.006$); and "Human capital plays an important role in realising the vision of our healthcare institution." ($t = 3.03$, $p = 0.003$).

The claims with statistically significant differences between the two samples with the significance level of $p < 0.05$, are: "Constant improvements make me uneasy." (a reverse-scored item) ($t = -2.29$, $p = 0.023$) and "Each employee is a mosaic in the image of the entire healthcare institution." ($t = 2.53$, $p = 0.012$).

It has been established that the average level of agreement is higher in Eastern Slovenia only in fourteen of the twenty-two claims, and that in the case of these claims, there were statistically significant differences in the answers between the two regions. The hypothesis can be confirmed only partially.

Discussion

The research results have shown that investing in human capital is a long-term investment (Central Slovenia: $M = 4.41$, Eastern Slovenia: $M = 3.74$), which is also mentioned in the research studies of various domestic and foreign authors. Without employees, the goals of the healthcare institution would not be attainable, which was confirmed by the results of the present research (Central Slovenia: $M = 4.47$, Eastern Slovenia: $M = 4.07$). Makarovič (22) is also of the opinion that the key to attaining organisational goals lies in the work team. Moreover, Mihalič (5) has found that without defining the expectations and clearly setting the goals, an organisation cannot succeed, which was also stated

by the surveyed nurses, who enjoy following the achievements of the healthcare institution at which they are employed (Central Slovenia: $M = 3.64$, Eastern Slovenia: $M = 3.95$).

The majority of the surveyed nurses agree that they are the foundation of every healthcare institution (Central Slovenia: $M = 4.51$, Eastern Slovenia: $M = 4.13$); that each employee is a mosaic

in the image of the entire healthcare institution (Central Slovenia: $M = 4.28$, Eastern Slovenia: $M = 4.03$); and that they have gained many new experiences in their working environment (Central Slovenia: $M = 4.21$, Eastern Slovenia: $M = 3.85$). This can also be seen in the opinions of Skela Savič and Kaučič (18), who believe that in healthcare institutions the people form a system and that

Table 1. Results of the t-test for independent samples for the differences between Central and Eastern Slovenia

Statements	Central Slovenia		Eastern Slovenia		t	df	P-value
	M	SD	M	SD			
My salary matches my knowledge and abilities.	2.26	1.12	3.32	0.98	-10.13 ¹	391.54	.000***
My manager gives me a sense of security.	2.68	1.26	3.73	0.99	-9.34 ¹	376.76	.000***
Investing in human capital is a long-term investment.	4.41	0.71	3.74	1.05	7.48 ¹	349.59	.000***
I am aware that I am very important in the organisation.	2.89	1.23	3.55	1.13	-5.55	398	.000***
The manager and I have made a joint plan of my professional development.	2.11	1.18	2.73	1.16	-5.29	398	.000***
Without us employees, the company's goals would not be attainable.	4.47	0.80	4.07	0.90	4.78	398	.000***
I can share emotional events with my co-workers.	3.06	1.16	3.46	1.13	-3.50	398	.001**
Employees are the foundation of every healthcare institution.	4.51	0.74	4.13	0.93	4.57 ¹	379.69	.000***
I have gained many new experiences in my working environment.	4.21	0.91	3.85	1.04	3.74	398	.000***
I enjoy following the achievements of the healthcare institution.	3.64	1.10	3.95	0.94	-3.02 ¹	388.79	.003**
At work, I have the opportunity to suggest improvements.	3.19	1.20	3.49	1.01	-2.74 ¹	386.69	.006**
Constant improvements make me uneasy. ²	2.53	1.09	2.79	1.14	-2.29	398	.023*
Each employee is a mosaic in the image of the entire healthcare institution.	4.28	0.90	4.03	1.10	2.53	398	.012*
Human capital plays an important role in realising the vision of our healthcare institution.	4.24	0.72	4.00	0.86	3.03	398	.003**
In the past, the management let me know that I was free to leave if I did not agree with something. ²	3.06	1.37	3.30	1.28	-1.81	398	.071
I discuss only work-related matters with my manager.	3.13	1.28	3.36	1.16	-1.89	398	.060
I care about whom I share a shift with.	3.62	1.16	3.83	1.02	-1.87 ¹	391.78	.062
A good co-worker is able to separate his/her personal problems from work problems.	3.94	1.09	4.10	0.83	-1.65 ¹	371.15	.100
As an organisation, we are prominent and irreplaceable.	3.46	1.28	3.57	0.92	-1.03 ¹	360.05	.303
I feel anxious when heading to work. ²	2.67	1.24	2.74	1.13	-0.59 ¹	394.64	.556
All of the knowledge gained by an individual contributes to the success of the organisation.	4.04	0.88	4.05	0.78	-0.12	398	.904
At work, we cooperate in an interdisciplinary way.	3.44	1.10	3.45	1.16	-0.09	398	.930

Note. The items have been listed according to the decreasing differences between the two groups.

¹Because the assumption of the equality of variances was violated, a t-test for unequal variances was used; ²a reverse-scored item; *** the differences are statistically significant at the level of $p < .001$; ** the differences are statistically significant at the level of $p < .01$; * the differences are statistically significant at the level of $p < .05$.

their gained knowledge and experiences continue to circulate and enrich, which is why in healthcare institutions human capital has an important role in realising the set vision.

The nurses have also established that human capital has an important role in realising the vision of their healthcare institution (Central Slovenia: $M = 4.24$, Eastern Slovenia: $M = 4.00$), but that it cannot be achieved without constant improvements, which they have the opportunity to suggest in their working environment (Central Slovenia: $M = 3.19$, Eastern Slovenia: $M = 3.49$), even though constant improvements make them uneasy (Central Slovenia: $M = 2.53$, Eastern Slovenia: $M = 2.79$). Similar conclusions were reached in the research study by Starc and Ilič (1), who had emphasised that human capital is a resource which aids in the development of the organisation.

This is also highlighted by Armstrong (17), who believes that human capital is the most important development factor of an organisation.

Nowadays, knowledge is the crucial generator of change in today's world (23) and represents the "invisible" wealth of each nation. That is to say, knowledge is the key capital and most powerful weapon in the struggle for competitive advantage (6); it is the virtue of the best – of the individual, the organisation and the country (24). The surveyed nurses are also aware of this, because they realise that all of the knowledge gained by an individual contributes to the success of the organisation (Central Slovenia: $M = 4.04$, Eastern Slovenia: $M = 4.05$). Dimovski et al. (24) agree with this and claim that the competitive advantage of a modern company is founded on knowledge that is derived from experiences, hidden practices and personal values.

Gruban (26) has stated that the success of an organisation depends on how it treats its employees, on how it enables their personal and professional development, and on how it selects and motivates them. The research results have shown that the management does not devote enough attention to its treatment of employees, because the surveyed nurses were informed in the past that they were free to leave if they did not agree with something (Central Slovenia: $M = 3.06$, Eastern Slovenia: $M = 3.30$).

Not all managers give them a sense of security (Central Slovenia: $M = 2.68$, Eastern Slovenia: $M = 3.73$); or make a joint plan of their professional

development (Central Slovenia: $M = 2.11$, Eastern Slovenia: $M = 2.73$); with them they discuss only work-related matters with their managers (Central Slovenia: $M = 3.13$, Eastern Slovenia: $M = 3.36$). Seeing that the success and efficiency of an organisation is demonstrated by satisfied, successful, motivated and loyal employees, the management should focus more on developing their social competences and on establishing more effective communication with the nurses.

The research results have shown that the nurses are aware of their importance for their healthcare institution (Central Slovenia: $M = 2.89$, Eastern Slovenia: $M = 3.55$); that they are aware of the importance of interpersonal relationships, because they can share emotional events with their co-workers (Central Slovenia: $M = 3.06$, Eastern Slovenia: $M = 3.46$); that they can separate personal problems from work problems (Central Slovenia: $M = 3.94$, Eastern Slovenia: $M = 4.10$); that they care about whom they are on the nursing team with (Central Slovenia: $M = 3.62$, Eastern Slovenia: $M = 3.83$); and that they have the opportunity to work with one another in an interdisciplinary way (Central Slovenia: $M = 3.44$, Eastern Slovenia: $M = 3.45$). Good interpersonal relationships, friendship and collegiality at the workplace have a positive impact on the organisation and on individuals. Interpersonal relationships can be defined as short-term or long-term relationships between two or more people. In a narrower relationship context (relationships at the workplace), they are understood as the relationships between people in a specific environment who are connected through their work. These interpersonal relationships consist of daily interactions between co-workers, or between workers and managers, and are a natural element of the working environment.

The research results have also shown that nurses' salaries do not match their knowledge and abilities (Central Slovenia: $M = 2.26$, Eastern Slovenia: $M = 3.32$). In order to provide quality healthcare and nursing care to patients, nurses must keep up with innovations, be proficient in modern technology, and continuously undergo further training and life-long learning (27). Their professional competences demonstrate their capability to use their knowledge and abilities in order to fulfil their job requirements and their specific work roles (28).

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Factor validity and consistency of the Maslach burnout inventory - general survey among Lithuanian general practitioners, community nurses and social workers

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Abstract

Factor validity and consistency of the Maslach burnout inventory - general survey among Lithuanian general practitioners, community nurses and social workers

Introduction: Burnout is important for the consequences of burnout are potentially very serious for the staff, the clients, and the larger institutions in which they interact. The Maslach Burnout Inventory (MBI) is currently the most widely used research instrument to measure burnout. The aim of his study was to perform the validation of MBI-GS (MBI-general service) questionnaire among human-service providers' population in Lithuanian language.

Methods: This was a cross-sectional survey of 426 medicine workers: 162 family practitioners, 175 nurses and 89 social workers, practicing in Kaunas region, Lithuania. The reliability, exploratory and confirmatory analysis was performed.

Results: The internal consistency of questionnaire was acceptable (0.78) and Cronbach's alpha in separate scales ranged between 0.75 and 0.90. The factor structure was examined using exploratory and confirmatory factor analysis. Exploratory factor analysis discovered only one question does not perfectly fit the proposed MBI-GS questionnaire, the other factors fall in predesigned groups. The three factor MBI-GS questionnaire's structure of emotional exhaustion, professional efficacy and cynism subscales showed rather good, but not perfect fit.

Conclusions: The Lithuanian version of the MBI-GS showed adequate reliability and validity. Further studies involving other professional groups are needed.

Key Words: General practitioners, community nurses, social workers, burnout, the Maslach Burnout Inventory, validation, Lithuania

Introduction

Burnout among physicians and other primary care providers has been becoming an increasingly important concern, due to both its high prevalence [1, 2] and reported associations with patient care and personal well-being [3]. A tendency of increasing risk and prevalence of burnout [4,5,6] has been observed. According to estimations, burnout rates among physicians might range from 2.4% to 72% [7], varying across nations and occupational groups and depending on the burnout measuring method [25]. Burnout triggers feelings of depression, anxiety, worthlessness and physical illness [8], decreases the job performance [9,10] and increases job turnover as well as absenteeism of healthcare professionals [11,12]. Higher burnout among healthcare providers is related to lower quality of health services [13], lower satisfaction of patients and increased discontinuity of care [14].

The present research indicates that high physical demands as well as high emotional demands – the requirement to display emotions that are not felt – resulting from interaction with clients [15], combination of high emotional dissonance and stressor [16] increase the probability of burnout. This is the reason why professionals interacting with clients intensively, i.e. nurses, physicians and social workers, are especially vulnerable to develop burnout [17]. Affected individuals are unable to cope with emotional stress at work and develop negative, cynical feelings and attitudes towards their colleagues and patients. They often feel unsatisfied with their work and accomplishments [17].

Burnout of health care providers also has a negative impact on their health status. According to the findings of the research, burnout is considered a risk factor for incidence of chronic heart disease [18],

the type 2 diabetes [19] and musculoskeletal pain [20]. Moreover, burnout causes mental dysfunction. Burnout and insomnia recursively predict each other's development, it precipitates negative effects in terms of mental health such as anxiety, depression, drops in self-esteem [9]. In addition, links between burnout and various forms of substance abuse [9] have been found. Burnout increases demands on social security. The study carried out in Finland has demonstrated that severe risk of having a medically certified sickness absence lasting over 9 workdays was higher for both men and women with burnout than for their colleagues who were free of burnout, even after adjusting for mental disorders and physical illnesses. [21].

Over the last two decades, burnout studies revealed that burnout is due largely to the nature of the job rather than to the characteristics of an individual employee. Maslach and Leiter [2] developed a burnout model that focuses on the degree of match between the individual and the key aspects of his organisational environment. The greater is the mismatch between a person and job, the greater is a likelihood of burnout.

The gold standard for measurement of burnout is the Maslach Burnout Inventory (MBI). Currently, the Maslach Burnout Inventory is the most widely applied research instrument for measurement of burnout [22]. The Maslach Burnout Inventory – Human Services Survey (MBI-HSS) – was originally developed for measurement of burnout as an occupational issue for people providing human services. The inventory contains 22 items representing three aspects of the burnout syndrome: the Depersonalization (DP) dimension (five items), the Personal Accomplishment (PA) dimension (eight items) and the Emotional Exhaustion (EE) dimension (nine items) [23].

A great range of studies measuring burnout is available. For example, the Scottish psychiatric nurse study revealed that 42% of the respondents exhibited a high level of emotional exhaustion [24], whereas EGPRN (European General Practice Research Network) study found that 43%, 35% and 32% of respondents scored high for emotional exhaustion burnout, depersonalisation and professional accomplishment respectively with 12% scoring high burnout in all three dimensions [25]. According to the Lithuanian cardiac surgeon

and anaesthesiologist study, 19.3% of physicians reported high emotional exhaustion, 25.9% had high depersonalisation and 42.3% demonstrated low personal accomplishment at work [28]. As the Lithuanian gynaecologist study shows, 36.6 % of respondents reported high overall burnout, whereas 19%, 10% and 21% scored high for emotional exhaustion, depersonalisation and low personal accomplishment respectively [29].

