17th INTERNATIONAL CONGRESS

ASSOCIATION OF GYNECOLOGISTS AND OBSTETRICIANS OF SERBIA, MONTENEGRO AND REPUBLIC OF SRPSKA

BELGRADE
3–5 DECEMBER 2020

Supported by:

FIGO
International Federation of Gynecology and Obstetrics
THE GLOBAL VOICE FOR WOMEN'S HEALTH

UGOSCGRS

GAS SLD

Republic of Serbia
MINISTRY OF HEALTH

UNIVERSITY OF BELGRADE
SCHOOL OF MEDICINE

This year's Congress marks the 100th anniversary of the Faculty of Medicine, University of Belgrade

CLINICAL CENTRE OF SERBIA

SERBIAN ACADEMY
OF SCIENCES AND ARTS

BOOK OF ABSTRACTS

Title:
17th International Congress of the Association of Gynecologists and Obstetricians of Serbia, Montenegro and Republic of Srpska
Book of abstracts

Editor:
Prof. dr Aleksandar Stefanović

Publisher:
UGOSCGRS – Association of Gynecologists and Obstetricians of Serbia, Montenegro and Republic of Srpska, Belgrade

Media recording:
UGOSCGRS – Association of Gynecologists and Obstetricians of Serbia, Montenegro and Republic of Srpska, Belgrade

Copies and format::
10, digital

Year:
2020

ISBN:
978-86-919137-4-8

CIP - Каталогизација у публикацији - Народна библиотека Србије, Београд

618(048)(0.034.2)

УДРУЖЕЊЕ гинеколога и опстетричара Србије, Црне Горе и Републике Српске.

Међународни конгрес (17 ; 2020 ; Београд)

Book of abstracts [Elektronski izvor] / 17th International Congress of the Association of Gynecologists and Obstetricians of Serbia, Montenegro and Republic of Srpska, Belgrade 3 - 5 December 2020 ; [editor Aleksandar Stefanović]. - Belgrade : UGOSCGRS - Association of Gynecologists and Obstetricians of Serbia, Montenegro and Republic of Srpska, 2020 (Belgrade: UGOSCGRS - Association of Gynecologists and Obstetricians of Serbia,Montenegro and Republic of Srpska). - 1 elektronski optički disk (CD-ROM); 12 cm

Sistemski zahtevi: Nisu navedeni. - Nasl. sa naslovne strane dokumenta. -

Apstrakti na srp. i engl. jeziku. - Tiraž 10. - Bibliografija uz svaki apstrakt.

ISBN 978-86-919137-4-8

a) Гинекологија - Апстракти b) Акушерство - Апстракти

COBISS.SR-ID 27066121

ORGANIZER:

Association of Gynecologists and Obstetricians of Serbia, Montenegro and Republic of Srpska

PRESIDENT:

Prof. Aleksandar Stefanović

CO-PRESIDENTS:

Prim. Vojislav Miketić

Prof. Vesna Ećim Zlojutro

SECRETARY GENERAL:

Prof. Miroslava Gojnić Dugalić

HONORARY CHAIRS:

Prof. Dragoljub Mladenović
Prof. Petar Drača
Prof. Spasoje Petković
Ass. Paja Momčilov

AUSPICE:

Republic of Serbia, Ministry of Health

University of Belgrade, Faculty of Medicine (celebrating 100th anniversary)

Clinical Centre of Serbia

Serbian Academy of Sciences and Arts

FIGO – International Federation of Gynecology and Obstetrics

SCIENTIFIC BOARD:

Prof. Aleksandar Stefanović
Prim. Vojislav Miketić
Prof. Vesna Ećim Zlojutro
Prof. Carlos Fuchtner
Prof. Faysal El Kak
Prof. Jeanne A. Conry
Prof. Chittaranjan Purandare
Prof. Dame Lesley Regan
Prof. Mary Ann Lumsden
Prof. Sabaratnam Arulkumaran
Prof. Gian Carlo Di Renzo
Prof. Joseph Schenker
Prof. Kypros Nikolaides
Prof. Philippe Morice
Prof. Nadeem Abu-Rustum
Prof. Giuseppe Benagiano
Prof. Željko Miković
Prof. Saša Kadija
Prof. Mladenko Vasiljević
Prof. Tihomir Vejnović
Prof. Miroslava Gojnić Dugalić
Prof. Olivera Kontić Vučinić
Prof. Adolf Lukanovič

EXECUTIVE BOARD:

Prof. Aleksandar Stefanović
Prim. Vojislav Miketić
Prof. Vesna Ećim Zlojutro
Doc. Katarina Stefanović
Ass. Zoran Vilendečić
Ass. Igor Pilić
Dr Miloš Radojević

BOOK OF ABSTRACTS:

Available at: congress.ugoscgrs.rs

ACREDITATION INFO:

Congress is accredited as the International Congress under No. A-1-1807 / 20. Number of points for speakers: 15. Number of points for attendance: 10.

Dear colleagues and friends,

It is my sincere pleasure to invite you to the 17th International Congress of the Association of Gynecologists and Obstetricians of Serbia, Montenegro and the Republic of Srpska (UGOSCGRS) which will be held from December 3rd – 5th, 2020. This year, we meet with the same mission to strengthen connections between gynecologists-obstetricians of the region but enriched with new experiences.

Since the Association has re-established its work, we have not hesitated to invest all our efforts to improve the work of the Association, predominantly by means of organization of annual meetings since 2015 (in 2015 and 2017 in Serbia, in 2016 and 2019 in Montenegro and in 2018 in Republic of Srpska), but also by participation in other regional and international meetings.

Many things have happened since our last Congress in Bečići in September 2019. In light of the COVID-19 pandemic, as a profession, we have faced one of the greatest challenges in modern history. We had to learn quickly and to adjust to new circumstances without possibility to take a break and think it through, even in the most difficult moments. Extremely difficult times usually bring out the best of each of us. So it was the same with Gynecology and Obstetrics and that is something we should all be proud of.

Having in mind that course of COVID-19 pandemics is fairly predictable and that the health of everyone is the most important, we have decided to organize this year's meeting as an on-line event.

This year Faculty of Medicine (University of Belgrade) celebrates 100 years since it was established and our Congress is a part of the celebration of this wonderful jubilee.

We are sincerely honored that this congress is supported by FIGO. FIGO Presidential Session will host the following eminent speakers: Prof. Carlos Fuchtner – FIGO President, Prof. Faysal El Kak – Vice President, Prof. Jeanne Conry – President-Elect, Prof. Chittaranjan Purandare – Past President, Prof. Dame Lesley Regan – Honorary Secretary, Prof. Mary Ann Lumsden – Chief Executive and Prof. Sabaratnam Arulkumaran – Past President.

The 17th Congress of the Association of Gynecologists and Obstetricians of the Republic of Srpska hosts many eminent experts and the program includes various attractive topics from gynecological oncology, IVF, infertility, perinatology, gynecological surgery, practical obstetrics etc.

In the hope that the Congress will meet your expectations, I am looking forward meeting you again.

Prof. Aleksandar Stefanović, MD, PhD
The President of the Association of Gynecologists and Obstetricians of Serbia, Montenegro and the Republic of Srpska

CONFIRMED INVITED SPEAKERS:

FIGO PRESIDENTIAL SESSION

- **Prof. Carlos Fuchtner,** President of FIGO, former President of Latin American Federation of Obstetrics and Gynecology Societies (FLASOG), Bolivia
- **Prof. Faysal El Kak,** Vice President of FIGO, President of FAGOS (Federation of Arab Gynecology Obstetric Societies), Lebanon
- **Prof. Jeanne Conry,** President Elect of FIGO, Past President of ACOG, USA
- **Prof. Chittaranjan Purandare,** Past president of FIGO, Dean of The Indian College of Obstetricians and Gynaecologists, India
- **Prof. Dame Lesley Regan,** Secretary General of FIGO, Immediate Past President of the Royal College of Obstetricians and Gynaecologists, Head of Obstetrics and Gynaecology at St Mary's Hospital campus, Imperial College London, UK
- **Prof. Mary Ann Lumsden,** Chief Executive of FIGO, University of Glasgow, UK
- **Prof. Sabaratnam Arulkumaran,** Former President of FIGO, former President of the Royal College of Obstetricians and Gynaecologists (RCOG), UK

List of lecturers in alphabetical order:

- **Prof. Nadeem Abu-Rustum,** Chief Gynecology Service in The Sloan Kettering Institute (SKI), Weill Cornell Medical College, New York, USA
- **Dr. Milena Aćimović,** Chair of Department of Gynecology and Obstetrics, Medical Centre Užice, Serbia
- **Prof. Fedro Alessandro Peccatori,** Scientific Director at the European School of Oncology (ESO), Director of the Fertility and Procreation Unit within the Division of Gynecologic Oncology in the Department of Gynecology at the European Institute of Oncology, Milan, Italy
- **Prof. Diogo Ayres-de-Campos,** Future President European Association of Perinatal medicine (EAPM), Secretary general of of the Portuguese Federation of Obstetrics and Gynaecology Societies, Chair of the Department of Obstetrics at the Santa Maria Hospital in Lisbon, University of Lisbon, Portugal
- **Prof. György Bártfai,** President of Diczfalusy foundation, Faculty of Medicine, University of Szeged, Hungary
- **Prof. Giuseppe Benagiano,** Former Secretary general of FIGO, Dean of School of Gynecology and Obstetrics, La Sapienza University, Rome, Italy
- **Prof. Dieter Bettelheim,** Department of Obstetrics and Feto-maternal medicine, General Hospital Vienna; Medical University Vienna, Austria
- **Prof. Tatjana Božanović,** Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prim. Snežana Buzadžić,** Vice President of Serbian Urogynecological Association (SUGA), Clinic for Gynaecology and Obstetrics, Clinical Centre of Serbia, Serbia
- **Assist. Prof. Miljan Ćeranić,** Clinic for digestive surgery of First surgical clinic, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. George Creatsas,** Honorary President of the International Federation of Pediatric and Adolescent Gynecology (FIGIJ), former Dean of the University of Athens Medical School and former Vice Rector of the University of Athens, Greece
- **Prof. Gian Carlo Di Renzo,** FIGO Honorary Secretary, Reproductive and Perinatal Medicine Center, University of Perugia, Italy
- **Prof. Aleksandra Dimitrijević,** Director of Clinic for Gynecology and Obstetrics, Clinical Center of Kragujevac, Faculty of medical sciences, University in Kragujevac, Serbia

- **Prof. Goran Dimitrov,** President of the MSCPC (Macedonian Society for Colposcopy and Cervical Pathology – member of IFCPC, EFC), President of Macedonian Medical Association, Northern Macedonia
- **Prof. Yulia Dobrokhotova,** Head of Department of Obstetrics and Gynecology, Medical Faculty, N.I. Pirogov Russian National Research Medical University, Moscow, Russia
- **Assist. Prof. Milan Dokić,** Secretary general of Section for Gynecology and Obstetrics of Serbian Medical Society, Clinical Centre of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Miroslav Đorđević,** Chief of board for postgraduate and specialist studies in pediatric surgery, Co-director of surgery in Belgrade University Childrens Hospital, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Srđan Đurđević,** Former President of Society for Gynecological Oncology of Serbia (UGOS), Head of Department of operative gynecology in Genesis hospital, Novi Sad, Serbia
- **Prof. Vesna Ećim Zlojutro,** Vice President of UGOSCGRS and President of Society of Gynecologist and Obstetrics of Republic of Srpska, Clinic for Gynecology and Obstetrics, Clinical Center of Republic of Srpska, University of Banja Luka, Republic of Srpska
- **Prof. Dejan Filimonović,** Head of department for high-risk pregnancies in Clinic for Gynecology and Obstetrics Narodni Front, Faculty of Medicine, University of Belgrade, Serbia
- **Assist. Prof. Cristian Furau,** European Society of Contraception and Reproductive Health (ESC) Board member, Obstetrics and Gynecology, Western University "Vasile Goldis" Arad, Romania
- **Assist. Prof. Rajko Fureš,** Head of the Institute of Gynecology, Obstetrics and Minimally Invasive Gynecological Surgery. Faculty of Dental Medicine and Health Osijek, Josip Juraj Strossmayer University of Osijek, Croatia
- **Prof. Eliana Garalejić,** Advisor for sterility issues at Gynecology and Obstetrics Clinic "Narodni Front", Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Miroslava Gojnić Dugalić,** Secretary general of UGOSCGRS, Head of department of pathological pregnancies, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Marija Hadži Lega,** Department of Fetal medicine, Danat Al Emerat Hospital, UAE
- **Dr. Azis Haliti,** Clinic for Gynecology and Obstetrics, Clinical Center of Montenegro, Montenegro
- **Prof. Herman Haller,** Director of the Clinic for Gynecology and Obstetrics, Medical Center of Rijeka, University of Rijeka, Croatia
- **Prof. Moshe Hod,** President European Association of Perinatal medicine (EAPM), Chairman FIGO Hyperglycemia in pregnancy working group, Obstetrics and Gynecology, Sackler Faculty of Medicine, Tel-Aviv University, Israel
- **Prof. Tatjana Ilić-Mostić,** Assistent Director of Center for Anestesiology and Reanimatology, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Assist. Prof. Jelena Jeremić,** Clinic for burns, plastic and reconstructive surgery, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Saša Kadija,** Deputy General Manager and chief of department of general gynecology of the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Dr. Ashish Kale,** Ashakiran hospital, Pune, India
- **Assist. Prof. Nataša Karadžov Orlić,** Clinic for Gynecology and Obstetrics Narodni Front, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Deni Karelović,** Director of the Clinic for Gynecology and Obstetrics, Medical Center of Split, University of Split, Croatia
- **Prof. Vesna Kesić,** President of the Society for Colposcopy and Cervical Pathology of Serbia, Former President of ESGO, Head of department of policlinic gynecology, Clinic for Gynecology and Obstetrics Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia

- **Prof. Borut Kobal,** Head of Clinic of Gynaecology and Obstetrics at Ljubljana University Medical Centre, Slovenia
- **Prof. Christhardt Köhler,** Head of Department of Advanced Operative and Oncologic Gynecology at Asklepios Hospital Altona, Hamburg, University of Cologne, Köln, Germany
- **Prof. Olivera Kontić Vučinić,** President of Section for Gynecology and Obstetrics of Serbian Medical Society, president of South Eastern European Society of Perinatal Medicine (SEESPM), head of department of human reproduction, Clinic for Gynecology and Obstetrics, Clinical Centre of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Vesna Kopitović,** Ferona Fertility Clinic Novi Sad, European Center for Peace and Development (ECPD), Belgrade, University for Peace Established by the United Nation, Serbia
- **Prof. Miroslav Kopjar,** President of Croatian Society for Gynecological Endoscopy, Croatia
- **Prof. Nebojša Lađević,** President of Serbian Society of anestesiologysts and Intesivists (UAIS), Director of Center for Anestesiology and Reanimatology, Clinical Center of Serbia, University of Belgrade, Serbia
- **Academician Prof. Nebojša Lalić,** Full member of Serbian Academy of Sciences and Arts (SANU), Dean of the Faculty of Medicine, University of Belgrade, Director of Clinic for endocrinology, diabetes and metabolic diseases, Clinical Center of Serbia, Serbia
- **Assist. Prof. Ivana Likić Lađević,** Head of 2nd surgical department, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Adolf Lukanovič,** President of the Slovene Association of Gynecologists and Obstetricians, Chairman of the Division of Gynecology and Obstetrics, University Medical Centre Ljubljana, Slovenia
- **Asist. David Lukanović,** Division of Gynecology and Obstetrics, University Medical Center Ljubljana, Slovenia
- **Ass. Rastko Maglić,** Clinic for Gynecology and Obstetrics Narodni Front, Faculty of Medicine, University of Belgrade, Serbia
- **Dr. Tahir Mahmood,** Former President of the European Board and College of Obstetrics and Gynaecology (EBCOG), Spire Edinburgh Hospitals Murrayfield and Shawfair Park, UK
- **Prof. Aljoša Mandić,** President of Society for Gynecological Oncology of Serbia (UGOS), Institute for oncology of Vojvodina, Faculty of Medicine, University of Novi Sad, Serbia
- **Assist. Prof. Vesna Mandić Marković,** Clinic for Gynecology and Obstetrics Narodni Front, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Dror Meirow,** Immediate Past president International Society of Fertility Preservation (ISFP) and Head of the Clinical Center for Fertility, Preservation and the Fertility Preservation at Sheba, Medical Center, Tel-Hashomer, Israel, Sackler Faculty of Medicine, Tel-Aviv University, Israel
- **Ass. Srđan Mijatović,** Secretary general of Serbian Association of Endoscopic Surgens (SAES), Chief of 1st surgery department, Emergency Center, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prim. Vojislav Miketić,** Vice President of UGOSCGRS and President of the Association of Gynecologists and Obstetricians of Montenegro, Clinic for Gynecology and Obstetrics, Clinical Center of Montenegro, Montenegro
- **Prof. Željko Miković,** Director of Clinic for Gynecology and Obstetrics Narodni Front, Faculty of Medicine, University of Belgrade, Serbia
- **Dr. Tanja Milić Radić,** Clinic for Gynecology and Obstetrics, University Clinical Center of Republic of Srpska, Banja Luka, Republic of Srpska
- **Doc. Srboljub Milićević,** Head of department of ultrasound, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Dr. Marijana Milović Kovačević,** Clinic for medical oncology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