The aforementioned MBI-HSS subscales, however, were not consistently maintained across other occupational groups such as military, computer programmers, civil servants [26].

The apparent need for a more universal instrument measuring burnout in different occupational groups has prompted the development of another versions of the Maslach Inventory such as the Maslach Burnout Inventory – General Survey (MBI-GS) [27]. The MBI-GS comprises three subscales that are parallel to original MBI-HSS, i.e. EX (exhaustion), CY (cynicism) and PE (professional efficacy) [23], and can be used in both human and non-human services settings to investigate levels of burnout. MBI-GS also includes a few different items referring to more general, non-social aspects of the job. Bakker [27] and Leiter [26] have demonstrated that the MBI-GS questionnaire may be applied to different occupations (human and non-human services) retaining the same factor structure.

In Lithuania, several attempts were made to measure burnout of health care workers through application of the MBI-HSS instrument: cardiac surgeons and cardiac anaesthesiologists [28] as well as gynaecologists [29] were surveyed, whereas separated (detached) scales such as 7 items from the emotional exhaustion subscale of the MBI-HSS questionnaire was applied among nurses [30].

To the best of our knowledge, however, no studies in Lithuania validating the MBI-GS questionnaire on human services providers in Lithuanian language have been carried out.

The present study aims to validate the MBI-GS questionnaire among Lithuanian general practitioners, community nurses and social workers in order to develop a universal burnout measuring instrument that could be applied among both human and non-human services providers.

Methods

Method

The study is a part of the two-year (2012–2013) project funded by the Lithuanian Research Council that aims to assess the potential of collaborative working between PHC (Primary Health Care) and social services in Lithuania in order to respond better to health and social care needs of families at social risk.

In 2012 the Bioethics Centre at the Lithuanian University of Health Sciences gave approval for the ethical aspects of this study. The permission was to carry out an anonymous survey of CNs (Community Nurses), GPs (General Practitioners) and SWs (Social Workers) that was accomplished in Kaunas region being the most central area in Lithuania with less than one fifth of residents living in rural areas. The population of Kaunas region constitutes almost 15% of the total population of Lithuania, whereas economic indicators in the region (e.g. salary) are equal to the average of Lithuania.

At the beginning of 2012, 50 PHC centres, both public or private, providing PHC services under the contract with the National Health Insurance Fund, and private institutions working under the contract with the National Health Insurance Fund and providing free PHC services to all insured patients were operating in Kaunas region. The total list of PHC institutions contained 18 large facilities with 5000 and more patients and 32 small settings with less than 5000 registered patients. 36 PHC institutions (12 large and 24 small) were randomly selected for this study. After inviting them to take part in the study, 33 PHC facilities agreed (10 large and 23 small) to participate.

Cochran's [31] sample size formula and finite population adjustment assuming $p=0.5$ (maximum variability), a 95% confidence level and $\pm 5\%$ precision were used to determine the sample size (calculated sample size amounted to 325 respondents). Referring to the latest studies [32], no better than 73.5% response rate is expected and some respondents fail to fill in all the required data, therefore, 572 questionnaires have been decided to be sufficient to distribute.

The survey was carried out from January to March of 2013. Each community nurse, general practitioner and social worker working for se-

lected PHC institutions was invited to take part in the study. All primary health care workers were informed that they were not supposed to fill in the questionnaire, and there will be *no negative consequences for those* who do not wish to participate. They also were informed in writing about the selection procedure, the purpose of the questionnaire and the planned publications. CNs, GPs and SWs were ensured absolute confidentiality with respect to their responses. Then anonymous questionnaires were distributed to 224 GPs, 237 CNs and 111 SWs. A total of 169 questionnaires were collected from GPs (response rate 75.4%), 180 ones from CNs (response rate 75.9%) and 89 ones from SWs (response rate 80.2%).

Respondents

Data was entered in the database and afterwards was cleaned dropping out respondents failing to fill the MBI-GS inventory completely. Final analysis included 162 GPs, 175 CNs and 89 SWs.

The majority of respondents (95.6 %) were females (Table 1). Slightly more than a quarter of respondents (27.0 %) practised at private health care centres operating under the contract with the National Health Insurance Fund, while the remainder practised at public health care centres (68.3%) or had mixed practice, i.e. worked for both private and public health care institutions (4.7 %). All the social workers were practising at public health care centres. The average age of participants was 44 ± 11.9 years (95 percent CI was 42.8 to 45.8). The greatest group of respondents comprised 40 years old and younger (37.2 %) primary health care providers with 10 or less years of professional experience (37.6%). Additional characteristics of the respondent sample as well as description of GPs, CNs and SWs groups are presented in Table 1.

Instrument

The Maslach Burnout Inventory (MBI) (2) was applied for measurement of burnout. This standardized questionnaire with 16 items includes three validated subscales: emotional exhaustion (EX), professional efficacy (PE) and cynicism (CY). Using a 7-point rating scale (0 = never, 6 = every day) participants were asked to indicate the extent to which they agreed with each statement. High scores on emotional exhaustion, professional effi-

Table 1. Sample Characteristics of the Survey of General Practitioners (GPs), Community Nurses (CNs) and Social Workers (SWs)

Variable	GPs		CNs		SWs		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Total [#]	162	(38.0)	175	(41.1)	89	(20.9)	426	(100)
<i>Gender:***</i>								
female	149	(92.0)	174	(100)	84	(94.4)	407	(95.6)
male	13	(8.0)	0	(0)	5	(5.6)	18	(4.2)
not given	0		1		0		1	
<i>Age: ***</i>								
≤ 40-year-old	41	(26.5)	59	(35.1)	52	(61.2)	152	(37.2)
41-50-year-old	41	(26.5)	43	(25.6)	22	(25.9)	106	(26.0)
≥ 51-year-old	73	(47.0)	66	(39.3)	11	(12.9)	150	(36.8)
not given	7		7		4		18	
<i>Years of professional experience:***</i>								
≤ 10 years	59	(37.1)	28	(16.6)	69	(79.3)	156	(37.6)
11-20 years	81	(51.0)	38	(22.5)	17	(19.6)	136	(32.8)
≥ 21 years	19	(11.9)	103	(60.9)	1	(1.1)	123	(29.6)
not given	3		6		2		11	
<i>Type of the institution:</i>								
public	96	(59.3)	106	(60.6)	89	(100)	291	(68.3)
private	59	(36.4)	56	(32.0)			115	(27.0)
public & Private	7	(4.3)	13	(7.4)			20	(4.7)
not given	0		0				0	

[#] percentage is calculated from the total sample; ** $p \leq 0.01$ and *** $p \leq 0.001$ comparing three groups (χ^2 test).

cacy and cynicism subscales are indicative of burnout. Drawing on the theory of burnout as a tripartite construct, Maslach suggests considering the scores for each of the three subscales separately [2]. For each MBI-GS subscale, categorisation was used as proposed by Maslach: low (PE 0-23; EX 0-10; CY 0-5), moderate (PE 24-29; EX 11-15; CY 6-10) and high (PE ≥ 30 ; EX ≥ 16 ; CY ≥ 11).

The original Maslach Burnout Inventory instruments and scoring guides were received from the authors. A licence to reproduce and administer a fixed number of copies of an existing Mind Garden instrument was obtained from Mind Garden, Inc. on 27 June 2012. Firstly, the questionnaire was translated into Lithuanian and then back-translated into English by a professional translator. Then the discrepancies were identified and discussed until final consensus was reached. The understandability of the language of the instrument was reviewed by 20 PHC providers: 10 GPs, 10 CNs and 10 SWs. During the completion of the questionnaire, GPs, CNs and SWs specified no difficulties in understanding

the item wording and meaning that demonstrated the face validity of the instrument.

Data analysis procedure

The data were analysed with SPSS, version 21.0, and AMOS, version 21.0. Interim consistency measures the degree to which the items in a set measure the same construct, and in this case coefficient alpha was used. The average and standard deviation of each subscale were first calculated and reliabilities of each subscale and the summated scale were also examined. Cronbach's $\alpha \geq 0.70$ was considered acceptable [33]. Furthermore, item-total correlations were investigated. Exploratory factor analysis using principal component estimation was employed to test the original three-factor structure of the MBI-GS. The appropriateness of factor analysis was evaluated by the Bartlett's test of sphericity and Kaiser-Meyer Olkin (KMO) measure of sampling adequacy ($p < 0.001$ and $KMO > 0.5$). A principal component analysis and rotation (varimax with Kaiser

normalisation) was applied for identification of independent subscales. Factors were selected referring to the break point of successive eigenvalues (>1), identification on screen plot, item factor loadings (>0.4) and meaningful content [34]. The dimensionality of the MBI-GS scale was assessed through confirmatory factor analysis. Confirmatory factor analysis was carried out to test the validity of the MBI-GS questionnaire Lithuanian version. The following fit indices were used: CFMIN/df (chi-square and degree of freedom ratio), CFI (comparative fit index), GFI (goodness of fit index), AGFI (adjusted GFI) and RMSEA (root mean square error of approximation), PCLOSE (null hypothesis test that RMSEA is no greater than .05). The model fit was considered suitable for χ^2/df values below 5, CFI and GFI above 0.90, AGFI above 0.90 and root mean square error of approximation (RMSEA) below 0.10 [35, 36, 37]. Use of the chi-squared goodness-of-fit index was the first step as a low chi-square indicates a better fitting model. However, chi-square does not adjust for the effect of sample size meaning larger samples will always lead to greater chi-square values; more constraints mean good fit is harder to achieve and, therefore, increase the probability of rejecting the hypothesised models, thus it was not used in our study.

Results and discussion

Results

Reliability of MBI-GS

Internal consistency of the inventory was measured using the Cronbach's coefficient alpha. The overall Cronbach's alpha of MBI-GS inventory was good, 0.78. The Cronbach's alpha of subscales was also good: for professional efficacy (PE) 0.76, for exhaustion (EX) excellent 0.90, for cynicism (CY) good, 0.75. The subscale means

and standard deviations for all respondents on the MBI-GS are shown in Table 2.

Validity of the MBI-GS

To determine the suitability of the data for principal components analysis, the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (KMO) and Bartlett's Test of Sphericity were calculated. The KMO was found to be meritorious (0.85). The Bartlett's Test of sphericity was highly significant ($\chi^2 = 2926.44, p < .001$) supporting the suitability of the data for principal components analysis.

The exploratory factor analysis tested the construct validity of the original three-factor structure employing the data of the present study. Three factors with an eigenvalue 1 or above corresponding to each subscale of the MBI-GS were extracted. Table 3 presents the rotated loadings on the three principal components for 16 items. The emotional exhaustion (EX) factor accounted for 31.1%, whereas the professional efficacy (PE) factor and the cynicism (CY) factor accounted for 18.17% and 8.5% of the total variance respectively. In this three-factor solution, the factors accounted for 57.77% of the total variance.

All the three subscale items have positive loadings greater than 0.40 on the anticipated factors. Item No 6 – "I feel burned out from my work" – loaded on both EX and CY subscales, but mainly on EX as expected (loading on EX value is 0.7 and loading on CY value is 0.41). Item No 13 – "I just want to do my job and not be bothered" – had a rather low loading in the CY subscale (0.22). The communalities of the items were mainly > 0.40 . However, the communalities of three items (7, 13, and 16) were 0.38, 0.18 and 0.35 respectively. The factor loadings on the own factors of these items, however, ranged between 0.22 and 0.35 (Table 3). The highest loadings was demonstrated by the EX subscale (0.7-0.88), whereas the lowest was dis-

Table 2. The Internal Consistency Of The MBI-GS Questionnaire

Scale	Mean	SD	Cronbach's alpha	Overall MBI-GS Cronbach's alpha [2]
PE	30.07	6.19	0.76	0.76-0.84
EX	14.62	7.80	0.90	0.87-0.89
CY	10.60	6.66	0.75	0.73-0.84
Summed scale			0.78	

Table 3. Exploratory Factor Analysis Loadings on 3-Component Matrix. Factor Structure of the MBI-GS Using Principal Component Analysis

Item No	Item definition	Component loadings			Communalities	Corrected item-total correlation
		EX	PE	CY		
1	I feel emotionally drained from my work	.88			0.82	0.83
2	I feel used up at the end of the workday	.88			0.81	0.8
3	I feel tired when I get up in the morning and have to face another day on the job	.74			0.62	0.69
4	Working all day is really a strain for me	.86			0.78	0.79
5	I can effectively solve the problems that arise in my work		.67		0.45	0.51
6	I feel burned out from my work	.70		.41	0.66	0.69
7	I feel I am making an effective contribution to what this organization does.		.58		0.38	0.44
8	I've become less interested in my work since I started this job			.79	0.68	0.61
9	I have become less enthusiastic about my work			.78	0.71	0.67
10	In my opinion, I am good at my job		.70		0.50	0.50
11	I feel exhilarated when I accomplish something at work		.76		0.62	0.60
12	I have accomplished many worthwhile things in this job		.72		0.52	0.53
13	I just want to do my job and not be bothered			.22	0.18	0.20
14	I have become more cynical about whether my work contributes anything			.75	0.59	0.59
15	I doubt the significance of my work			.72	0.57	0.53
16	At my work, I feel confident that I am effective at getting things done		.58		0.35	0.40
	Eigenvalues % of Variance explained	4.97 31.1	2.91 18.17	1.36 8.50		

played by the CY subscale (0.22-0.79). Items in the scale consistently show good item-total correlations (0.4–0.83), except Item 7 (0.44), Item 13 (0.20), Item 16 (0.4) (Table 3). The item-total correlation shows that Item 13 does not correlate very well with the scale overall, therefore, it possibly may be dropped.