- **Prof. Predrag Miljić,** Clinic of Hematology, Clinical Centre of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Ana Mitrović Jovanović,** President of the Serbian Society for Reproductive health, Head of daily hospital department at Clinic for Gynecology and Obstetrics Narodni Front, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Philippe Morice,** President of European Society of Gynaecological Oncology (ESGO), Head of the Departments of Surgery, Institute Gustave Roussy, Villejuif, France, University Paris-Sud, Paris, France
- **Dr. Tatjana Motrenko Simić,** Member of the ESHRE Executive Committee, Human Reproduction Centre, Budva, Montenegro
- **Prim. Danko Natalić,** Clinic for Gynecology and Obstetrics, Clinical Center of Montenegro, Montenegro
- **Ass. Lazar Nejković,** Vice President of Society for Gynecological Oncology of Serbia (UGOS), Clinic for Gynecology and Obstetrics Narodni Front, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Kypros Nikolaides,** Founder and Chair of the Fetal Medicine Foundation, Director of the Harris Birthright Research Centre for Fetal Medicine at King's College Hospital, Kings college London, UK
- **Prof. Branka Nikolić,** Assistent Director and Head of department of general gynecology of the Clinic for Gynecology and Obstetrics Narodni Front, Faculty of Medicine, University of Belgrade, Serbia
- **Prim. Ljubinka Nikolić,** Head of department of internal medicine and hematologic laboratory with transfusiology, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Serbia
- **Prim. Tatjana Nikolić,** Head of department of neonatal intensive care unit and advisor for neonatology og the director of Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Serbia
- **Prof. Ivana Novaković,** President of section of Serbian Genetics Society, Institute for human genetics, Faculty of Medicine, University of Belgrade, Serbia
- **Ass. Sveto Pantović,** Head of OR, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Rešad Pašić,** Director of the Fellowship in Minimally Invasive Gynecologic Surgery at the Department of Obstetrics and Gynecology and Women's Health at the University of Louisville; President of the Board of Trustees of the International Society of Gynecologic Laparoscopists ISGE, USA
- **Dr. Vesna Perković Maksimović,** Department of Gynecology and Obstetrics, Hospital Bijeljina, Republic of Srpska
- **Prof. Ljubomir Petričević,** President of the science board and member of executive board of International Society for Infectious Diseases in Obstetrics and Gynaecology (ISIDOG), AKH, University Clinic in Vienna, Austria
- **Prof. Miloš Petronijević,** Head of department of high-risk pregnancies, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Sergey Petrovich Sinchihin,** Department of Obstetrics and Gynecology, Astrakhan State Medical University, Russia
- **Dr. Vladimir Petrović,** Director of Institute for Public Health of Vojvodina, Serbia
- **Ass. Igor Pilić,** Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Snežana Plešinac,** President of Serbian association of fetal and neonatal medicine, Head of department of fertility control, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia

- **Prof. Mario Poljak,** President of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Head of Laboratory for Molecular Microbiology and Slovenian HIV/AIDS Reference Centre, Institute of Microbiology and Immunology at Faculty of Medicine, University of Ljubljana, Slovenia
- **Dr. Bojana Popović,** Clinic for Gynecology and Obstetrics, Clinical Center of Republic of Srpska, University of Banja Luka, Republic of Srpska
- **Prof. Zoran Protrka,** Clinic for Gynecology and Obstetrics, Clinical Center of Kragujevac, Faculty of medical sciences, University in Kragujevac, Serbia
- **Dr. Miloš Radović,** Vice President of Serbian Urogynecological association (SUGA), Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Serbia
- **Prof. Snežana Rakić,** former president of the Section for Gynecology and Obstetrics of Serbian Medical Society Head of delivery room, Clinic for Gynecology and Obstetrics Narodni Front, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Pedro Ramirez,** Director of Minimally Invasive Surgical Research and Education, Department of Gynecologic Oncology and Reproductive Medicine, MD Anderson Cancer Center, University of Texas, Houston, Texas, USA
- **Prof. Goran Relić,** Faculty of medical sciences, University in Priština with base in Kosovska Mitrovica, Serbia
- **Prof. Ferit Saracoglu,** General Director at FemCARE Women's Clinic, Atlanta, Georgia, USA; Hacettepe University, Ankara, Turkey
- **Prof. Joseph Schenker,** President of International Academy of Human Reproduction, Hadassah Medical Centre, Hebrew University, Jerusalem, Israel
- **Dr. Katarina Sedlecky,** Republic center for family planning, Institute for health protection of mother and child, Sebia
- **Dr. Branka Semiz,** Head of department of gynecology and obstetrics, Hospital Serbia, Eastern Sarajevo, Republic of Srpska
- **Prof. Sanja Sibinčić,** National coordinator for sexual and reproductive health of Republic of Srpska, Clinic for Gynecology and Obstetrics, Clinical Center of Republic of Srpska, University of Banja Luka, Republic of Srpska
- **Prof. Svetlana Spremović Rađenović,** Head of department of gynecological endocrinology, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prim. Gordana Sredanović,** Head of department of gynecology and obstetrics, General Hospital in Doboj, Republic of Srpska
- **Prim. Ljiljana Stamatović,** Clinic for medical oncology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia
- **Prof. Jelena Stamenković,** Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Dr. Zoran Stanković,** Head of the Republic center for family planning, Institute for health protection of mother and child, Sebia
- **Prof. Michael Stark,** President of the The New European Surgical Academy, Berlin, Germany; Chairman of the Department of Obstetrics and Gynaecology, HELIOS hospitals group, Fulda, Germany
- **Assist. Prof. Katarina Stefanović,** Head of department of oncofertility, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Assist. Prof. Jelena Stojnić,** Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Nicolae Suciu,** former President of Romanian Society of Obstetrics and Gynecology, General Manager of the National Institute for Mother and Child Health "Alessandrescu-Rusescu", Bucharest, Romania

- **Prof. Iztok Takač,** Head of Department of Gynecologic Oncology and Breast Oncology, Clinic for Gynecology and Perinatology, University Clinical Center, Maribor; Faculty of Health Sciences, University of Maribor, Slovenia
- **Prof. Karl Tamussino,** Head of the Gynecology Department, Women and Obstetrics University Clinic, Medical University of Graz, Austria
- **Prof. Vasilis Tanos,** Scientific Director of the European Academy for Gynaecological Surgery (EAGS), Past Co-ordinator of the ESHRE Certification Reproductive Endoscopic Surgery (ECRES), Head of Reproductive medicine and surgery and IVF, St George's University London; Aretaeio Hospital, Medical School, University of Nicosia, Cyprus
- **Ass. Gordana Tomash,** Clinic for general gynecology, Medical University of Graz, Austria
- **Prof. Bruno van Herendael,** Medical Director at International society for gynecologic endoscopy (ISGE), Head of gynecology and obstetrics, Medical center Antwerp, Belgium
- **Prof. Mladenko Vasiljević,** Head of department of sterility and department for artificial technologies of general gynecology of the Clinic for Gynecology and Obstetrics Narodni Front, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Tihomir Vejnović,** Vice President of the Diczfalusy Foundation; former president of the Section for Gynecology and Obstetrics of Serbian Medical Society, Clinic for Gynecology and Obstetrics, Clinical Center of Vojvodina; Faculty of Medicine, University of Novi Sad, Serbia
- **Prof. René Verheijen,** President of the Society of European Robotic Gynaecological Surgery (SERGS), University Medical Center Utrecht, Netherlands
- **Prof. Snežana Vidaković,** Head of department of minimal invasive surgery and department of artificial reproductive technologies, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Ass. Zoran Vilendečić,** Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Prof. Svetlana Vrzić Petronijević,** Head of of polyclinic perinatology department, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Serbia
- **Assist. Prof. Joško Zekan,** President of South Eastern Europe HPV forum, Clinic for gynecology and obstetrics, Clinical center of Zagreb, Faculty of Medicine, University of Zagreb, Croatia
- **Prof. Radomir Živadinović,** Clinic for Gynecology and Obstetrics, Clinical Center of Niš, Faculty of Medicine, University of Niš, Serbia

3rd of December, 2020

09.00 – 09.30 **Opening Ceremony**

Assist. Prof. Zlatibor Lončar
Minister of Health of Republic of Serbia

Academician Prof. Vladimir Kostić
President of Serbian Academy of Sciences and Arts

Academician Prof. Nebojsa Lalić
Dean of Medical Faculty Univerisity of Belgrade

Prof. Vesna Ećim Zlojutro
Vice president of the UGOSCGRS; President of the Association of Gynecologists and Obstetricians of Republic Srpska

Prim. Vojislav Miketić
Vice-President of UGOSCGRS; President of the Association of Gynecologists and Obstetricians of Montenegro

Prof. Olivera Kontic Vučinić
Presedent of Section for Gynecology and Obstetics of Serbian Medical Society

Prof. Aleksandar Stefanović
President of UGOSCGRS

09.30 – 11.15 **FIGO PRESIDENTIAL SESSION (AM)** zoom

Chairs: Prof. Aleksandar Stefanović, Prof. Chittaranjan Purandare

Caesarean section rates in a changing world
Prof. Chittaranjan Purandare (India)

Essential women's health services
Prof. Dame Lesley Regan (UK)

PPH – lessons, confidential inquiries and recent advances
Prof. Sabaratnam Arulkumaran (UK)

11.15 – 11.45 **KEYNOTE SESSION** K zoom

Chairs: Prof. Aleksandar Stefanović, Prof. Snežana Vidaković, Prof. Ana Mitrović Jovanović, Prof. Vasilis Tanos

Ovarian hyperstimulation syndrome – updates
Prof. Joseph Schenker (Israel)

VIRTUAL LECTURE HALL A

11.45 – 13.40 **SESSION: COVID-19 1** zoom

Chairs: Prof. Vesna Ećim Zlojutro, Prim. Vojislav Miketić, Dr. Tahir Mahmood, Prof. Miroslava Gojnić Dugalić, Prof. Tihomir Vejnović, Prof. Olivera Kontic Vučinić

Treatment and outcome of pregnancies with COVID-19 in UDK **Banjaluka**
Prof. Vesna Ećim Zlojutro (Republic of Srpska)

Obesity, COVID-19 and obstetrics
Dr. Tahir Mahmood (UK)

COVID 19 –what do we know about pregnancy complications and risks
Prof. Olivera Kontić Vučinić (Serbia)

Covid-19 and pregnancy: molecular aspects
Prof. Nicolae Suciu (Romania)

Fetal heart anomalies screening in COVID-19 pandemic
Prof. Svetlana Vrzić Petronijević (Serbia)