The two- and four-component exploratory factor analysis was carried out, but no one demonstrated better fit. In four-factor exploratory factor analysis, Item 13 became alone in a separate group with loading 0.84 with no meaningful content.

A path diagram of confirmatory factor analysis illustrates standardised estimates in Figure 1. Regression weights are all statistically significant,

critical ratio for all items exceeds 2, indicating all items sensitive on the dimensions (Table 4). PE and CY as well as EX and CY factors were moderately correlated (-0.57 and 0.59 respectively), whereas EX and PE factors had weak correlation (-0.36). Standardised regression weights show Item 16 and Item 10 as the poorest among indicators of professional efficacy (0.21 and 0.24 respectively); for the EX subscale, all the items are good; for the CY subscale, Item 13 has the lowest standardised regression weight (0.23) (Table 5). Additionally, squared multiple correlations display Item 10 (0.06) and Item 16 (0.05) as the poorest indicators of PE, whereas Item 13 (0.05) is the poorest indicator of CY (Figure 1).

Table 4. MBI – GS Questionnaires’ Confirmatory Factor Analysis. Regression Weights

			Estimate	S.E.	C.R.	P
Item 16	<---	PE	1,000			
Item 12	<---	PE	2,110	,531	3,976	***
Item 11	<---	PE	2,645	,749	3,532	***
Item 10	<---	PE	,698	,203	3,438	***
Item 7	<---	PE	4,309	1,221	3,529	***
Item 5	<---	PE	1,965	,542	3,626	***
Item 6	<---	EX	1,000			
Item 4	<---	EX	1,042	,044	23,613	***
Item 3	<---	EX	,972	,041	23,494	***
Item 2	<---	EX	,907	,045	20,166	***
Item 1	<---	EX	,990	,041	24,336	***
Item 15	<---	CY	1,000			
Item 14	<---	CY	1,125	,094	11,984	***
Item 13	<---	CY	,502	,091	5,502	***
Item 9	<---	CY	1,675	,138	12,166	***
Item 8	<---	CY	1,609	,138	11,630	***

*** - $p < 0.001$

Table 5. Estimates of the Three-Factor Model of the MBI-GS Scale Obtained from Confirmatory Factor Analysis

Standardised Regression Weights			Estimate
I 16. At my work, I feel confident that I am effective at getting things done	<---	PE	,213
I 12. I have accomplished many worthwhile things in this job	<---	PE	,479
I 11. I feel exhilarated when I accomplish something at work	<---	PE	,857
I 10. In my opinion, I am good at my job	<---	PE	,244
I 7. I feel I am making an effective contribution to what this organization does	<---	PE	,642
I 5. I can effectively solve the problems that arise in my work	<---	PE	,409
I 6. I feel burned out from my work	<---	EX	,827
I 4. Working all day is really a strain for me	<---	EX	,866
I 3. I feel tired when I get up in the morning and have to face another day on the job	<---	EX	,799
I 2. I feel used up at the end of the workday	<---	EX	,805
I 1. I feel emotionally drained from my work	<---	EX	,834
I 15. I doubt the significance of my work	<---	CY	,581
I 14. I have become more cynical about whether my work contributes anything	<---	CY	,576
I 13. I just want to do my job and not be bothered	<---	CY	,230
I 9. I have become less enthusiastic about my work	<---	CY	,896
I 8. I have become less interested in my work since I started this job	<---	CY	,832
Correlations			
PE	<-->	EX	-,356
PE	<-->	CY	-,573
EX	<-->	CY	,592

PE, EX, CY - emotional exhaustion (EX), professional efficacy (PE) and cynicism (CY) subscales

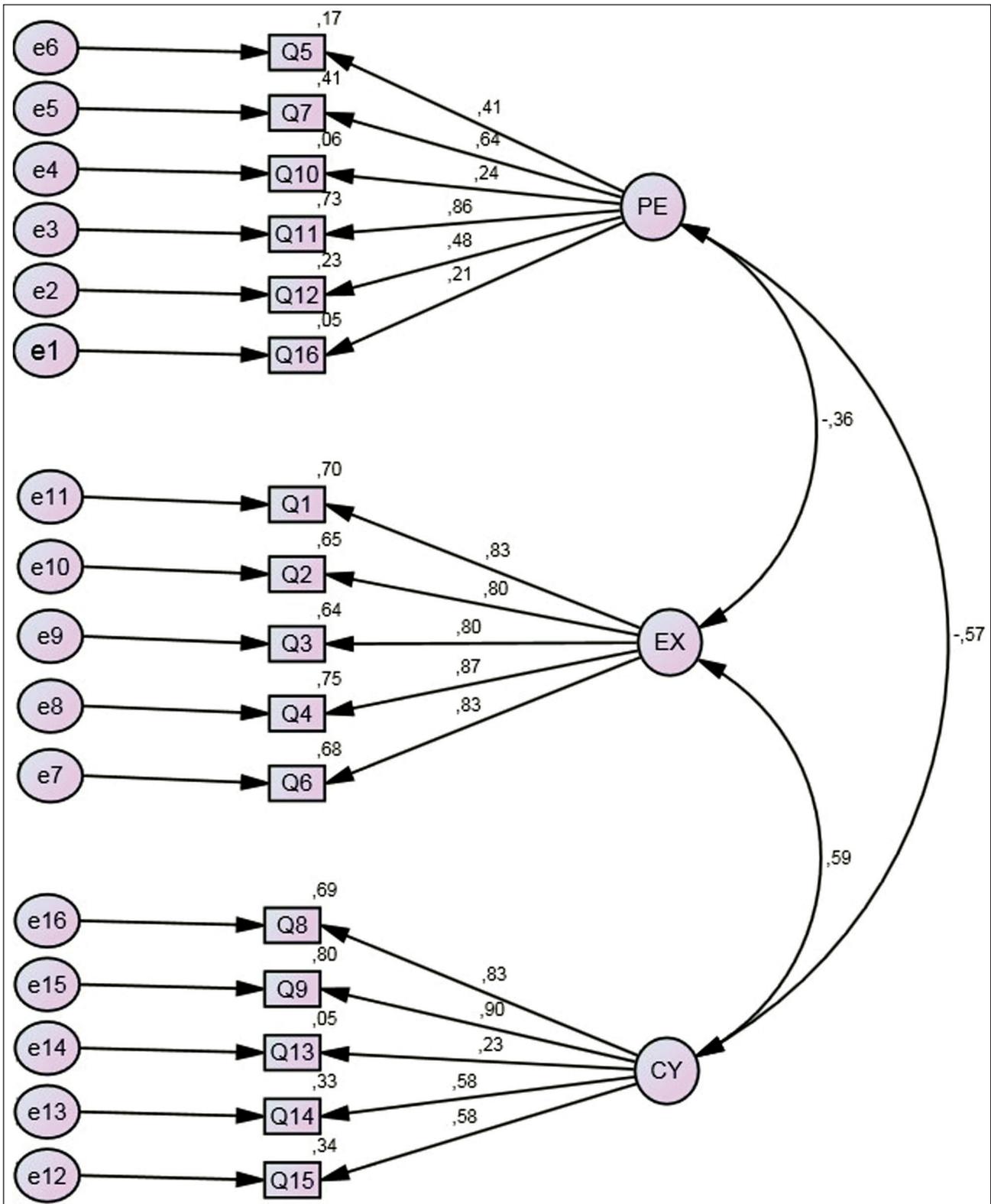


Figure 1. Path Diagram of Confirmatory Factor Analysis with Standardised Regression Weights and Squared Multiple Correlations (R^2)
 e1-e16 – errors, Q1- Q16 observed variables, PE, EX, CY - emotional exhaustion (EX), professional efficacy (PE) and cynicism (CY) subscales.

Table 6. Confirmatory Factor Loadings, Three-Factor Structure for the MBI-GS Questionnaire

Model	d.f.	X ²	CFMIN/d.f.	RMSEA	PCLOSE	AIC	GFI	AGFI	CFI
CFA – all items	92	216.59	2.35	0.049	0.12	304.59	0.95	0.93	0.87
CFA – all except Item 13	83	207.23	2.50	0.06	0.05	281.60	0.94	0.92	0.85
p=0.405 (between models)*									

*models do not differ statistically

During confirmatory factor analysis, the goodness-of-fit indices for this three-factor model suggested an acceptable fit for the data (Table 6), with CFMIN/df 2.35, RMSEA 0.049, PCLOSE 0.12, AIC 304.59, GFI 0.95 and AGFI 0.93. Only one index – CFI – is not fully acceptable (0.87).

PCLOSE being 0.12 is greater than .05, therefore we cannot accept the null hypothesis that RMSEA is no greater than 0.05; FI (0.95) and AGFI (0.93) were at acceptable level indicating good model fit.

X² statistics of significance revealed that compared to the original structure confirmatory factor analysis dropping out Item 13 does not differ statistically significantly (Table 6). But confirmatory factor analysis indices show some deterioration of the model without Item 13 (RMSEA 0.06, PCLOSE 0.05, deterioration of GFI and AGFI).

Discussion

The purpose of this study was to validate the MBI-GS questionnaire among Lithuanian general practitioners, community nurses and social workers in order to have a universal burnout measuring instrument in Lithuanian language that could be used among both human and non-human services providers.

The study focused on assessment of the factor structure and confirmatory factor analysis of the answers submitted by human services providers to the MBI-GS questionnaire and on questionnaire validation in Lithuanian language.

The reliability of the MBI-GS questionnaire was assessed by a Cronbach's alpha. An alpha value between .70 and .95 was regarded as acceptable reliability [38]. As Table 2 shows, the PE, EX, CY subscales and the summed scale yielded acceptable reliabilities [39]. Internal consistency (Cronbach's alpha) of the whole scale was at acceptable level, 0.78, whereas acceptable reliabilities had

separate scales on PE (0.76), EX (0.90) and CY (0.75) subscales. These internal consistency statistics were similar to those reported by Maslach *et al.* [2] and to those presented by Bakker and Demerouti [27], who revealed that internal consistency of each of the MBI-GS's subscales was equally high in each of eight occupations.

Respondents of our study reported more frequently high levels in the PE scale, but moderate scores in EX and CY subscales.

The principal component analysis is the most frequently applied and the most appropriate method if the goal is to reduce data [40]. The suitability for principal component analysis was found good (0.85). It exceeded the recommended minimum value of 0.60 [41]. The Bartlett's test of sphericity was highly significant ($\chi^2 = 2926.44, p < .001$) supporting the suitability of the data for principal components analysis.

The factor structure has been the matter of discussion since introduction of the MBI questionnaire into use [42]. Previous analyses of the MBI-HSS factor structure found that its emotional exhaustion and depersonalisation subscales tended to be reduced to a single factor when the MBI was applied for populations outside the human services professions [42].

In the Internet study, Bakker compared burnout of human and non-human services providers [27]. A series of confirmatory factor analyses confirmed the three-factor structure of the MBI-GS questionnaire for eight different occupations including such diverse professions as managers, software engineers, technicians and human services professionals. The three-factor model fitted the data for each of eight groups equally well suggesting that exhaustion, cynicism and professional efficacy constitute three independent dimensions of burnout, thereby indicating that the MBI-GS is a measure of burnout that can be applied in any occupational context. This study replicated Leiter's and

Schaufeli's [26] findings by providing evidence for the invariance of the MBI-GS's factor structure among human services providers and people working with objects or information.

Several studies revealed the MBI-GS questionnaire's factor structure different from original ones. Storm and Rothmann [43] confirmed the three-factor structure of the MBI-GS in a sample of 2 396 SAPS (South African Police Services) members, but recommended to drop Item13 from the questionnaire. During analysis of the answers provided by male amateur rugby union players, Creswell and Eklund [44] revealed two weak loading items in the MBI-GS cynicism subscale: Item 13 ("*I just want to do my job and not be bothered*") and Item 14 ("*I have become more cynical about whether my work contributes anything*"). These findings give an idea that the MBI-GS questionnaire's factor structure can vary across occupational groups and some items might be inappropriate in certain situations.

In our study, we indentified low exploratory factor analysis loading on Item 13 (0.22) in the cynicism subscale, low standardized regression weights on Item 13 (0.23) in the cynicism subscale, low loadings of Items 10 (0.24) and 16 (0.21) in the PE subscales. However, we support the item structure proposed by Maslach. Exploratory factor analysis confirmed the three-factor structure model, Item 13 seems not to fit perfectly the CY subscale, whereas Item 10 and Item 16 seem not to fit the PE subscale, but no other than the three-factor structure appeared to fit better. CFA models with the two- and four-factor structure failed to fit. Model comparison with and without Item 13 revealed no statistically significant differences between models. Confirmatory factor analysis confirmed that the three-factor structure using all items fits slightly better than the three-factor model without Item 13. Item 10 and Item 16 are required for the factor structure as without them the model is stated unidentified. Although CFI was lower than required (0.87) [45], RMSEA (0.049), GFI (0.95), AGFI (0.93) and CFMIN/df (2.35) were within tolerable level [46, 47]. RMSEA 0.049 indicates good fit [48].

The reason that perfect model fit was not obtained might be related to the fact that the sample was not uniform (physicians, nurses, social workers) as previous studies show there might be some

variance between multilanguage and occupational groups [49, 50], and also to the fact that the persons in our study were dominantly female gender as previous studies reveal that females score higher in exhaustion and cynicism than males [27], therefore, equal distribution of males and females in the database could be a solution. In Lithuania, this requirement is hardly accomplished as the dominant gender in the primary health care system is female.

Hence, further studies involving other professional groups with more proportional distribution of men and women are required.