13.40 – 14.00 **Commercial Lecture** **BONIFAR**

Vulvovaginal infections, complications and treatment in pregnancy

14.00 – 15.55 **SESSION: GYNECOLOGY 1**

Medical termination of pregnancy – treatment and outcome
Prim. Vojislav Miketić (Montenegro)

Adolescent and emergency contraception
Prof. George Creatsas (Greece)

European consensus statement on basic colposcopy
Prof. Vesna Kesić (Serbia)

Mayer-Rokitansky-Kuster-Hauser syndrom (MRKH): surgical treatment and outcomes
Prof. Miroslav Đorđević (Serbia)

Aging Europe demographic trends in our geographical region – the issue of reproductive health
Prof. György Bártfai (Hungary)

15.55 – 16.15 **Commercial Lecture** **NEOMEDICA**

AcuPulse Duo Femtouch – different applications in gynecology field

16.15 – 18.15 **FIGO PRESIDENTIAL SESSION (PM)** zoom

Chairs: Prof. Aleksandar Stefanović, Prof. Carlos Fuchtner, Prof. Faysal El Kak

SDG in the COVID era
Prof. Carlos Fuchtner (Bolivia)

Changing pregnancy care under COVID-19
Prof. Faysal El Kak (Lebanon)

Reproductive health and the environment: obstetricians and gynecologists take notice
Prof. Jeanne Conry (UK)

Menopause: FIGO's approach to healthy aging
Prof. Mary Ann Lumsden (UK)

VIRTUAL LECTURE HALL B

11.45 – 13.40 SESSION: INFERTILITY & IVF

OHSS: prevention and treatment
Prof. Snežana Vidaković (Serbia)

Infertility treatment and factors affecting outcome
Prof. Ana Mitrović Jovanović (Serbia)

„Freeze all" technique – the future of IVF or option only in pandemic?
Prof. Vesna Kopitović (Serbia)

Intersection between genetics, epigenetics and therapy of infertility
Prof. Svetlana Spremović Rađenović (Serbia)

Ovarian stimulation in intrauterine insemination: letrozole or clomiphene-citrate?
Assist. Prof. Jelena Stojnić (Serbia)

Ovarian Hyperstimulation in ART
Dr. Tatjana Motrenko Simić (Montenegro)

13.40 – 14.00 Commercial Lecture BONIFAR

Vulvovaginal infections, complications and treatment in pregnancy

14.00 – 15.55 SESSION: MINIMALLY INVASIVE SURGERY 1

Vaginal laparoscopy vs laparoscopic hysterectomy: which method to choose – ISGE Guidelines
Dr. Bruno van Herendael (Belgium)

Hysteroscopic myomectomy
Assist. Prof. Milan Dokić (Serbia)

Complications of laparoscopic versus open myomectomy
Prof. Vasilis Tanos (Cyprus)

Laparoscopic Burch, condition and perspectives
Prof. Miroslav Kopjar (Croatia)

Total laparoscopic hysterectomy: condition and perspectives
Assist. Prof. Rajko Fureš (Croatia)

4th of December, 2020

VIRTUAL LECTURE HALL A

09.00 – 11.00 **SESSION: OBSTETRICS 1**

Long-term cesarean section complications in different operative techniques
Prof. Tihomir Vejnović (Serbia)

The evidence based cesarean section: risks of its overuse and possible influence on human evolution
Prof. Michael Stark (Germany)

How to improve intrapartum fetal monitoring
Prof. Diogo Ayres-de-Campos (Portugal)

Postpartum rehabilitation in patients with pelvic floor dysfunction
Prof. Yulia Dobrokhotova (Russia)

The outcomes of induced deliveries
Prof. Snežana Rakić (Serbia)

11.00 – 11.20 **Commercial Lecture** **PHARMA SWISS**

Iron therapy – how to choose

11.20 – 13.30 **SESSION: PERINATOLOGY 1** zoom

Chairs: Prof. Željko Miković, Prof. Vesna Ećim Zlojutro, Prim. Vojislav Miketić, Prof. Moshe Hod, Prof. Tihomir Vejnović, Prof. Miloš Petronijević, Prof. Goran Relić

Breast cancer during pregnancy
Prof. Fedro Alessandro Peccatori (Italy)

Role of thrombophilia testing after pregnancy failure
Prof. Željko Miković (Serbia)

The life cycle approach to pregnancy complications – FIGO Perinatal Initiatives
Prof. Moshe Hod (Israel)

Maternal mortality in Serbia
Prof. Miloš Petronijević (Serbia)

Reproduction in breast cancer patients
Prof. Dror Meirow (Israel)

Preterm delivery: great obstetrical syndrom – ethiology and treatment
Prof. Goran Relić (Serbia)

13.30 – 13.50 **Commercial Lecture** **AMICUS**

Stress urinary incontinence in women – Bulkamid

13.50 – 15.55	**SESSION: PERINATOLOGY 2**	zoom

Chairs: Prof. Gian Carlo Di Renzo, Prof. Miroslava Gojnić Dugalić, Prof. Giuseppe Benagiano, Prof. Diogo Ayres-de-Campos, Prof. Aleksandar Stefanović

Keynote 1: **Shortening of pregnancy: what can we do now for prevention?**

Keynote 2: **NIPT: expand or not the menu?**
Prof. Gian Carlo Di Renzo (Italy)

Therapy of the diabetes in pregnancy: possibilities of novel technology
Academician Prof. Nebojša Lalić (Serbia)

The placental bed: from spiral arteries remodeling to the great obstetrical syndromes
Prof. Giuseppe Benagiano (Italy)

Modern perinatology: fetal programming in diabetes in pregnancy
Prof. Miroslava Gojnić Dugalić (Serbia)

15.55 – 16.15	**Commercial Lecture**	**ASTRA ZENECA**

Personalized therapy of BRCAm ovarian cancer

16.15 – 18.15	**SESSION: ONCOLOGY 3**	zoom

Chairs: Prof. Aleksandar Stefanović, Prof. Philippe Morice, Prof. Vesna Kesić, Prof. René Verheijen

Keynote: **Management of borderline ovarian tumors**
Prof. Philippe Morice (France)

Fertility preservation: up to date
Assist. Prof. Katarina Stefanović (Serbia)

Keynote: **Modern staging of endometrial cancer with sentinel node mapping**
Prof. Nadeem Abu-Rustum (USA)

Keynote: **Update on radical hysterectomy after LACC Trial: Open surgery a new standard of care**
Prof. Pedro Ramirez (USA)

V – Y sliding skin flap in vulvar cancer surgery
Prof. Srđan Đurđević (Serbia)

18.15	**KEYNOTE SESSION**	zoom

Chairs: Prof. Aleksandar Stefanović, Prof. Željko Miković, Prof. George Creatsas, Prof. Joseph Schenker

Prevention of preterm birth
Prof. Kypros Nikolaides (UK)

VIRTUAL LECTURE HALL B

09.00 – 11.00	**SESSION: ONCOLOGY 1**	
	Can we still perform laparoscopic surgery in oncologic (or cervical cancer) patients Prof. Christhardt Köhler (Germany)	
	Role of laparoscopy in neoadjuvant treatment of ovarian cancer Prof. Deni Karelović (Croatia)	
	NACT in cervical cancer – pros and cons Prof. Aljoša Mandić (Serbia)	
	Lymphadenectomy in gynecologic cancer: An Update Prof. Karl Tamussino (Austria)	
	Genital-perineal reconstructions after cancer surgery Assist. Prof. Jelena Jeremić (Serbia)	
	The role of prophylactic HPV vaccine in prevention of cervical cancer – additional evidence Dr. Vladimir Petrović (Serbia)	
11.00 – 11.20	**Commercial Lecture**	**PHARMA SWISS**
	Iron therapy – how to choose	
11.20 – 13.30	**SESSION: ONCOLOGY 2**	
	Role of ultra-radical surgery in the treatment of ovarian cancer Prof. René Verheijen (Netherlands)	
	Pregnancy following choriocarcinoma treatment Prof. Saša Kadija (Serbia)	
	Up-to-date surgical approach to ovarian cancer Prof. Herman Haller (Croatia)	
	Radical vaginal trachelectomy after ten years: oncologic and reproductive results Prof. Borut Kobal (Slovenia)	
	Advances in the surgical treatment of ovarian cancer Prof. Iztok Takač (Slovenia)	
	Radio guided detection of sentinel lymph node in vulvar cancer: achievements and limitations Assist. Prof. Joško Zekan (Croatia)	
13.30 – 13.50	**Commercial Lecture**	**AMICUS**
	Stress urinary incontinence in women – Bulkamid	

13.50 – 15.55	**SESSION: GYNECOLOGY 2**	

Postgraduate education in sexual and reproductive health of adolescents and young girls
Dr. Katarina Sedlecky, Dr. Zoran Stanković (Serbia)

Feticide: Last exit for desperate parents in selected situations or violation of ethical limits
Prof. Dieter Bettelheim (Austria)

Global overview of commercially available HPV tests: 2020 update
Prof. Mario Poljak (Slovenia)

Vaginal microbiome
Prof. Ljubomir Petričević (Austria)

Chronic postoperative pain: new ICD definition
Prof. Nebojša Lađević (Serbia)

New approach to the treatment of female urinary infections
Assist. Prof. Ivana Likić Lađević (Serbia)

15.55 – 16.15	**Commercial Lecture**	**ASTRA ZENECA**

Personalized therapy of BRCAm ovarian cancer

16.15 – 18.15	**SESSION: UROGYNECOLOGY & RECONSTRUCTIVE SURGERY**

Posterior compartment pelvic disorders
Prof. Adolf Lukanovič (Slovenia)

Urogynecology implants: complications and recommendations
Ass. Sveto Pantović (Serbia)

Native tissue vs MESH repair of POP: outcomes comparison
Prim. Snežana Buzadžić (Serbia)

Combined approach to UI magnetic stimulation and laser treatment
Asist. David Lukanović (Slovenia)

Traditional urogynecological surgery vs polypropylene grafts? Mesh or mess? Controversy
Dr. Miloš Radović (Serbia)

How to prevent apical prolapse during hysterectomy
Prof. Rešad Pašić (USA)

5th of December, 2020

VIRTUAL LECTURE HALL A

09.00 – 10.45	**SESSION: PERINATOLOGY 3**
	Preterm delivery: could it be prevented Prof. Snežana Plešinac (Serbia)
	Prenatal diagnosis of neuromuscular diseases: an overview of methods and our experience Prof. Ivana Novaković (Serbia)
	Early detection of anomalies CNS, head and neck Doc. Srboljub Milićević (Serbia)
	Thrombophilia and pregnancy – impact and treatment Dr. Vesna Perković Maksimović (Republic of Srpska)
	Treatment of premalignant and malignant cervical lesions in pregnancy Prof. Zoran Protrka (Serbia)
10.45 – 11.00	**Break**
11.00 – 13.00	**SESSION: COVID-19 2**
	Delivery in COVID-19 patients Prof. Jelena Stamenković (Serbia)
	COVID-19 and fertility Prof. Eliana Garalejić (Serbia)
	New coronavirus infection and other respiratory viral diseases in pregnant women Prof. Sergey Petrovich Sinchihin (Russia)
	IVF and COVID-19 Prof. Sanja Sibinčić (Republic of Srpska)
	SARS-CoV-2 infection: Arad's Maternity Ward experience during this pandemic Assist. Prof. Cristian Furau (Romania)
	Fetal intravascular transfusion in COVID center Prof. Dejan Filimonović (Serbia)
13.00 – 13.15	**Break**
13.15 – 15.00	**SESSION: MINIMALLY INVASIVE SURGERY 2**
	Role of minimally invasive surgery in the treatment endometriosis Prof. Mladenko Vasiljević (Serbia)

Development and implementation of LAPSERB – is it useful method for laparoscopic gynecological surgical training?
Assist. Prof. Miljan Ćeranić (Serbia)

Minimally invasive myomectomy – our experiences
Ass. Rastko Maglić (Serbia)

Laparoscopy in the treatment of the acute abdomen
Ass. Srđan Mijatović (Serbia)

Rate of spontaneous pregnancy after laparoscopic cystotomy in patients with endometriosis
Dr. Milena Aćimović (Serbia)

15.00 SESSION: OBSTETRICS 2

Labor induction with prostaglandin E1 - our experience
Prim. Danko Natalić (Montenegro)

Episiotomy – pros and cons
Prim. Gordana Sredanović (Republic of Srpska)

Venous thromboembolism in obstetrics
Prof. Tatjana Ilić-Mostić (Serbia)

Delivery of fetuses with intrauterine grow restriction
Assist. Prof. Vesna Mandić Marković (Serbia)

Role of microbiome in pregnancy and newborn
Prim. Tatjana Nikolić (Serbia)

Cesarean Section – where are we now
Dr. Branka Semiz (Republic of Srpska)

VIRTUAL LECTURE HALL B

09.00 – 10.45 SESSION: ONCOLOGY 4

Do oncogenic potential and genotypic prevalence of HPV change annually
Prof. Radomir Živadinović (Serbia)

HPV genotype - specific risk for CIN and cancer
Prof. Goran Dimitrov (Northern Macedonia)

Quality indicators for advanced ovarian cancer surgery
Assist. Prof. Miljan Ćeranić (Serbia)

The use of stem cells in oncology
Prof. Tatjana Božanović (Serbia)

An update on prophylactic salpingectomy
Ass. Gordana Tomash (Austria)

10.45 – 11.00 Break

11.00 – 13.00	**SESSION: GYNECOLOGY 3**
	Diagnostic labyrinth: persisting elevated hCG in non-gravid woman Prof. Branka Nikolić (Serbia)
	Deep-infiltrating endometriosis Dr. Ashish Kale (India)
	Non-invasive diagnosis of congenital uterine anomalies Prof. Aleksandra Dimitrijević (Serbia)
	Rational use of blood and blood components in Ob & Gin Prim. Ljubinka Nikolić (Serbia)
	Premalignant lesions of the cervix Dr. Tanja Milić Radić (Republic of Srpska)
13.00 – 13.15	**Break**
13.15 – 15.00	**SESSION: ONCOLOGY 5**
	The role of predictive models in evaluation of adnexal masses Ass. Zoran Vilendečić (Serbia)
	Fertility preserving surgery in gynecological oncology Ass. Igor Pilić (Serbia)
	Endometrial cancer: genetic classification and new herapeutic approach Ass. Lazar Nejković (Serbia)
	Solo-2 results: Maintenance therapy with Lynparza extends survival in relapsed ovarian cancer Dr. Marijana Milović Kovačević (Serbia)
	Innovations in systemic treatment of advanced cervical and endometrial cancer Prim. Ljiljana Stamatović (Serbia)
15.00	**SESSION: PERINATOLOGY 4**
	Infertility, pregnancy and thrombophilia – evidence based approach Prof. Predrag Miljić (Serbia)
	Screening performance of congenital heart defects in the first trimester using simple cardiac scan Assist. Prof. Nataša Karadžov Orlić (Serbia)
	Congenital heart disease–prenatal detection Prof. Marija Hadži Lega (UAE)
	Preterm delivery Dr. Bojana Popović (Republic of Srpska)
	Perinatal microbiota and fetal programming Prof. Ferit Saracoglu (Turkey)

TABLE OF CONTENTS

COVID-19

COVID 19 AND PREGNANCY

Prof. Vesna Ećim Zlojutro

Vice President of UGOSCGRS and President of Society of Gynecologist and Obstetrics of Republic of Srpska
Clinic for Gynecology and Obstetrics, Clinical Center of Republic of Srpska, University of Banja Luka, Republic of Srpska

With the Covid-19 outbreak, the whole world faced numerous problems because the virus was new and its effects on the human organism were not known. Gynaecologists and obstetricians found that they did not know how much the virus affects the condition of the mother, whether there is any transfer to the fetus, and what kind of harmful consequences there can be for pregnant women and newborns. As time went by, based on experiences from colleagues from China, and then from Great Britain, papers started being published on the frequency, symptoms, manner of delivery and consequences to newborns from pregnancies where the mother had COVID-19. We know that the incubation period for the new coronavirus is between 2 and 14 days. Still, infected persons may transmit the infection even before developing symptoms, if they come into close contact with a non-infected person.

Pregnant women are advised to:wear masks,avoid gatherings,minimise personal contacts,increase personal hygiene.

They should report to a physician immediately if any of these symptoms occur:fever, dry cough

fatigue and muscle pain,difficult breathing, congested nose, sneezing ,loss of sense of smell and taste,diarrhoea,neurological symptoms.Over 90% cases are asymptomatic or with mild symptoms, around 5% have severe disease with bilateral pneumonia, need for oxygen or mechanical ventilation, and the death rate is around 1-2%.

In the past 8 months, the WHO and gynaecologists from various countries, after gaining more knowledge and experience on the diagnostics, treatment and manner of delivery of COVID-positive pregnant women, have issued recommendations for diagnostics and treatment of pregnant women during the pandemic. The recommendations have been revised several times. Unfortunately, there are more and more infected pregnant women in different gestational weeks and with varying medical states.The latest recommendations state that pregnant women must follow all the provided safety measures, that vaginal delivery is advised whenever there are no obstetrical indications for a C-section. If a C-section is necessary, it should be done with spinal anaesthesia. The mothers, if permitted by their medical state, can breastfeed their babies while taking all the necessary safety measures, with masks and clean hands. COVID-19 in itself is not an indication for termination of the pregnancy.In relation to the medical state, lab tests, lung CT and in agreement with specialists from other branches, the patient is prescribed antibiotics, antipyretics, saline solutions, low-molecular-weight heparin, corticosteroids, antivirotics.In case of aggravated medical states, the patient is transferred to the intensive care unit.From the earliest stage, the Clinic of Gynecology and Obstetrics at the University Clinical Centre of the Republic of Srpska adapted all its human resources and facilities to working under the COVID-19 pandemic, and organized work with outpatients in facilities outside of the space of the Clinic.

In the period between 20 March 2020 to 20 October 2020, there were 57 check-ups, of which 37 were admitted to the COVID section, with 13 C-sections and four vaginal deliveries, and in the grey

zone, there were 26 admissions and 5 vaginal deliveries.The primary aim during the pandemic is to protect health workers from getting infected, so that they could provide proper health protection to our patients.

Prof. Vesna Ećim Zlojutro. Radno iskustvo: Dom zdravlja Banjaluka 1985-1992. , kao ljekar radila u seoskim i gradskim ambulantama; Klinika za ginekologiju i akušerstvo Banjaluka 1992. godine do danas; kao specijalista ginekologije i akušerstva radila na svim odjeljenjima; 2004-2007 .godine Šef na odjeljenju perinatologije; 2016. godine do danas načelnik Klinike za ginekologiju i akušerstvo UKC Republike Srpske.