Conclusions

The Lithuanian version of the Maslach Burnout Inventory – General Survey displayed adequate reliability and validity. This universal burnout inventory could be applied for assessment of burnout levels among human and non-human services professionals.

List of abbreviations used

MBI - The Maslach burnout inventory
 MBI-GS – The Maslach burnout inventory - general survey
 MBI-HSS - The Maslach burnout inventory – human services survey
 DP - Depersonalization
 PA - Personal accomplishment
 EE - Emotional exhaustion
 EGPRN - European general practice research network
 EX – Exhaustion
 CY – Cynicism
 PE - Professional efficacy
 PHC - Primary health care
 CN –Community nurse
 GP - General practitioner
 SW - Social worker
 SPSS – Statistical package for the social sciences
 KMO - Kaiser-Meyer-Olkin
 CFMIN/df - Chi-square and degree of freedom ratio
 CFI - Comparative fit index
 GFI - Goodness of fit index
 AGFI - Ajusted goodness of fit index
 RMSEA - Root mean square error of approximation
 PCLOSE - Null hypothesis test that root mean square error of approximation is no greater than .05

Authors' contributions

RG cleaned, analyzed the data, wrote the paper.

JL developed the original idea of the study, edited the paper.

All authors read and corrected draft versions. Both authors approved the final version of this manuscript.

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Outcomes of IVF procedures based on the number of oocytes in COS with short antagonist protocol in woman with unexplained infertility

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Abstract

Objective: European Society of Human Reproduction and Embryology (ESHRE) defines three basic categories of infertile patients based on the ovarian response to ovulation induction: poor ovarian response, patients with normal response, and patients with excessive response. The objective of the study was to determine the efficacy of a short antagonist protocol and the clinical pregnancy rate in women with unexplained infertility, with special emphasis on the sub-optimal group.

Method: The study is a prospective-retrospective cohort study, covering 200 patients and 200 in vitro fertilization (IVF) cycles, divided into 4 groups (Group 1: ≤ 3 oocytes; group 2: 4-9 oocytes; group 3: 10-15 oocytes, group 4: >15 oocytes), in the period between 1 January 2016 and 30 June 2016, at the HCI “Medico-S”, Centre for Human Reproduction and IVF, Banja Luka. Primary outcome point was the clinical pregnancy rate per patient/cycle.

Results: From a total of 200 IVF procedures, statistically ($p < 0.05$) the highest representation was that of group 3 (69.5%). The largest number of patients aged over 40 years was significantly higher in group 2 ($p < 0.05$). In group 4, a statistically significant ($p < 0.05$) number of produced oocytes was recorded when compared to other groups. The pregnancy rate was lowest in group 1 (8%) in comparison with other groups. The pregnancy rate was highest in group 4 (47%). In group 2, a statistically significant lower number of

oocytes and a lower clinical pregnancy rate were recorded as compared to group 3.

Conclusion: In the group of patients with normal response (norm responder patients), there is a group with lower response in terms of the number of oocytes and the clinical pregnancy rate (sub-optimal group), while the highest response was recorded in group 4 in terms of the number of oocytes and the clinical pregnancy rate.

Key words: IVF, COS, oocyte number, unexplained infertility, clinical pregnancy

Introduction

Controlled ovarian stimulation (COS) is an important part of the reproduction treatment. This method serves to stimulate a larger number of follicles during one cycle, to produce a sufficient number of mature egg cells that are suitable for the IVF procedure. This increases the chances of producing a larger number of high-quality embryos and having more successful pregnancies and more live births (1, 2). However, one of the most common complications encountered in stimulation is the ovarian hyper stimulation syndrome (OHSS), which leads to various metabolic, endocrine and respiratory problems, with possible lethal outcome (3). On the other hand, this method, which is financially demanding, with complications such as hyper stimulation, in addition to medical problems, also represents a financial burden on those who pay for the procedure (4). Also, a significant portion of produced oocytes is discarded, because

these do not meet the selection criteria in different stages of the laboratory part of the procedure (5). Because of all these factors, a lot has been done to optimize the strategy of ovarian stimulation and to coordinate all the above factors.

Widely used controlled ovarian stimulation (COS) leads to a challenge of recognizing individuals with different responses to stimulation. (7) Conventional stimulation is part of COS and it implies appropriate daily doses of gonadotropins. European Society of Human Reproduction and Embryology (ESHRE) defines three basic categories of patients: 1) poor ovarian response (POR), patients in whom the number of produced oocytes are <3 ; 2) patients with normal ovarian response, 4 to 15 oocytes; 3) excessive response, with > 15 oocytes. (8) From group 2, consisting of patients with normal response (4 to 15 egg cells), a new group with suboptimal response, with 4 to 9 produced egg cells, was isolated. Pregnancy rate and number of live births in this category was 20 to 30% lower in comparison with the group of patients of the same age who had 10 to 15 produced egg cells. The objective of the study was to determine the efficacy of a short antagonist protocol and the clinical pregnancy rate in women with unexplained infertility; to categorize patients according to the number of egg cells produced in COS in the IVF procedure, with special emphasis on optimal and suboptimal group, as well as to determine predictors involved in obtaining the optimal number of cells for achieving pregnancy.

Material and methods

Study design: The study is a prospective-retrospective cohort study. The analysis covered 200 patients with unexplained cause of infertility, who underwent the IVF procedure in the period between 1 March 2016 and 30 June 2016 in the Centre for Human Reproduction and IVF – “Medico-S” Banja Luka. The study did not cover patients who underwent the IVF procedure in a spontaneous menstrual cycle, patients with modified cycle, and patients who were treated with long antagonist protocol.

Study population: All 200 patients who were analysed had a normal basal hormonal status before undergoing the procedure, prior to the stimulation they were treated with contraceptives for 1

to 2 months, and the group is largely standardized. Patients were divided into four groups, depending on the number of produced oocytes: group 1: ≤ 3 ; group 2: 4-9; group 3: 10-15; group 4: >15

Treatment: Purified human menopausal gonadotropin hMG (Menopur, Ferring, Denmark) was used for the stimulation, with recombinant r-hFSH (Gonal F, Merck-Serono, Switzerland) and GnRH antagonist, cetrorelix (Cetrotide, Merck-Serono, Switzerland). Gonadotropin therapy was initiated on the second day of bleeding, in a dose of 112.5 – 300 IU, after an obligatory ultrasound test. All patients were given r-hFSH (on the second and third day of bleeding) and hMG afterwards, followed by the inclusion of cetrorelix in a daily dose of 0.25 mg. Initial therapy dose was determined on the basis of BMI, hormonal characteristics, anti-Mullerian hormone and antral follicle count, but these parameters are not subject of this study. The following ultrasound test was done on the 5th or 6th day of the cycle, in order to control folliculometry and possible inclusion of GnRH antagonists. Therefore, all the protocols are strictly individualized. Stimulation was monitored by means of ultrasound; in patients with poor ovarian response by means of serum estradiol levels every second day before the ultrasound examination. Follicles were monitored every second day or every day after the administration of cetrorelix. A dose of 5,000-10,000 IU hCG (Profasi®, Serono) was chosen when two or more follicles reached the growth and development up to 18-19 mm. Oocyte aspiration was done 36 hours after ovulation trigger. All patients were given general intravenous anaesthesia during the aspiration. During the aspiration, no complications were recorded in patients. ICSI was performed in all patients. Embryo transfer took place on the 2nd, 3rd or 5th day, depending on the number and quality. One patient in group 1 did not have embryo transfer because she had one oocyte which was not fertilized, while two patients in group 2, who had more than 20 embryos, did not have embryo transfer because of possible hyperstimulation complications. After embryo transfer, patients used Utrogestane (Utrogestane 200 mg, Besins manufacturing, Belgium) 3x1 or 100 mcg 3x2 suppositories for the luteal phase support.

Statistical analysis: Differences between treatment arms are presented as mean \pm SD and absolute number, percentages with corresponding 95%

CI and *P*-values for each comparison made for continuous and categorical variables respectively. Differences between groups were assessed by using the student's *t*-test for independent samples and Fisher's exact tests or by Pearson Chi-square test for continuous and categorical variables. All tests were two-sided and a *P*-value of <0.05 was considered statistically significant. Data were analysed using SPSS21.

Results

From 1 March 2016 to 30 June 2016, the study covered a total of 200 infertile women/cycles with unexplained infertility. There were 200 women/200 cycles, divided into 4 groups, based on the number of oocytes. Basal characteristics of the patients in all groups are listed in Table 1.

Table 1 shows the average age by group, as well as the number of patients aged over 40 years. Age

groups range from (36.64) in group 1, (34.44) in group 2, (33.20) in group 3 and (31.65) in group 4, without significant differences. The largest number of women aged 40 years and over are in the suboptimal group 2 and this is correlated with the number of patients ($p < 0.05$). The number of previous cycles is also presented in Table 1; it is statistically significant that in group 4, with the highest number of produced oocytes (20.65) (Table 2), we have 91.30% of women who are in the cycle for the first time (Table 1). The highest number of repeated cycles was recorded in group 1 (48.64%). Group 2 and group 3 are equal in terms of the number of first and second IVF attempts. Clinical pregnancy rate was significantly higher ($p < 0.05$) in group 3 (41%) and group 4 (47%) than in group 2 (35%) and group 1 (8.1%).

Table 2. presents characteristics of IVF cycle. No statistically significant difference was recorded between the groups in terms of the total number of

Table 1. Basal characteristics of age and number of IVF procedures

	Group 1 (0-3)	Group 2 (4-9)	Group 3 (10-15)	Group 4 (>15)
Number of cycles	37	100	39	23
Average age	36.64 ±2.42	34.44 ±2.25	33.20 ±2.15	31.65 ±2.15
Number of patients aged over 40 years	8	16 ^{a,b,c}	1	0
First IVF, (n, %)	19(51.36%)	62 (62%)	26 (66.66%)	21 (91.30%)
Second IVF	17 (45.94%)	30 (30%)	12 (30.77%)	2 (8.7%)
Third IVF and over	1 (2.7%)	8 (8%)	1 (2.57%)	0 (0%)
Clinical pregnancies	3/37 (8,10%)	35/100 (35%)	16/39 (41%) ^{a,c}	11/23 (47%) ^{b,d}

Note: Values are the mean ± SD number %, ^a $P < 0.05$ for Group 2 vs. Group 3, ^b $P < 0.05$ for Group 2 vs. Group 4, ^c $P < 0.05$ for Group 2 vs. Group 1, *t*-test or chi square test with $p < 0.05$, ^d $P < 0.05$ for Group 4 vs. Group 1, IVF-In vitro fertilisation. $\chi^2 = 23,92$; $p < 0.05$.

Table 2. Characteristics of IVF cycle by group

	Group 1 (0-3)	Group 2 (4-9)	Group 3 (10-15)	Group 4 (>15)	F	P	Total (M ± SD)
Average number of gonadotropins	25.62 ±8.25	26.64 ±6.51 ^d	24.08 ±6.27	21.57 ±6.87	3.97	0.00	25.36 ±7.01
Average Number of antagonists	3.05 ±1.03	3.3 ±0.98	3.26 ±1.12	3.26 ±1.21	0.62	0.60	3.26 ±1.04
Length of therapy	9.89 ±1.68	10.65 ±1.57	10.72 ±1.55	10.70 ±1.49	2.47	0.063	10.53 ±1.60
Number of oocytes	2.3 ±.74 ^{a,b,c}	6.41 ±1.63 ^{d,e}	11.62 ±2.40 ^f	20.65 ±91	500.90	0.001	8.31 ±5.67
Number of fertilized oocytes (Fertilization)	1.62 ±.86 ^{a,b,c}	3.66 ±1.73 ^{d,e}	6.47 ±2.40 ^f	9.17 ±3.83	77.25	0.00	4.46 ±31
Number of returned embryos	1.57 ±0.80 ^{ab}	2.22 ±0.61	2.28 ±0.51 ^d	1.83 ±0.83	11.19	0.00	2.07 ±0.71

Note: Values are the mean ± SD, Number of returned embryos. ^a $p < 0.01$ for group 2 vs. group 3, ^b $p < 0.01$ for group 1 vs. group 3; ^c $p < 0.01$ for group 1 vs. group 4; ^d $p < 0.01$ for group 2 vs. group 3; ^e $p < 0.01$ for group 2 vs. group 4; ^f $p < 0.01$ for group 3 vs. group 4, *t*-test with $p < 0.05$.

Table 3. Number of returned embryos by group

	Group 1 (0-3)	Group 2 (4-9)	Group 3 (10-15)	Group 4 (> 15)	χ^2	p
With one embryo	20 ^{a,b,c} (69.00%)	9 (31.00%)	0 (0%)	0 (0%)	4.17	p<0.05
With two embryos	8 (25.80%)	21 ^{a,d,e,g} (67.70%)	2 (6.53%)	0 (0%)	18.25	p<0.05
With three or more embryos	8 (5.80%)	70 ^{a,d,e,g} (51.10%)	36 (26.30%)	23 (16.80%)	61.22	p<0.05

Note: Values are the mean \pm SD, Number of returned embryos. ^ap<0.01 for group 2 vs. group 3, ^bp<0.01 for group 1 vs. group 3; ^cp<0.01 for group 1 vs. group 4; ^dp<0.01 for group 2 vs. group 3; ^ep<0.01 for group 2 vs. group 4; ^fp<0.01 for group 3 vs. group 4, ^gp<0.01 for group 2 vs. group 1, Chi-square test analysis (RR, 95% CI, p<0.05).

gonadotropin and antagonist ampoules, length of therapy, and the number of returned embryos. The highest statistically significant difference (p<0.05) was recorded in group 4, in the number of oocytes (20.65) and in the number of fertilized oocytes (9.17) as compared to other groups.