Obrazovanje: 24.4.2014. izabrana za redovnog profesora na Katedri za ginekologiju i akušerstvo Medicinskog fakulteta u Banjaluci; Osnovna škola Georgi Stojkov Rakovski Banjaluka- 1967-1975, završila odličnim uspjehom; Gimnazija Banjaluka - 1975-1979. –završila odličnim uspjehom; Medicinski fakultet Banjaluka- 1979-1984. prosječna ocjena 8,26; Postdiplomski studij-Medicinski fakultet Banjaluka 1989-1991; Specijalistički ispit iz ginekologije i akušerstva polagala na Institutu za ginekologiju i akušerstvo u Beogradu 1994. godine i položila sa odličnim uspjehom; Magistrirala na Medicinskom fakultetu Banjaluka 1999. sa temom „Vrijednosti acidobaznog statusa kao parametar u ocjeni težine EPH gestoza“; Doktorsku disertaciju odbranila na Medicinskom fakultetu u Banjaluci 2001. godine sa temom „ Značaj i prednosti mjerenja protoka kroz arteriju cerebri mediju, fetalnu aortu i umbilikalnu arteriju collor dopler tehnikom u odnosu na kardiotokografju kod gestoza“.

Na Medicinskom fakultetu radila kao stručni saradnik, asistent, viši asistent, docent , vanredni profesor i sada redovni profesor. Završila mnogobrojne škole i kurseve iz ultrazvuka, perinatologije, interventog ultrazvuka, kolposkopije, laparoskopije. Prisustvovala mnogobrojnim kongresima, simpozijumima u inostranstvu i kod nas kao predavač ili autor radova. Napisala kao autor i koautor 2 knjige i 3 monografije , i mnogobrojne stručne i naučne radove. Član Društva doktora medicine Republike Srpske. Član Komore dokrora medicine Republike Srpske. Predsjednik Udruženja ginekologa i obstetričara Republike Srpske (organizovala mnogobrojne stručne sastanke, simpozijum, Prvu Školu ultrazvuka u Republici Srpskoj, 1, Kongres ginekologa i obsteričara u Republici Srpskoj sa međunarodnim učešćem). Podpredsjednik Udruženja ginekologa i bstertričara Republike Srbije , Crne Gore i Republike Srpske.

COVID 19 – ŠTA ZNAMO O RIZICIMA I KOMPLIKACIJAMA TRUDNOĆE

Prof. Olivera Kontić Vučinić

Predsednik ginekološko-akušerske sekcije Srpskog lekarskog društva
Predsednik udruženja perinatalne medicine jugoistočne Evrope
Načelnik odeljenja humane reprodukcije
Klinika za ginekologiju i akušerstvo, Klinički Centar Srbije
Medicinski fakultet, Univerzitet u Beogradu, Srbija

Nove informacije o COVID-19 ekstremno brzo pristižu, zbog čega privremeni vodiči koje objavljuju brojne stručne organizacije moraju stalno da se prilagođavaju i proširuju. US Centers for Disease Control and Prevention (CDC) je objavio da su među preko 23000 evaluiranih trudnica i preko 386000 negravidnih žena reproduktivne dobi sa simptomatskom, laboratorijski potvrđenom SARS-CoV-2 infekcijom, trudnice imale višu stopu prijema u Jedinicu intenzivne nege (JIN), invazivne ventilacije i smrti (1). Upravo zbog toga, sve trudnice treba da budu praćene u smislu razvoja simptoma i znakova COVID-19, posebno ukoliko su imale blizak kontakt sa potvrđenim slučajem ili osobom koja je pod sumnjom na infekciju. Pozitivan test na SARS-CoV-2 generalno potvrđuje dijagnozu COVID-19, ali su i lažno pozitivni i lažno negativni rezultati mogući i zabeleženi u populaciji trudnica (2).

Kliničke manifestacije COVID-19 u trudnica, slične su onima u negravidnih žena. Najčešći simptomi su kašalj i glavobolja, s tim da trudnice nešto ređe prijavljuju febrilnost i gušobolju. Treba, međutim istaći i da su mnoge pacijentkinje asimptomatske, ali da proporcija asimptomatskih slučajeva nije dobro definisana (3, 4).

Kada govorimo o međusobnoj relaciji COVID-19 i trudnoće, treba reći da trudnoća i porođaj generalno ne povećavaju rizik za dobijanje ove infekcije, ali mogu pogoršati njen klinički tok u poređenju sa negravidnim ženama iste životne dobi. Ipak, većina (>90%) inficiranih majki se oporavi i bez prethodnog podvrgavanja porođaju (1, 3, 5). Trudnice, međutim, jesu pod povećanim rizikom od teške forme bolesti, koja zahteva prijem u JIN i mehaničku ventilaciju. Riziko faktori udruženi sa teškom bolešću ili prijemom u JIN uključuju starost ≥35 godina, gojaznost, hipertenziju i preegzistirajući dijabetes (6). Iako su zabeleženi smrtni ishodi trudnica, oni nisu češći u odnosu na negravidne žene reproduktivne dobi.

Postoji nekoliko klasifikacija bolesti, ali je bez obzira na to što je napravljena za negravidne pacijentkinje, verovatno najprimenjivija National Institutes of Health (NIH) kategorizacija na pet grupa, prema težini bolesti: asimptomatske/presimptomatske, blaga, umerena, teška i kritična forma bolesti (7). Komplikacije COVID-19 mogu obuhvatiti gotovo sve organske sisteme i dovesti do teških respiratornih, kardiovaskularnih, tromboembolijskih, gastrointestinalnih, neuroloških, bubrežnih, kožnih poremećaja, sekundarnih infekcija i slično (1).

Još uvek se istražuje da li dolazi do vertikalne transmisije ili ne, jer ne postoje opšte prihvaćeni kriterijumi za definitivno dolazivanje kongenitalne infekcije. Objavljeno je nekoliko slučajeva infekcije novorođenčadi i infekcija placente, koje sugerišu da je maternalno-fetalna transmisija moguća, ali retka. Nije moguće isključiti ni postnatalnu transmisiju (8, 9).

Iako limitirani, do sada objavljeni podaci ukazuju da u slučaju COVID-19, učestalost spontanih pobačaja u prvom trimestru nije povećana (10). Sa druge strane, u mnogim, ali ne i u svim

studijama, objavljen je porast stope preterminskih porođaja i carskih rezova u inficiranih trudnica (11, 12, 13). Ovaj trend se odnosi posebno na trudnice koje su razvile pneumoniju, te se smatra uzročno povezanim sa težinom maternalne bolesti. Kako je, međutim, ova tendencija zabeležena i u trudnica koje nemaju ozbiljnu respiratornu bolest, skreće se pažnja na elektivne carske rezove i posledični prematuritet, zbog uverenja da će terminacija trudnoće olakšati lečenje majke.

Do sada objavljeni podaci ne ukazuju na povećani rizik od fetalnih anomalija (10). I pored manjkavosti u konzistentnosti prikupljenih podataka, na koje se skreće pažnja, jer mogu uticati na kvalitet studije, pa time i validnost rezultata, beleži se povećani rizik od mrtvorođenosti u slučajevima maternalne infekcije COVID-19 (14, 15). Imajući u vidu dostupne informacije, veruje se da reproduktivne odluke (planiranje trudnoće, terminacija trudnoće), ne treba bazirati primarno na zdravstvenim brigama vezanim za COVID-19 (16, 17).

Preko 95% neonatusa je u dobroj kondiciji na porođaju; neonatalne komplikacije su u najvećem delu u vezi sa preterminskim rođenjem i nepovoljnom sredinom u uterusu koja je posledica kritične bolesti majke (3).

Dijagnostički pristup je sličan onome u opštoj populaciji. Trudnice treba da budu podvrgnute skriningu u slučaju kliničkih manifestacija koje govore u prilog COVID-19, pre nego što uđu u bolničku sredinu. U sredinama sa prevalentnom infekcijom, trebalo bi testirati sve pacijentkinje pre porođaja, ili dana kada je zakazan prijem u bolnicu, brzim testom za SARS-CoV-2 (18).

Trudnice koje daju anamnestički podatak o kontaktu sa potvrđeno ili verovatno zaraženom osobom, ili osobom sumnjivom na infekciju, treba izolovati i pratiti simptome. Inkubacioni period je do 14 dana. Dijagnostičko testiranje na SARS-CoV-2 infekciju zavisi od dostupnosti testova. Dalja evaluacija i tretman pacijentkinja koje postanu simptomatske, zavisi od težine bolesti, preegzistirajućeg komorbiditeta i kliničkog statusa. One koje imaju infekciju koja se klasifikuje najmanje kao umerena forma bolesti, treba hospitalizovati.