The analysis of the number of returned embryos is presented in Table 3. Results presented in Table 3 indicate that the number of cases with only one returned embryo was statistically significant (p<0.05) only in group 1 (69%) in comparison with other groups. In group 2, statistically significant (p<0.05) was the higher number of cases with two returned embryos (67.7%) and three returned embryos (51.1%) as compared to other groups.

In conclusion, the results of this study indicate a correlation between pregnancy rates and the most important variables. Pregnancy rate was negatively correlated with age ($r=-0.61$, p<0.01), while pregnancy rate was positively correlated with the number of produced oocytes ($r=0.17$, p<0.01). Pregnancy rate was positively correlated with the number of returned embryos ($r=0.178$, p<0.01).

Discussion

This study was aimed at analysing the correlation between the number of oocytes and the outcome of in vitro fertilization. Although there are numerous divisions and scientific nonconformity when it comes to the number of oocytes and their division during the stimulation, this study complies with the ESHRE definition regarding grouping according to the number of produced oocytes (Group 1: 0-3 oocytes, group 2: 4-9 oocytes, group 3: 10-15 oocytes, group 4: >15 oocytes) (7, 3). Published meta-analyses indicate that the optimal number of oocytes for COS and

conventional stimulation should be approximately 10 (8) HFEA analysis indicates that the ideal number of oocytes (up to 15) maximizes the live birth rate in all age groups (9, 10). The category of patients with normal response is most often based on the exclusion of "poor responders", that is, of patients with excessive response to the stimulation; less frequently, it is based on specific inclusion criteria. Explanation of categorizing patients with normal ovarian response should refer to the chance of achieving pregnancy with minimal risk of ovarian hyperstimulation syndrome (OHSS) (11). An analysis of the average duration of hormonal stimulation in all groups of our patients indicates that in all four groups the number of days was almost equal and there were no statistically significant differences in terms of amounts of gonadotropins and GnHR antagonists. However, a statistically significant difference was recorded in terms of women's age and the number of produced oocytes, as well as in terms of the number of fertilized oocytes. The highest percentage of clinical pregnancies was achieved in group 4, i.e. in patients with >15 oocytes. Studies carried out on the population in the Great Britain and in the USA indicate that the optimal live birth rate was achieved with 10 to 15 produced oocytes, while more than 15 produced oocytes increased the risk of OHSS and reduced the live birth rate in fresh cycles (4,5). Our results indicate that the number of oocytes is highly positively correlated with achieved clinical pregnancies, which is statistically significant ($r=0.79$, p=0.05), while the number of oocytes is directly positively correlated with the number of fertilized embryos ($r=0.98$, p=0.05); this suggests that if we have a larger number of oocytes we will also have a higher number of fertilized embryos, and therefore a higher number of clini-

cally established pregnancies. However, there is a fine line between producing 10-15 oocytes and producing >15 of them, where we have the hyperstimulation phase, with all possible complications. In the group with excessive number of produced oocytes, we also had two cancelled embryo transfers, due to hyperstimulation complications. Our results are in line with other available data which indicate that even though this group has the highest number of clinical pregnancies, it also has the largest complications and the highest number of cancelled embryo transfers; this reduces the value of this group in final correlation to the number of successful pregnancies (20, 21). When it comes to other groups, the highest number of pregnancies was recorded in group 3, in which the number of produced oocytes is 10-15, in comparison with groups 1 and 2. This is the optimal group, because no embryo transfers were cancelled in it and complications are kept to a minimum, as confirmed by other authors (4). However, we also found it surprising that 50 % of the total number of patients were in the suboptimal group. Correlations with other parameters have shown that the number of produced oocytes depends on age, suggesting that patients aged over 40 years should be treated more aggressively, with a higher number of gonadotropins or other conventional protocols. The literature suggests that in 10 to 15% of young patients with normal response, who show a suboptimal response, this happens, among other reasons, due to genetic characteristics (19).

The study was aimed at clarifying certain dilemmas regarding human reproduction, in terms of divisions and categories of the number of aspirated oocytes and their further prognostic development and correlation with the IVF outcome.

Conclusion

In the group of patients with normal response (normorespondent patients), there is a group with a statistically lower response in terms of the number of oocytes and the number of clinical pregnancies, the so-called suboptimal group. The highest statistically significant response was recorded in group 4, in terms of the number of oocytes and clinical pregnancy rate.

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Chronic inflammatory syndrome – markers in the study of the metabolic syndrome in primary health care

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Abstract

Background: The proinflammatory status in the MS associated with the insulin resistance and the endothelial dysfunction represents a liaison between inflammation and the complex metabolic processes, being accompanied by the deterioration of the vascular functions and the increase of the risk of main cardiovascular events.

Aim: To characterize proinflammatory status present on a population with metabolic syndrome (MetS).

Study design: Observational case-control study.

Methods: We compared CRP, lipids, uric acid, fibrinogen, white blood count levels in the subjects with or without MetS.

Results: The atherogenic index defined by the total Chol/HDL-cholesterol ratio is significantly higher ($P < 0.001$), as compared to the subjects in the control group. We noticed that the serum level of the uric acid was higher in the group with MetS, a significant difference ($P < 0.0001$). Also, there is a significant difference from a statistical point of view between the fibrinogen values ($P < 0.001$). In leukocytes, we obtained significant differences in eosinophils only, their average value being significantly higher in the group with MetS as compared to the control group ($P < 0.001$).

Conclusions: Within the metabolic syndrome, even though we found statistically significant differences between the values of certain markers of the chronic inflammation and of atherogenesis (fibrinogen, eosinophils, Non-HDL-cholesterol, uric acid, atherogenic index), the analysis of the AUC areas framed the determinations of these parameters in the category of the reduced accuracy tests. As a consequence, the diagnostic of the chronic inflammation in the metabolic syndrome has to be complemented with tests having a higher sensitivity and specificity.

Key words: inflammation markers, metabolic syndrome, eosinophils.

Introduction

Metabolic syndrome (MS) is a cluster of cardiometabolic risk factors. It's an observational case-control study (1, 2), which aimed at studying the markers of the chronic inflammation (3, 4, 5, 6) in the metabolic syndrome (7, 8, 9, 10). We considered the markers which can be performed in ambulatory care and which are frequently performed. The study was carried out during 12 months, over the period from January 1st, 2013 to December 31st, 2013, on Family Medicine Practice patients.

Material and methods

The study comprises subjects of both genders, with the age between 18-91 years old, divided into two groups: the group with metabolic syndrome (MS group) and the control group (without metabolic syndrome).

The study group was approved by the Ethics Committee of the University of Medicine and Pharmacy “Grigore T. Popa” of Iasi based on the informed consent of patients, according to World Medical Association, Helsinki Declaration (2013 Revision, Brazil).

MS group a) inclusion criteria: age more than 18; recruitment based on the signing of the informed free consent; metabolic syndrome diagnosed based on the *Harmonized I* criteria (11). **b) exclusion criteria:** age less than 18, denial to sign the informed free consent, women during pregnancy or lactation. Anthropometric data (body weight, height, waist circumference, and body mass index), systolic blood pressure, and diastolic blood pressure were recorded and assessed.

After overnight fasting, blood samples were collected for measurement of white blood count, erythrocyte sedimentation rate (ESR), fibrinogen and biochemical analyses, including an assessment of C-reactive protein (CRP) and uric acids levels.

Statistical analysis

In order to create the database, we used the *MS diagnostic algorithm* drafted by us together with the *Arhilog Soft Company*, and for the statistical treatment of the studied parameters, we used the programs *Microsoft Office Excel 97-2003* and the application *Medcalc Statistical Software – 13.3.3*. In order to compare the continuous variables in the studied population, we used the *t Student* test, in order to compare the nominal (categorical) variables we used the *Chi square* test, and *z - test* was used in order to compare the proportions. The *receiver - operating characteristic* (ROC) curves were studied in order to determine the sensitivity and the specificity of the diagnostic tests. The AUC areas (*area under the curve*) were determined in order to compare the predictive power of the markers of the metabolic syndrome and of the chronic inflammation, as follows: AUC between 0.9-1 – excellent accuracy;

AUC between 0.7- 0.9 – moderate accuracy; AUC between 0.5 - 0.7- reduced accuracy. AUC equal to 1 corresponds to a perfect test (100% sensitivity and 100% specificity) (12); *p* value lower than 0.05 was considered as statistically significant (13, 14, 15).

Results

Group with the metabolic syndrome (MS group) was formed of the 389 patients diagnosed with MS according to the criteria of the *Harmonised I*. The MS group included 185 men and 204 women, the ratio men/women being of 0.90 (95%: CI:0.73-1.12). The characteristics of the patients included in the group with MS were introduced in *Table 1*. The age of the patients in the MS group was between 23 and 89 years, and the average age of the patients with MS included in the study was of 59.76 ± 13.22 years, with no significant differences between men and women (*t- Test*, *P* = 0,3354).

The control group (without MS) (Table 2) comprised the 1,141 participants who did not meet the diagnostic criteria of the metabolic syndrome. Of the 1,141 subjects, 530 were men and 611 were women, the ratio men/women being of 0.87 (95%:

Table 1. Characteristics of the MS group

	Average	DS	Minimum	Maximum
Age (years old)	59,763	13,2238	23,000	89,000
Waist circumference (WC)(cm)	98,802	11,1859	72,000	134,000
Body Mass Index (BMI) kg/m ²	30,089	5,1732	20,000	45,000
Systolic BP (SBP) (mmHg)	127,137	13,2843	95,000	190,000
Diastolic BP (DBP) (mmHg)	79,301	8,1958	60,000	115,000
Glucose (mg/dl)	106,604	33,6844	72,000	400,000
HDL- chol (mg/dl)	43,070	10,9920	20,000	64,000
Triglycerides (TG) (mg/dl)	170,019	98,4802	60,000	879,000
Total chol (mg/dl)	217,255	56,3711	88,000	391,000
LDL- chol (mg/dl)	138,432	47,9930	42,000	282,000
Non-HDL (mg/dl)	177,674	56,8445	54,000	339,000
Ratio chol_ total/HDL	5,409	2,1417	1,591	14,091
Uric acid (mg/dl)	5,424	1,5737	1,520	11,000
ESR (mm/1h)	19,562	13,7319	4,000	66,000
Fibrinogen (mg/dl)	330,297	62,6668	139,000	590,000
CRP (mg/dl)	1,525	2,555	0,000	14,170
White cells/mm ³	6974,656	1785,409	2340,000	13600,000
PMN/mm ³	4014,425	1405,727	300,000	8310,000
Lymphocytes/mm ³	2317,769	778,7794	530,000	6440,000
Monocytes/mm ³	478,408	199,8644	40,000	1180,000
Eosinophils/mm ³	221,942	165,4714	20,000	1140,000

Table 2. Characteristics of the Control (Non - MS) Group

	Average	DS	Minimum	Maximum
Age (years old)	43,332	17,48	18,00	91,00
WC (cm)	84,75	11,75	56,00	116,00
BMI (kg/m ²)	24,60	3,97	19,00	37,30
Systolic BP (mmHg)	73,95	7,87	60,00	115,00
Diastolic BP (mmHg)	114,23	14,92	90,00	185,00
Total chol (mg/dl)	201,28	45,84	92,00	302,00
LDL- chol (mg/dl)	123,59	42,50	22,00	268,00
HDL - chol (mg/dl)	48,36	9,52	21,00	92,00
Non-HDL (mg/dl)	154,71	48,20	28,00	279,00
Ratio chol _{total} /HDL-chol	4,42	1,82	1,43	11,90
TG (mg/dl)	105,77	42,71	48,00	394,00
Glucose (mg/dl)	90,49	12,34	72,00	149,00
Uric acid (mg/dl)	4,67	1,40	2,00	9,20
ESR (mm/h)	18,82	12,17	2,00	52,00
Fibrinogen (mg/dl)	296,80	43,36	202,00	420,00
CRP (mg/dl)	1,55	2,88	0,00	13,50
White cells/mm ³	6936,70	2024,42	3770,00	16100,00
PMN/mm ³	2307,16	658,45	1060,00	4500,00
Lymphocytes/mm ³	167,88	101,65	30,00	530,00
Monocytes/mm ³	481,71	175,87	150,00	1010,00
Eosinophils/mm ³	3860,65	1524,49	1440,00	10900,00

CI: 0.77-0.97). The age of the subjects included in the group without metabolic syndrome was comprised between 18 and 91 years old and the average age of the participants in the control group was of 43.33 ± 17.48 years.

The calculated average value of **LDL-cholesterol** for the subjects in the control group had the value of 123.59 ± 42.50 mg/dl, while for the patients with MS, we calculated the average value of LDL- Chol of 138.43 ± 47.99 mg/dl, significantly higher as compared to the subjects in the control group ($P = 0.0002$). The measurement of the **Non-HDL-cholesterol** showed the presence of a significant difference between the two groups, the average value of the Non-HDL-cholesterol was significantly higher ($P < 0.0001$) in the group with metabolic syndrome (177.67 ± 56.84 mg/dl) as compared to the control group ($154, 71 \pm 48.20$ mg/dl). We assessed the sensitivity and the specificity of the Non-HDL-cholesterol as a diagnostic test of the metabolic syndrome (figure 1).

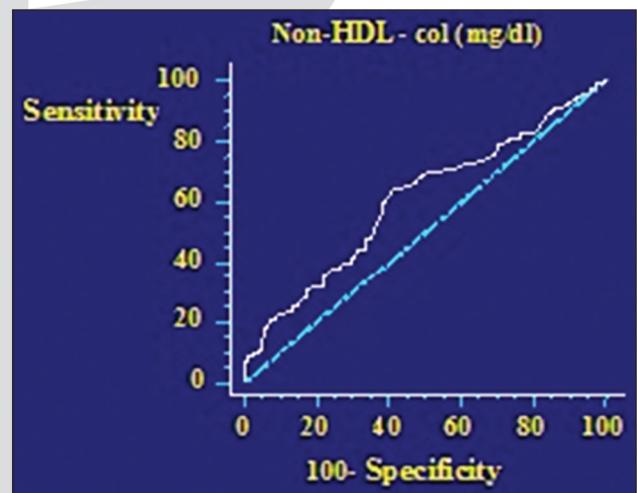


Figure 1. ROC curve for Non-HDL-cholesterol

The value of the Non-HDL-cholesterol which predicts with the highest accuracy the presence of the metabolic syndrome was of 151 mg/dl (the "cut-off" point), for which we calculated a sensitivity of 64.27% and a specificity of 58.72%. The calculation of the AUC area provided the value of 0.605 and therefore the determination of the serum concentration of the parameter of the Non-HDL-cholesterol has the value of a reduced accuracy

test in the diagnostic of the metabolic syndrome. We studied the values of the ratio **total chol/HDL-cho**l in the two groups and we noticed that in the patients with MS, the average value of the atherogenic ratio is significantly higher as compared to the ratio value determined in the control group. For the studied atherogenic ratio, the analysis of the ROC curve (Figure 2) showed that the values higher than the “cut-off” point of 4.31 predict the presence of the metabolic syndrome with the highest sensitivity (63.81 %) and specificity (65.82%).

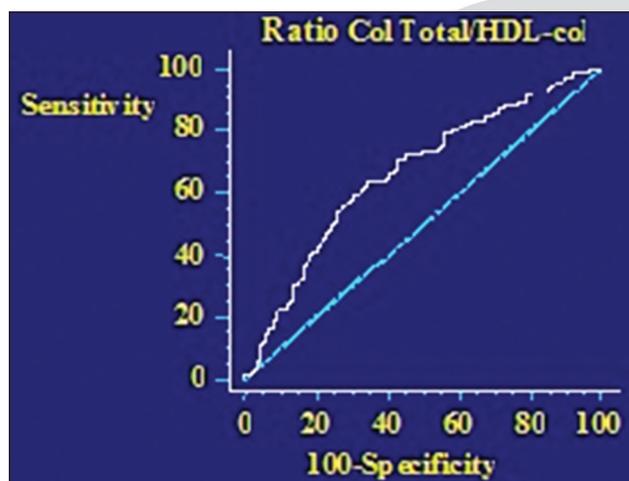


Figure 2. ROC curve: ratio total chol/HDL-Chol

Figure 2 shows that AUC value is of 0.667 and as a consequence, in the study of the metabolic syndrome, the atherogenic index is considered as being a reduced accuracy marker. Then, we analyzed the **markers of the inflammation and of the endothelial dysfunction**: uric acid, fibrinogen, ESR, C reactive protein. Therefore, we comparatively studied in the two groups the average values of the **uric acid** and we noticed that in the control group, the determined average value of the uric acid in the subjects without MS was significantly lower than in the group of the patients with MS.

We investigated the importance of the uric acid as a biomarker in the metabolic syndrome (Figure 3). Acid values higher than 4.3 mg/dl predict the diagnostic of MS with the highest sensitivity (81.07%) and specificity (53.28%). AUC having the value of 0.655 frames the determination of the serum uric acid among the reduced accuracy tests in the diagnostic of the metabolic syndrome.

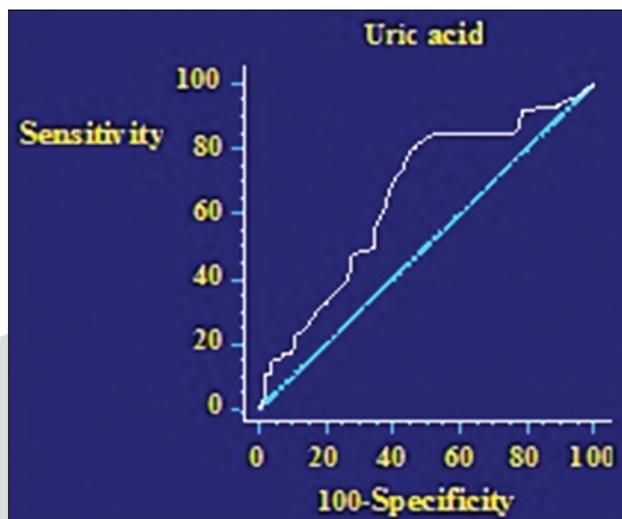


Figure 3. ROC curve serum uric acid

White blood cells. The average value of the white blood cells in the MS group was of $6,974.65 \pm 1,785.40$ elements/mm³, while in the control group it was of $6,936.65 \pm 2,024.42$ elements/mm³. Figure 4. A shows that we did not obtain significant differences between the two groups, when we refer to the average values of the total white blood cells (*t*-Test, $P = 0.765$).

Instead, we obtained statistically significant differences when we compared the average values of the number of **eosinophils** in the two groups (*t*-Test, $P < 0.0001$; Figure 4. B). Therefore, the determined average value of the number of eosinophils was significantly higher in the group with metabolic syndrome (221.93 ± 165.47 Eo/mm³) as compared to the control group, where we calculated an average value of 167.88 ± 101.65 Eo/mm³. The average values of the number of **lymphocytes** were determined and we obtained an average value of $2,307.16 \pm 658.45$ Ly/mm³ for the control group, respectively $2,317.66 \pm 777.77$ Ly/mm³ for the MS group. The analysis of the average values of the number of lymphocytes did not show statistically significant differences between the two groups (*t*-Test, $P = 0.8652$; fig. 4C). For **monocytes**, the average value of the number of these cells in the group of the patients with metabolic syndrome was of 478.40 ± 199.86 Mo/mm³, while in the control group, it was of 481.71 ± 175.87 Mo/mm³. We did not obtain statistically significant differences (*t*-Test, $P = 0.340$; fig. 4.D). We noticed a tendency of increase of the number of **neutrophils** in the MS group, increase which did not accomplished

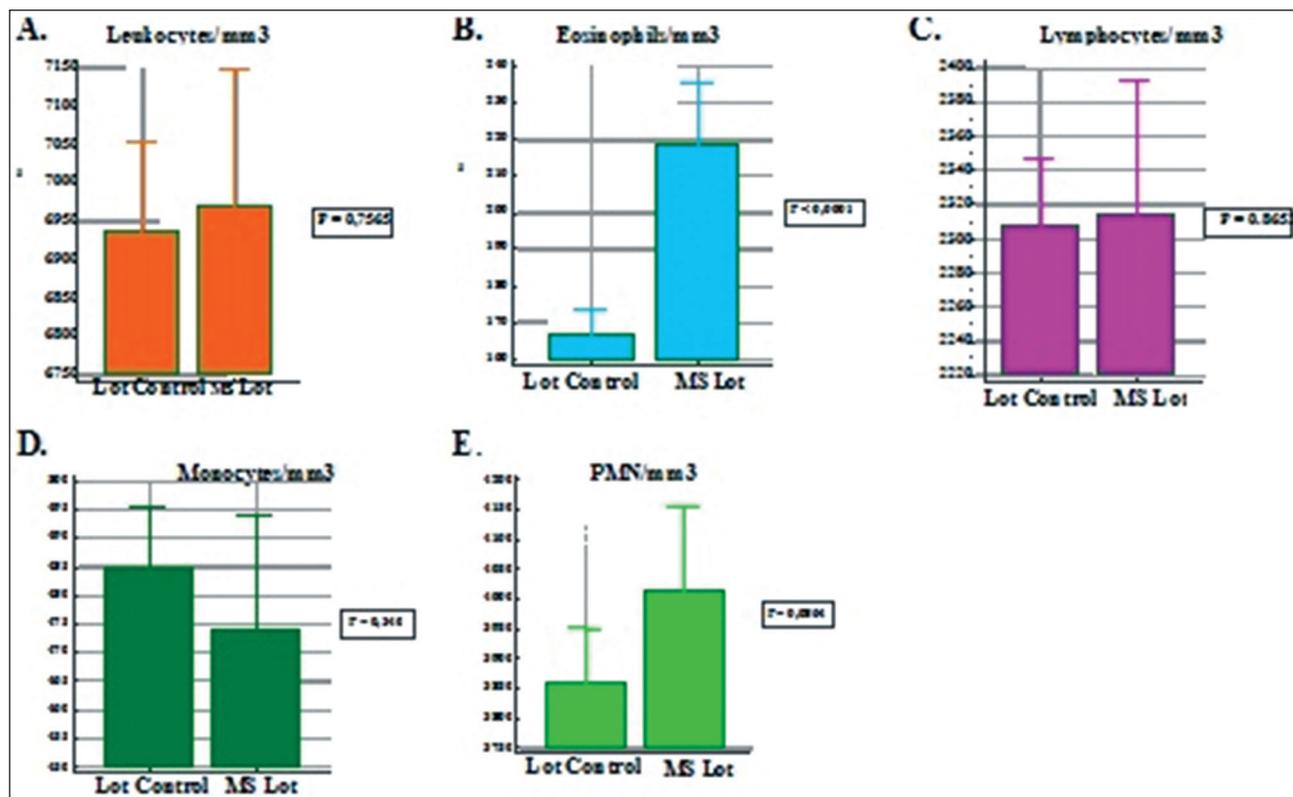


Figure 4. Comparison between the two groups with regard to the values of the white blood cells in the two groups: Total white blood cells (A); Eosinophils (B); Lymphocytes (C); Monocytes (D); Neutrophils (E)

the statistical significance threshold (*t*- Test, $P = 0.08$; fig. 4.E). Therefore, the average value of the number of PMN in the group of the patients with metabolic syndrome had the value of $4,014.42 \pm 1,405.72$ PMN/ mm³, while for the subjects in the control group, we obtained the value of $3,860.65 \pm 1,524.49$ PMN/ mm³.

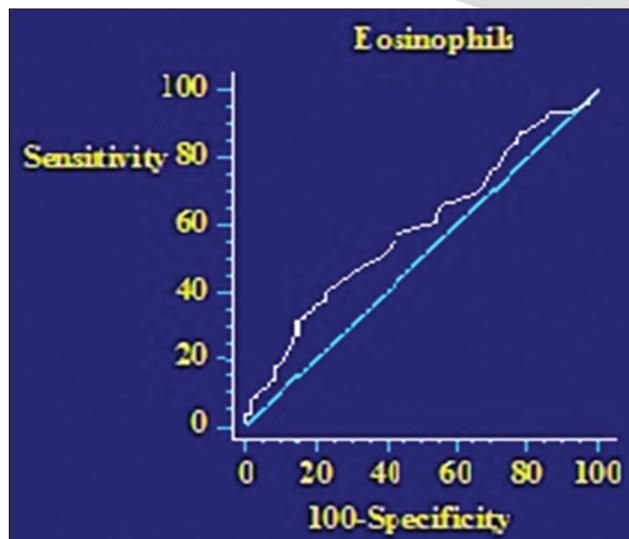


Figure 5. ROC curve for the circulating eosinophils count

The analysis of the ROC curve drawn for the values of the number of eosinophils in the blood of the subjects included in the two groups (figure 5) shows that the “cut-off” values higher than 200 Eo/mm³ can predict the presence of the metabolic syndrome with the highest specificity (77.05%) and sensitivity (39.78%). For the diagnostic of the metabolic syndrome, the calculation of the AUC area showed that the determination of the number of blood eosinophils has the value of a diagnostic test with reduced accuracy (AUC = 0.589).

Then we analyzed the values of the acute phase reactants: erythrocyte sedimentation rate (ESR), fibrinogen, C reactive protein. The average value of fibrinogen is of 330.29 ± 62.66 mg/dl for the group of patients with metabolic syndrome, while in the control group we determined an average value of 296.80 ± 43.36 mg/dl, a statistically significant difference, the average value of fibrinogen being higher in the group with metabolic syndrome (*t*-Test, $P < 0.0001$; figure 6).

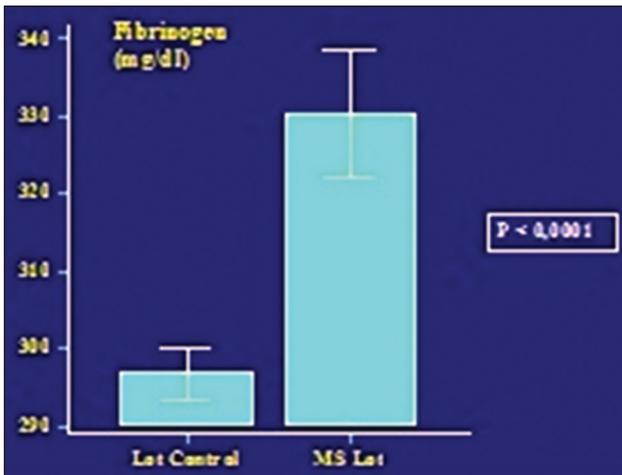


Figure 6. Comparison between the two groups regarding the determined values of fibrinogen

By means of ROC curve (figure 7) we determined that fibrinogen values higher than 306 mg/dl predict the metabolic syndrome with a sensitivity of 75.11% and specificity of 60.56%. Similarly to the other previously investigated markers of the chronic inflammation and atherogenesis, **fibrinogen** was framed in the category of the inflammatory markers with reduced accuracy, AUC having the value of 0.690 (figure 7).