Evaluacija hospitalizovanih pacijentkinja sa dokumentovanom ili sumnjivom COVID-19, treba da se fokusira na znake udružene sa teškom formom bolesti i identifikaciju disfunkcije organa ili druge komorbiditete, koji mogu komplikovati tok bolesti i potencijalnu terapiju. Evaluacija je ista, za gravidne i negravidne pacijentkinje. Trudnice sa COVID-19 treba hospitalizovati kada postoji:

- Blaga forma bolesti i komorbiditet (slabo kontrolisana hipertenzija, gestacioni/ pregestacioni dijabetes, hronična bubrežna bolest, hronična kardiopulmonarna bolest, imunosupresivni status)
- Temperature >39°C uprkos upotrebi Paracetamola
- Umereni ili teški znaci i simptomi (saturacija kiseonikom <95% na sobnom vazduhu i dok se kreće, broj respiracija >30 u minuti, brza eskalacija potrebe za suplementacijom kiseonikom)
- Kritična bolest – respiratorno otkazivanje, hipotenzija uprkos adekvatnoj hidrataciji i/ili pojava disfunkcije organa (promena mentalnog statusa, insuficijencija jetre ili bubrega, srčana disfunkcija)

Hospitalizovane trudnice sa teškom formom bolesti, potrebom za kiseonikom plus komorbiditetima, ili kritično obolele trudnice, treba da budu tretirane od strane multidisciplinarnog tima u tercijernim ustanovama sa mogućnošću akušerske intervencije i JIN za odrasle (19). Sam COVID-19 status nije obavezan razlog za transfer trudnica koje nisu kritično obolele, a suspektne su ili imaju potvrđenu COVID-19 infekciju.

Poseban problem čini monitoring fetusa koji su u vijabilnoj gestacionoj starosti. Potreba za fetalnim monitoringom i njegova frekvenca zavisi od gestacione starosti, stabilnosti majčinih vitalnih znakova i oksigenacije, kao i drugih maternalnih komorbiditeta. Antenatalni monitoring (CTG, BFP) po izlečenju trudnice, koristi se prema rutinskim opstetričkim indikacijama. Pacijentkinje koje su imale infekciju u prvom ili drugom trimestru trudnoće treba da budu upućene na morfološki ultrazvučni pregled u 18-24. nedelje gestacije (20).

Literatura

1. Zambrano LD, Ellington S, Strid P, et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–October 3, 2020. MMWR Morb Mortal Wkly Rep. ePub: 2 November 2020. http://dx.doi.org/10.15585/mmwr.mm6944e3 (Accessed on November 02, 2020).
2. Sethuraman N, Jeremiah SS, Ryo A. Interpreting Diagnostic Tests for SARS-CoV-2. JAMA. 2020;323:2249.
3. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320.
4. Yanes-Lane M, Winters N, Fregonese F, et al. Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: A systematic review and meta-analysis. PLoS One. 2020;15:e0241536.
5. Badr DA, Mattern J, Carlin A, et al. Are clinical outcomes worse for pregnant women at ≥20 weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching. Am J Obstet Gynecol. 2020;223:764.
6. Panagiotakopoulos L, Myers TR, Gee J, et al. SARS-CoV-2 Infection Among Hospitalized Pregnant Women: Reasons for Admission and Pregnancy Characteristics - Eight U.S. Health Care Centers, March 1-May 30, 2020. Morb Mortal Wkly Rep. 2020;69:1355.
7. NIH COVID-19 Treatment Guidelines.
8. Kirtsman M, Diambomba Y, Poutanen SM, et al. Probable congenital SARS-CoV-2 infection in a neonate born to a woman with active SARS-CoV-2 infection. CMAJ. 2020; 192:E647.
9. Von Kohorn I, Stein SR, Shikani BT, et al. In Utero SARS-CoV-2 Infection. J Pediatric Infect Dis Soc. 2020.
10. Woodworth KR, Olsen EO, Neelam V, et al. Birth and Infant Outcomes Following Laboratory-Confirmed SARS-CoV-2 Infection in Pregnancy — SET-NET, 16 Jurisdictions, March 29–October 14, 2020. Morb Mortal Wkly Rep. ePub: 2 November 2020.
11. Khalil A, von Dadelszen P, Draycott T, et al. Change in the Incidence of Stillbirth and Preterm Delivery During the COVID-19 Pandemic. JAMA. 2020.
12. Ahlberg M, Neovius M, Saltvedt S, et al. Association of SARS-CoV-2 Test Status and Pregnancy Outcomes. JAMA Netw Open. 2020;E1.
13. Berghella V, Boelig R, Roman A, et al. Decreased incidence of preterm birth during coronavirus disease 2019 pandemic. Am J Obstet Gynecol. 2020;2:100258.
14. Delahoy MJ, Whitaker M, O'Halloran A, et al. Characteristics and Maternal and Birth Outcomes of Hospitalized Pregnant Women with Laboratory-Confirmed COVID-19 - COVID-NET, 13 States, March 1-August 22, 2020. Morb Mortal Wkly Rep. 2020; 69:1347.
15. Knight M, Bunch K, Vousden N, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ. 2020;369:m2107.
16. Rasmussen SA, Lyerly AD, Jamieson DJ. Delaying Pregnancy during a Public Health Crisis - Examining Public Health Recommendations for Covid-19 and Beyond. N Engl J Med. 2020.
17. Juan J, Gil MM, Rong Z, et al. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. Ultrasound Obstet Gynecol. 2020;56:15.
18. 2020 UpToDate, Inc. and/or its affiliates.
19. Donders F, Lonnée-Hoffmann R, Tsiakalos A, et al. ISIDOG Recommendations Concerning COVID-19 and Pregnancy. Diagnostics (Basel) 2020;10.
20. Covid-19 and pregnancy. BMJ 2020; 369:m1672.

Prof dr Olivera Kontić-Vučinić je završila Medicinski fakultet Univerziteta u Beogradu, gde je stekla i zvanje magistra, a potom i doktora medicinskih nauka. Od 1991.godine zaposlena na Klinici za ginekologiju i akušerstvo Kliničkog centra Srbije, gde je stekla zvanje specijaliste ginekologije i akušerstva. Na klinici je obavljala poslove Šefa Jedinice terapije fetusa, Šefa Odseka za perinatalnu i reproduktivnu genetiku i endokrinologiju KGA KCS, a sada je na poziciji načelnice odeljenja Humana reprodukcija. Akademsku karijeru započela je 1999.godine najpre kao asistent, docent, vanredni profesor, a sada je redovni profesor na Medicinskom fakultetu Univerziteta u Beogradu.

Prof dr Kontić-Vučinić je bila i direktor Škole ultrazvuka u ginekologiji, opstetriciji i reproduktivnoj medicini srpskog udruženja za ultrazvuk u ginekologiji i akušerstvu i stalni predavač u Školi za perinatalnu medicinu. U okviru kontinuiranog usavršavanja u zemlji i inostranstvu boravila je godinu dana na postdoktorskim studijama iz feto-maternalne medicine na prestižnoj School of medicine, Yale University, New Haven, USA, gde je stekla i titulu Visiting professor. Autor i koautor u brojnim naučne publikacije. Zbog svog značajnog doprinosa radu udruženja, 2013. godine je izabrana za Generalnog sekretara South East European Society of Perinatal Medicine, a 2018.godine i za je Predsednicu ovog udruženja. Za Predsednicu Ginekološko akušerske sekcije SLD izabrana je 2019.godine.

PRENATAL DIAGNOSIS OF CONGENITAL HEART DEFECTS DURING COVID-19 PANDEMIC

Prof. Svetlana Vrzić Petronijević

Head of polyclinic perinatology department
Clinic for Gynecology and Obstetrics, Clinical Center of Serbia
Faculty of Medicine, University of Belgrade, Serbia

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, China. By now, over 50 million confirmed cases of COVID-19 have been reported.

Coronavirus disease 2019 (COVID-19) leads to severe conditions such as severe pneumonia and several affected pregnant women are in a critical condition. Vertical transmission can be antenatal or per-partum, although perinatal or postnatal transmission can also have severe consequences. During the antenatal period, transmission of infection has different effects across the three trimesters of pregnancy. In addition, transplacental passage of pathogens is influenced by advancing gestational age; as a result, the severity of fetal injuries decreases from embryopathy in the first trimester, fetal infection in the second trimester, to immune response derive damage and symptoms in the second and third trimester (1). The potential of viral infection through transmission of SARS-CoV-2 during early pregnancy via maternal blood can have implications for the success of implantation: future placental and fetal health (2).

Congenital anomalies of the fetal heart are the most common structural anomalies in the fetal period and a group of congenital defects which diagnosis often fail during a routine ultrasound examination. On the other hand, timely prenatal diagnosis of congenital heart defects can significantly improve the outcome in specific cardiac defects (3). The incidence of congenital heart defects is high, estimated at 4-13 / 1000 live births, while in pregnancy is significantly higher. Between 1950 and 1994, 42% of newborns with congenital anomalies reported to WHO had a congenital heart defect (4).

Fetal cardiology as a multidisciplinary specialty developed thanks to advances in technology and contributed to the rapid development of new branches - fetal medicine. The application of fetal echocardiography has started between 1970 and 1980. Thanks to the sophisticated ultrasound machines and software, today already in early pregnancy structural heart defects can be diagnosed with high accuracy. The fetus is treated as a patient, considering the significant differences between fetal and postnatal circulation and the fact that structural defects may have a more specific progression in utero (5). Function of perinatologists and pediatric cardiologists in the management of fetuses with structural heart defects, arrhythmias and cardiovascular dysfunction are becoming increasingly important and impose the need for constant improvement of standards in fetal medicine (6).

Screening for congenital heart defects in pregnancy is not yet implemented, although about 90% of heart defects occur in population of low-risk fetuses, without indication (high risk pregnancies) or presence of associated anomalies during usual prenatal ultrasound (7). Pregnant women who are at increased risk for giving birth to a child with a congenital heart defect require a more detailed exam of the fetal heart as well as those with a high risk for aneuploidy based on the combined screening (8).