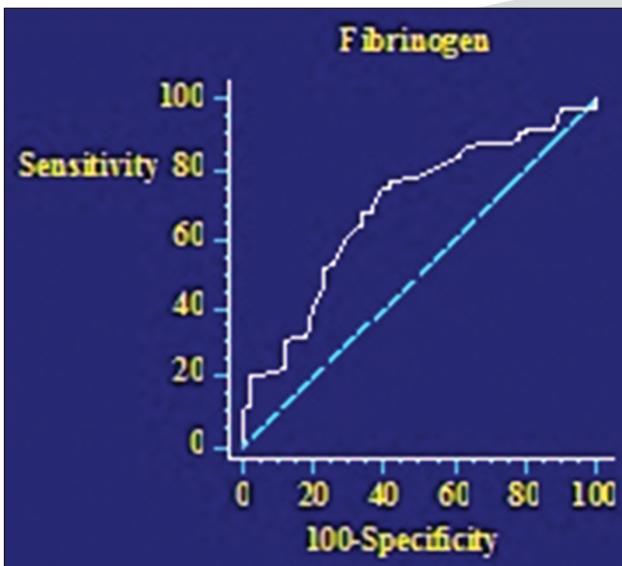


Figure 7. ROC curve for fibrinogen

Instead, when we studied the average values of the **sedimentation rate and of the C reactive protein**, we did not highlight significant differences between the two groups ($P > 0.05$; figure 8).

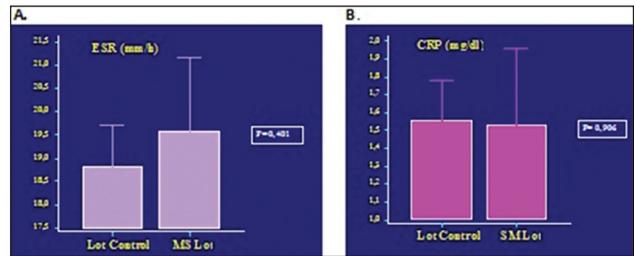


Figure 8. Comparison between the two groups regarding the determined values of ESR (A) and CRP (B)

In the study groups, we calculated the (AUC) areas corresponding to the diagnostic criteria of the metabolic syndrome. We noticed that in case of the *Harmonized I score*, the sensitivity and specificity are of 100%, and AUC is equal to 1.000. For the five diagnostic criteria, AUC had values between 0.636 (for the HDL-cholesterol variable) and 0.804 (for the abdominal circumference variable) (figure 9).

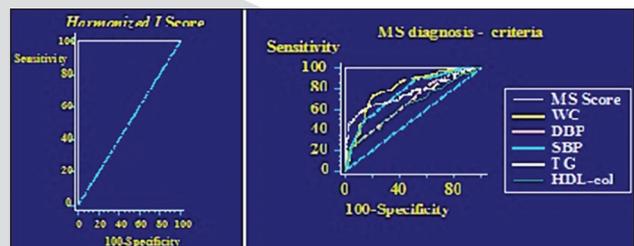


Figure 9. AUC analysis: MS diagnosis - criteria

We notice that AUC value for the studied markers is between 0.589 (in case of the eosinophils variable) and 0.690 (in case of fibrinogen). In the context of the metabolic syndrome, the accuracy of these markers of the chronic inflammation and of the endothelial dysfunction can be deemed as reduced, as $AUC < 0.7$ for all the investigated markers (figure 10).

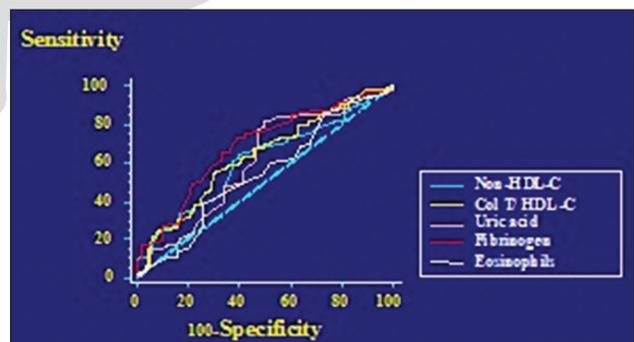


Figure 10. AUC analysis: markers of the MS, of the chronic inflammation and of the atherogenesis

However, the values of the areas of the parameters represented in the figure are close to AUC values of the variables of the diastolic blood pressure and of the HDL-cholesterol (fig.10) and therefore, they can be used in order to complement the diagnostic of metabolic syndrome.

Discussions

The proinflammatory status in the MS associated with the insulin resistance and the endothelial dysfunction represents a liaison between inflammation and the complex metabolic processes, being accompanied by the deterioration of the vascular functions and the increase of the risk of main cardiovascular events. We compared CRP level in the subjects with or without the MS, we did not find significant differences between the two groups ($P = 0.906$). This result can be explained by the fact that the study did not determine the hCRP fraction, but the total CRP and by the fact that all subjects were evaluated and then treated according to the therapeutic guides which include the statin therapy, the medicines which reduce the CRP (16, 17). The statistical analysis showed a statistically significant difference between fibrinogen values determined in the two groups ($P < 0.001$). We showed that fibrinogen values are higher in the MS as compared to the control group, both in men and in women, in concordance with the previous studies (17, 18, 19, 20). Fibrinogen assessment is important not only in the MS in order to define the proinflammatory and pro-thrombotic context, but also for the cardiovascular prediction in the normal subjects. Therefore, in the persons with moderate cardiovascular risk, complementing the initial screening of the classical cardiovascular risk factors with the analysis of the values of the C reactive protein and of the fibrinogen could be useful in the prevention of the main cardiovascular events (16, 17, 19, 20).

By studying the leukocyte populations, we obtained significant differences only in eosinophils, their average value being significantly higher in the MS group, as compared to the control group ($P < 0.001$). Eo involvement in the MS has been shaped over the last decade, these cells being involved in the recruitment of the macrophages in the adipose tissue (21). Experimentally, we no-

ticed that an increase of the Eo appeared as a consequence of the infection with helminths or stimulation with IL-5 is followed by the improvement of the glucose tolerance (22, 23). The number of Eo is significantly higher in the MS group, it can be interpreted either as a reaction of adaptation of the organism, of body weight regulation, either it can be related to the presence of an anomaly at the level of these cells. The control exercised by the eosinophils on macrophage activation could be the key of the intervention on obesity in the foreseeable future (22, 24, 25).

In compliance with the Guide of the European Society of Cardiology (26), it is important for the practice of the general practitioner that Non-HDL-cholesterol dosage is recommended both for the description of the hyperlipoproteinemia in MS and as therapeutic target (26, 27), while the determination of the total Chol /HDL chol ratio is not recommended as therapeutic target (6). We compared the values of the Non-HDL-cholesterol, we recorded statistically significant differences ($P < 0.0001$), the patients with metabolic syndrome having higher values as compared to the normal subjects. As we anticipated, the values of the triglycerides and of LDL-cholesterol were higher in the MS group ($P < 0.0001$), and the concentration of the HDL-cholesterol was significantly lower in the patients with MS ($P < 0.001$). Moreover, we mention that in the patients with metabolic syndrome, the atherogenic index defined by the ratio total Chol /HDL-chol is statistically higher ($P < 0.001$), as compared to the subjects in the control group. Therefore, we describe an atherogenic profile, with increased risk of main cardiovascular events.

Hyperuricemia, frequently associated with the MS, is known as an independent factor of cardiovascular risk (28). In concordance with this statement, in our study, we noticed that the serum level of the uric acid was higher in the MS group, a significant difference from a statistic point of view ($P < 0.0001$). Within the metabolic syndrome, even though we found statistically significant differences between the values of certain markers of the chronic inflammation and of atherogenesis (fibrinogen, eosinophils, Non-HDL-cholesterol, uric acid, atherogenic index), the analysis of the AUC areas framed the determinations of these parameters in the category of the tests with reduced accuracy.

As a consequence, the diagnostic of the chronic inflammation (29) in the metabolic syndrome must be complemented by tests having a higher sensitivity and specificity, which can investigate the pathological mechanisms, involved in the genesis of the cardio metabolic disorders (30) at genetic and molecular level. The assessment of the inflammatory markers in the context of the metabolic syndrome is useful in the complex evaluation of the cardio-metabolic risk factors, in the primary health care practice.

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Letrozole plus lower dose of Human menopausal Gonadotropins plus GnRH Antagonists Protocol for Women with Poor Ovarian Response Undergoing IUI Treatment Cycles: Randomized Controlled Trial

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Abstract

Objective: According to the American Society for Reproductive Medicine (ASRM), the definition of a poor responder implies 3 day FSH>10 IU/L, AMH 0.2-0.7 ng/mL, AFC 3 day 3-10 and clomiphene citrate challenge test (CCCT) day 10 FSH 10-22 IU/L, FSH day 10/ FSH day 3 >1.0.

The aim of this study was to determine whether the COS/IUI with a lower dose of human menopausal gonadotropins (hMG) plus letrozole plus Gonadotropins Releasing Hormone (GnRH) antagonists plus estradiol valerate (E2) is superior in terms of the outcome of clinical pregnancy rate in comparison with the treatment with hMG plus clomiphene citrate (CC) plus GnRH antagonists.

Method: A prospective randomized controlled trial (RCT) covered 60 subfertile women (118 cycles) with low ovarian reserve and infertility lasting over a year. Group A (n=30 patients/55 cycles) was treated with low doses of hMG +CC+ cetrotide, while group B (n=30 patients/63 cycles) was treated with low doses of hMG+letrozole+cetrotide+E2 until the target size of the follicles (≥ 17 mm) was reached. Primary outcome point was the clinical pregnancy rate per patient/cycle.

Results: The clinical pregnancy rate per patient/cycle in group A was significantly lower (5.4% vs. 6.3%, RR=0.85; 95%CI: 0.82-0.92, $p<0.05$), as well as the live birth rate per patient/cycle (3.6% vs. 4.7%; RR=0.76, 95%CI: 0.71-0.82, $p<0.02$) in comparison with group B. Miscarriage rate/cycle was 1.8% in group A, and 1.6% in group B, without significant differences (RR = 1.13; 95% CI :

1.10-1.19, $p<0.09$). The rate of cancelled cycles per patient was significantly higher in group A (33.3% vs. 26.6%, RR=0.80; 95%CI: 0.71-0.87, $p<0.03$) in comparison with group B.

Conclusion: Controlled ovarian stimulation/IUI with lower dose of hMG plus letrozole plus GnRH antagonists plus E2 (from the mid-luteal phase of the previous cycle) was superior to a lower dose of hMG+CC+ GnRH antagonists in terms of the clinical pregnancy rate, live birth rate, lower price and lower required amount of hMG ampoules in women with poor ovarian response.

Key words: Controlled ovarian stimulation; Intrauterine insemination; Letrozole; hMG; E2 supplementation; Poor ovarian response.

Introduction

Nowadays, a major problem in the Assisted Reproductive Technology (ART) methods is a low pregnancy rate in woman with poor ovarian response. Poor ovarian response is estimated in approximately 9 to 24% patients undergoing ART (1). Poor ovarian response to controlled ovarian stimulation (COS) remains one of the most important points of interest in assisted reproduction. Poor ovarian response to gonadotropins is clearly associated with reduced ovarian reserve in elderly women. The selection of optimal treatment protocols for women with poor response for to COS in ART cycles remains a contentious issue (2). Previous research indicated that the administration of high doses of gonadotropins had no beneficial effects on the ovarian reserve. Increased doses of

follicle-stimulating hormone (FSH) may reduce the number of cancelled cycles, but they may also reduce the clinical pregnancy rate and increase the fetal loss rate, due to poor-quality embryos (3). However, high doses of gonadotropins are expensive and cannot compensate for the poor quality of older eggs and low frequency of conception (4), while they may increase the aneuploidy rate (5). Moreover, such a demanding protocol represents a burden to the patient, especially in developing countries, where drugs and treatment costs are not covered by insurance (6). Thus, mild ovarian stimulation seems to be preferred for women who were treated with high doses of FSH in previous unsuccessful cycles, with poor ovarian response to stimulation (7). Clomiphene citrate and letrozole alone or combined with FSH were used in the mild protocol of ovarian stimulation (8, 9). Clomiphene citrate (CC) is a non-steroidal selective estrogen receptor modulator, which functions primarily by binding to estrogen receptors in the hypothalamus. This competitive inhibition results in increased secretion of gonadotropins (10). Letrozole is a strong non-steroidal aromatase inhibitor, used as a new approach to improving the ovarian response to stimulation. This drug leads to the inhibition of estradiol synthesis (E2), which through a negative feedback to the pituitary gland results in endogenous secretion of gonadotropins (11,12). The aim of this RCT study was to compare the effectiveness of letrozole combined with hMG and GnRH antagonists (cetrotide) and E2 supplementation with mild COS in women with poor ovarian response.

Material and Methods

Study design. A prospective randomized controlled trial (RCT) covered 60 women with poor ovarian response and infertility lasting over a year. The survey was conducted between January 2014 and December 2016 at the Institute of Human Reproduction “Dr. Hajder” Tuzla. Infertility was processed in accordance with the guidelines for infertility (13). All the couples underwent the following examinations: spermogram, analysis of sex hormones in the early follicular phase of the cycle, Anti-Mullerian hormone (AMH), ultrasound monitoring of the cycle (folliculometry, endometrial thickness, ovarian volume, antral follicle count – AFC),

microbiological and immunological treatment for infections, hysterosono-salpingography).

Study population. The study covered couples with unexplained infertility, mild endometriosis, pelvic inflammatory disease, previous operations on the ovary, and normal male factor. Definition. Infertility is defined as the failure to conceive after 12 months of unprotected sexual intercourse (14). The European Society of Human Reproduction and Embryology (ESHRE) consensus of the definition (15), and American Society for Reproductive Medicine (ASRM) define a poor responder (16).

Treatments. Patients were randomized into two groups and treated to target. Group A (n=30) was treated with clomiphene citrate (Clomid, Sanofi, Belgium) in a dose of 50 to 100 mg between the 3rd and 7th day of the menstrual cycle, hMG (Menopur, Ferring, Denmark) in a fixed dose of 150 IU beginning with the 5th day of the menstrual cycle until the hCG administration and GnRH antagonists, Cetrotide 0.25 mg (Cetrotide, Serono Laboratories, Aubonne, Switzerland) until reaching the target follicle of 17 mm. Group B (n=30) was treated with Letrozole (Femara®, Novartis, New York, NY), in a dose of 5 mg/day, between the 3rd and 7th day of the menstrual cycle and with fixed 150 IU daily dose of hMG (Menopur, Ferring, Denmark), initiated from the cycle day 5. As the dominant follicle reached 14 mm in mean diameter, 0.25 mg/day GnRH antagonist (Cetrotide, Serono, Aubonne, Switzerland) was started. When at least two follicles with a mean diameter of 17 mm were observed, 5000 IU hCG (Profasi®, Serono) was administered. Endometrial thickness and serum E2 levels were measured in the day of hCG injection. GnRH antagonist, cetrotide 0.25 mg to prevent premature lutenization, until the day of hCG administration. In group B, pre-treatment with oral estradiol valerate E2 (Estrofem 2mg, tablets, NovoNordisk, FemCare AG, Switzerland), two tablets daily treatment was initiated on the luteal day 21 of the preceding cycle and stopped at day 1 in the next menstrual cycle. Transvaginal ultrasound and serum estradiol, LH and FSH were arranged on day 3 of the period. In both groups, when mature leading follicle(s) reached 17 mm in diameter and the urinary LH test was negative, urinary hCG (Profasi®, Serono) in a dose of 5000 IU was given; IUI was then performed 36–40 hours later.

When the urinary LH test was positive, IUI was performed the next morning. After the IUI, women lay on their back for 15 to 20 minutes (17).

The criteria for cycle cancellation were no ovarian response after 7 days of ovarian stimulation. All patients received luteal phase support with vaginal suppositories (Utrogestan 200 mg, Besins manufacturing, Belgium) 3x daily starting on the day of the IUI and was continued until fetal heart activity was documented by ultrasound.

Outcome measures. Primary outcome was the Chemical pregnancy rate/cycle and Clinical pregnancy rate/cycle in group A vs. group B. Secondary outcome included the live birth rate, endometrial thickness, mature follicle count (17 mm or more in diameter) and miscarriage rate. Clinical pregnancy was defined when an intrauterine gestational sac(s) was visible by ultrasonography. Chemical pregnancy was defined by positive β -hCG, 12 days after embryos transfer. Clinical pregnancy was identified as observation of fetal heart activity by transvaginal ultrasonography that was performed three weeks after positive β -hCG (18). Spontaneous abortion was defined as loss of fetus with gestational age under 20 weeks (19).

Statistical analysis. Differences between treatment arms are presented as mean \pm SD and absolute number, percentages with corresponding 95% CI and *P*-values for each comparison made for continuous and categorical variables respectively. Differences between groups were assessed by using the student's *t*-test for independent samples and Fisher's exact tests or by Pearson Chi-square test for continuous and categorical variables. All

tests were two-sided and a *P*-value of <0.05 was considered statistically significant. IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

Results

From January 2014 to December 2016, the study covered a total of 60 infertile women with reduced ovarian reserve. Ten patients in group A (clomiphene citrate+hMG+GnRH antagonists) and eight women in group B (letrozole+hMG+GnRH antagonist+estradiol valerate) were excluded from the study due to poor response to the COS. There were 42 women/120 cycles, randomized into two groups. Thus, data were analyzed for 20 women in group A and 22 women in group B. Basal characteristics of the patients of both groups are listed in Table 1.

The groups did not differ significantly in terms of demographic characteristics, such as age, BMI, duration of infertility, cigarettes, and causal factors of infertility. The groups did not differ significantly in terms of hormonal characteristics either, such as basal day 3 FSH, LH, E2 and AMH. Also, there were no significant differences in the ovarian volume and the number of antral follicles (Table 2). In group A, estradiol levels on the day of hCG administration were significantly lower (950.4 vs. 1220.3, $p<0.04$), with lower endometrial thickness (8.29 vs.9.26, $p<0.04$), in comparison with group B (Table 2). In group A, the number of used hMG ampoules was significantly higher (24.4 ± 5.1 vs. 18 ± 4.5 , $p<0.001$) than in group B.

Table 1. Baseline characteristics of the patients in both groups with Poor Ovarian Response

Variable	Group A n=30	Group B n=30	P-value
Mean age (years)	37.4 \pm 4.4	36.9 \pm 5.9	0.08
BMI (kg/m ²)	23.6 \pm 3.7	24.2 \pm 3.5	0.09
Infertility duration (years)	9.4 \pm 2.7	8.9 \pm 3.1	0.07
Smoking (female) %	5/30 (16.7%)	4/30 (13.3%)	0.09
Unexplained (%)	18/30 (60%)	17/30 (56.7%)	0.08
Pelvic Inflammatory Disease (%)	2/30 (6.7%)	3/30 (10%)	0.07
Ovarian surgery (%)	1/30 (3.3%)	1/30 (3.3%)	0.09
Mild endometriosis (%)	4/30 (13.3%)	5/30 (16.7%)	0.08
Duration of hormonal stimulation (days)	12.9 \pm 2.6	10.6 \pm 1.7	0.05

Note: Values are the mean \pm SD, number %, range, $P<0.05$ for Group A vs. Group B, *t*-test or chi square test with $p<0.05$. BMI- body mass index.

Table 2. Hormonal characteristics of the patients in both groups patients with Poor Ovarian Response

Variable	Group A n=30	Group B n=30	P value
Day-3 FSH (IU/mL)	12.2±2.1	11.9±2.4	0.09
Day-3 LH (IU/mL)	9.9 ±3.4	9.6±3.7	0.08
Day- 3 E ₂ of the cycle (pg/mL)	34.1±3.3	35.2±3.1	0.09
Anti-Mullerian Hormone (ng/mL)	0.5±0.2	0.3±0.3	0.06
E level on the day of hCG (pg/mL)	950.4±316.5	1220.3±588.5	0.04
Ovarian Volume (cm ³)	2.4±0.5	2.5±0.4	0.07
Antral Follicle Counts (n)	2.1±0.8	2.2±0.6	0.08
No of mature follicles ≥ 17 mm	3.7±2.5	3.8±2.2	0.09
Endometrial thickness of day of hCG (mm)	8.29±0.6	9.26±1.2	0.04
No of ampoules hMG	24.4 ± 5.1	18 ± 4.5	0.001

Note: Values are the mean ± SD, P<0.05 for Group A vs. Group B: t-test with p<0.05, FSH Follicle- stimulating Hormone, LH- Luteinizing hormone, hMG-Human Menopausal Gonadotropin, E₂- estradiol, hCG-human chorionic gonadotropin.

Table 3. Pregnancy outcomes of the study groups

Outcome	Group A n=30patients/ n=55cycles	Group B n=30patients/ n=63cycles	Relative risk	P-value
Chemical pregnancy rate / Cycle, No (%)	4/55 (7.3%)	5/63 (7.9%)	0.92 (95%CI 0.85-0.98)	0.06
Clinical pregnancy rate/ Cycle, No (%)	3/55 (5.4%)	4/63 (6.3%)	0.85(95%CI 0.82-0.92)	0.05
Live –birth rate/ cycle, No (%)	2/55 (3.6%)	3/63 (4.7%)	0.76(95%CI 0.71-0.82)	0.02
Miscarriage rate/cycle, No (%)	1/55 (1.8%)	1/63 (1.6%)	1.13(95%CI 1.10-1.19)	0.09
Cancellation rate/patient, No(%)	10/30 (33.3%)	8/30 (26.6%)	0.80(95%CI 0.71-0.87)	0.03

Note: Values are expressed with absolute number; percentages with corresponding 95% CI. Chi-square test analysis (RR, 95% CI, p<0.05).

Treatment outcomes for both groups are presented in Table 3. Chemical pregnancy rate per patient/cycle in group A was lower (7.3% vs 7.9%, RR=0.92, 95%CI: 0.85-0.98, p<0.06) than in group B, but there were no significant differences. Clinical pregnancy rate per patient/ cycle in group A was significantly lower (5.4% vs. 6.3%, RR=0.85, 95% CI: 0.82-0.92, p<0.05), the live birth rate per patient/cycle (3.6% vs 4.7%, RR=0.76, 95% CI: 0.71-0.82, p<0.02) compared to group B. Miscarriage rate per cycle amounted to 1.8% in group A and 1.6% in group B, without significant differences (RR = 1.13, 95% CI : 1.10-1.19, p<0.09). The rate of cancelled cycles per patient was significantly higher in group A (33.3% vs. 26.6%,

RR=0.80, 95%CI: 0.71-0.87, p<0.03) in comparison with group B.

Discussion

In this randomized controlled trial (RCT), ovarian stimulation/IUI with lower doses of hMG (Menopur) plus letrozole plus GnRH antagonists (Cetrotide) plus estradiol valerate supplementation (Estrofem) was superior in terms of the clinical pregnancy rate, live birth rate, lower rate of cancelled cycles, less hMG ampoules used, lower number of stimulation days as compared the conventional protocol involving lower doses of hMG (Menopur) plus CC plus GnRH antagonists (Ce-

trotide) in infertile women with reduced ovarian reserve.

Poor responder definition: Older maternal age (≥ 40 years) or any other risk factor for the POR; and/or previous POR (≤ 3 oocytes with conventional stimulation protocol); and/or day 3 FSH >15 mIU/ml, E2 <500 pg/ml on the day of hCG, and/or abnormal ovarian reserve test (i.e. AFC 5-7 follicles or AMH 0.5 to 1.1 ng/ml) and or AMH level >1.0 ng/mL corresponding to the value of FSH >10.0 mIU/mL (95% CI: 9.3-10.8 mIU/mL) (15). Cut off level AMH of 0.5 ng/ml corresponds to the FSH level higher than 12 mIU/ml (95%CI: 11.4-12.7) (20). Clomiphene citrate challenge test (CCCT) is a superior test for the identification of poor responders (21). According to the ASRM definition, we have a poor responder if 3 day FSH >10 IU/L, AMH 0.2-0.7 ng/mL, AFC 3 day 3-10 and CCCT day 10: 10-22 IU/L, FSH day 10/ FSH day 3 >1.0 (16). Results of this study indicate that with the same stimulation with gonadotropins and GnRH antagonists, the introduction of Letrozole treatment has advantages in comparison with clomiphene citrate. Letrozole is an aromatase inhibitor which reduces the synthesis of estradiol from androstenedione, thus causing a reflex increase in FSH. Since letrozole does not bind to the estrogen receptor (ER), there is no direct effect on the endometrium. Letrozole enhances the endometrial gene expression of leukemia inhibitory factor (LIF), dickkopf homolog 1 (DKK-1) and fibroblast growth factor-22 (FGF-22), that have an important role in implantation (22). The study results indicate that Letrozole significantly increases the expression of mRNA for LIF, DKK1, LIFR and FGF-22, while CC only increases the endometrial expression of mRNA for LIF. Letrozole has a positive effect on numerous markers on endometrial receptivity in comparison with CC (23). Results of Chang et al. indicate that a new protocol of E2 administration in the luteal phase of the previous cycle and during ovarian stimulation, combined with gonadotropins and GnRH antagonists, significantly improves the follicular response, thereby improving the results in women with poor response. The number of cancelled cycles is significantly lower, implantation rate is higher, as well as pregnancy rates, and embryo quality is improved with the E2 adminis-

tration, in comparison with the protocol without estradiol valerate (24). The concept of luteal E2 support was first proposed by Fanchin et al. It is based on the premise that reducing the size and improving the homogeneity of early antral follicles optimizes ovarian response and enhances the effects of the cycle (25). E2 supplementation with GnRH antagonists in the luteal phase of the previous cycle suggests that women with poor response benefit from this protocol (26). Mohsen et al. suggest that the modified protocol of mild stimulation with clomiphene citrate, low doses of hMG and GnRH antagonists, preceded by luteal E2 support, results in a significantly higher clinical pregnancy rate in comparison with the conventional midluteal long protocol with GnRH antagonists and higher doses of hMG in women with poor response (27). Eftekhari et al. suggest that the stimulation protocol involving lower doses of hMG+GnRH antagonists+Letrozole was superior in terms of the endometrial thickness and rate of implantation in comparison with the protocol with low doses of hMG+GnRH antagonists+CC, with no significant differences in the rate of chemical and clinical pregnancies (28).

Conclusion

In conclusion, the COS/IUI protocol with low doses of hMG+Letrozole+ GnRH antagonists+ luteal E2 supplementation proved to be superior in terms of the clinical pregnancy rate, live birth rate, lower price and lower required amount of hMG to the conventional ovarian stimulation protocol involving low doses of hMG+CC+ GnRH antagonists without E2 supplementation in women with poor response.

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Abstract

In this paper the instructions for preparing camera ready paper for the Journal are given. The recommended, but not limited text processor is Microsoft Word. Insert an abstract of 50-100 words, giving a brief account of the most relevant aspects of the paper. It is recommended to use up to 5 key words.

Key words: Camera ready paper, Journal.

Introduction

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Table 1. Page layout description

Paper size	A4
Top margin	20 mm
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Right margin	18 mm
Column Spacing	5 mm

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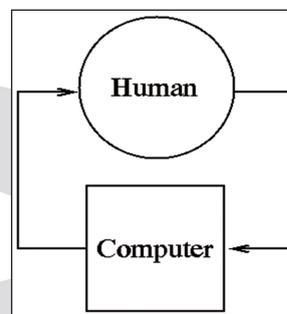


Figure 1. Text here

Conclusion

Be brief and give most important conclusion from your paper. Do not use equations and figures here.

Acknowledgements (If any)

These and the Reference headings are in bold but have no numbers.

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1. Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. *N Engl J Med* 1999; 341: 1284-1291.
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