In order to increase efficiency and achieve better results exam of the fetal heart should be done between 18 and 22 weeks of gestation, conviniently at the same time when usually evaluation of fetal anatomy is done. However, some defects can't be detected during this period, which is why control fetal echocardiography around 30th gestational week is recomended (9). Some anomalies can be detected in the late first or early second trimester, especially when there is an increased nuchal translucency (10). The latest models of ultrasound machines allow that.

It is recommended that screening for congenital heart defects should be done in two levels (11). The first level is performed by ob/gyn specialist during routine ultrasound exams and it includes a basic overview of fetal heart, four chamber view and cross section of the outflow tract of the fetal heart. If there is a suspicion on the anomaly, pregnant women are referred to higher level of exam in an institution of higher rank where specially trained gynecologist-specialist in perinatal medicine and pediatric cardiologist perform a detailed fetal echocardiography. Plan of further follow-up and frequency of exams, as well as the need for additional testing (karyotyping, MRI) are determined individually for each patient depending on the nature and severity of anomaly, progression mechanism and options for prenatal and perinatal treatment (12).

According to recent studies, prenatal diagnosis of congenital heart disease is associated with reduced neonatal morbidity and significantly reduced perinatal mortality because of planned surgical interventions (13).

Among 9055 fetuses from 8838 pregnancies (217 multiple) examined by a gynecologist-perinatologists or pediatric cardiologist at the Clinic for Gynecology and Obstetrics of Clinical Center of Serbia and University Children's Hospital in Belgrade between 1991-2014 year, 638 were diagnosed with congenital heart disease. Incidence of congenital heart disease in the study population was 7.2%, and the most common were structural anomalies (81%). The sensitivity of fetal echocardiography in our series was 95.9%, a specificity 99.9%, which is within the data from the world's literature (14). Live births with congenital heart anomaly, which had a good long-term prognosis was 46.2%, and early neonatal mortality rate was 10.6%. One third have had postnatal cardiac interventions.

The extent of vertical transmission of COVID-19 remains unclear. Thromboembolic findings identified in placenta after infection suggest possible cardiovascular fetal changes including CHD in case of early pregnancy COVID infection which is yet to be proven. Pregnancy outcome after the diagnosis of congenital heart defect depends on many factors, but it is certainly the most important type of defect, its prognosis and impact on quality of life.

References

1. Lamouroux A, Attie-Bitach T, Martinovic J, Leruez-Ville M, Ville Y. Evidence for and against vertical transmission for severe acute respiratory syndrome coronavirus 2. Am J Obstet Gynecol. 2020 Jul;223(1):91. e1-91. e4. doi: 10.1016/j.ajog.2020.04.039. Epub 2020 May 4. PMID: 32376317; PMCID: PMC7196550.
2. Weatherbee, Bailey A T, Glover, David M, Zernicka-Goetz, Magdalena. Expression of SARS-CoV-2 receptor ACE2 and the protease TMPRSS2 suggests susceptibility of the human embryo in the first trimester Open Biol. 2020;10(8):200162.
3. Meberg A, Otterstad JE, Froland G, Lindberg H, Sorland SJ. Outcome of congenital heart defects- a population-based study. Acta Paediatr. 2000; 89:1344-51.
4. Cuneo BF, Curran LF, Davis N, Elrad H. Trends in prenatal diagnosis of critical cardiac defects in an integrated obstetric and pediatric cardiac imaging center. J Perinatol. 2004;24:674-8.
5. Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, et al. Diagnosis and Treatment of Fetal Cardiac Disease A Scientific Statement from the American Heart Association. Circulation 2014; 2.
6. Allan LD. A practical approach to fetal heart scanning. Semin. Perinatol. 2000; 24:324-30.
7. Marantz P, et al. Prenatal diagnosis of CHDs: a simple ultrasound prediction model to estimate the probability of the need for neonatal cardiac invasive therapy. Cardiology in the Young. 2016; 26:347.
8. Donofrio i sar. Diagnosis and Treatment of Fetal Cardiac Disease. 2014;2-4.

9. Trines J, Hornberger LK. Evolution of heart disease in utero. Pediatr Cardiol. 2004;25:287-98.
10. Carvalho JS. Fetal heart scanning in the first trimester. Prenat Diagn 2004; 24: 1060-7.
11. Satomi G. Guidelines for fetal echocardiography. Pediatrics international. 2015,1:1-21.
12. Trines J, Hornberger LK. Evolution of heart disease in utero. Pediatr Cardiol. 2004;25:287-98.
13. Holland BJ, Myers JA, Woods CR Jr. Prenatal diagnosis of critical congenital heart disease reduces risk of death from cardiovascular compromise prior to planned neonatal cardiac surgery: a meta-analysis. Ultrasound Obstet Gynecol 2015;45:631.
14. Vrzić-Petronijevic S, Petronijević M, Parezanovic V, Stamenkovic-Dukanac J, Jestrovic Z, Bratic D. Fetal echocardiography - 25-year experience. Srpski arhiv za celokupno lekarstvo. 147. 18-18. 10.2298/SARH180130018V.

Dr. Svetlana Vrzić – Petronijević, MSci PhD, is Associate Professor of gynecology and obstetrics, Faculty of Medicine, University of Belgrade and head of the Policlinic for Perinatal Medicine at Clinic of Gynecology and Obstetrics in Clinical Center of Serbia in Belgrade. She is a specialist of obstetrics and gynecology and specialist of perinatology. The basic field of interest is perinatology, prenatal detection of congenital anomalies and fetal echocardiography. As a fetal medicine consultant, she performs over 2000 fetal echocardiographic and consultative sonographic examinations annually. Lecturer at the National School of Ultrasound in Obstetrics, Gynecology and Perinatology. In 2006, she was trained at the Universitätsklinikum Hamburg - Eppendorf where she had the opportunity to be introduced to work of one of the leading experts in the field of fetal medicine, Prof. Dr. Kurt Hecher. A one-year education for fetal echocardiography in University Children's Hospital in Belgrade, under the guidance of the leading pediatric cardiology specialist resulted in the subspecialisation thesis in the field of fetal echocardiography. She is an active member of Hydrocephalus and Spina Bifida Association of Serbia (HISBAS) and lecturer at the National School of Ultrasound in Obstetrics, Gynecology and Perinatology. Member of The International Society of Ultrasound in Obstetrics and Gynecology. Author and co-author of over 150 papers published in relevant publications and presented at professional meetings and congresses, invited lecturer at meetings with national and international participation and over 20 chapters in textbooks and monographies in the field of gynecology and obstetrics, editor of official University textbook "Hypertension in pregnancy".

COVID 19 - VREME I NAČIN PORODJAJA

Prof. Jelena Stamenković

Klinika za ginekologiju i akušerstvo, Klinički Centar Srbije
Medicinski fakultet, Univerzitet u Beogradu, Srbija

Trenutna pandemija izazvana je Corona virusom tipom SARS CoV-2 koji je identifikovan krajem 2019. godine. Osobina mu je da se širi globalno velikom brzinom sa osnovnim reprodukcionim brojem (RO) 2-2,5, što znači da će 2-3 osobe biti zaražene od indeksnog pacijenta. Ukupno je do novembra 2020. godine zaraženo 55,6 miliona pacijenata, izlečenih je 35,8 miliona, a umrlo je 1,34 miliona.

Ovako veliki broj zaraženih predstavlja ozbiljnu vanrednu situaciju u zdravstvu, a posebno je smrtonosna za populaciju sa rizikom (stara populacija, populacija sa komorbiditetom) i za pojedine populacione grupe/zajednice (neobrazovana populacija, siromašna zajednica).

Trudnice i njihovi fetusi predstavljaju visoko rizičnu populaciju tokom izbijanja zaraznih bolestise.

Obzirom da su populacija visokog rizika trudnice bi trebalo da poštuju iste preporuke kao i opšta populacija koje su predvidjene za smanjenje izloženosti virusu (npr. fizička distance od najmanje 2 metra, nošenje dvoslojne ili troslojne zaštitne maske kada su van spostvenog domaćinstva, izbegavanje zatvorenih prostora kao što su barovi i restorani, gužve na otvorenom, da se sprovodi često pranje ili dezinfekcija ruku, dezinfekcija površina koje često dodiruju). Naročito treba da izbegavaju bliske kontakte sa bolesnim osobama.

Vellika studija Centers for Disease Control and Prevention (CDC) COVID-19 je anlizirala procenat ispoljavanja simptoma u populaciji trudnica uporedjujući sa ženskom populacijom u reproduktivnom period koja nije gravidna i dokazala da se učestalost simptoma u grupama posebno ne razlikuje. Kao najčešće simptome bolesti naveli su kašalj (50,3%), glavobolja (42,7%), bolovi u mišićima (36,7%), groznica (32,0%), bol u grlu (28,4%), kratkoća daha (25,9%), gubitak ukusa ili mirisa (21,5%) .Ostali simptomi koji se redje javljaju su mučnina ili povraćanje, umor, dijareja i rinoreja.

Medjutim kod mnogih trudnica klinička slika izostaje (asimptomateske su). U meta centričnoj studiji Aloteja i saradnika 7 posto trudnica koje su testirane i pozitivne na COVID-19 tri četvrtine njih je bilo asimptomatsko od. bez ispoljavanja kliničke slike.

Osim asiptomatskih trudnica kod nekih je klinička slika veoma blaga i ispoljlava se kroz simptome koji se javljaju u normalnoj – zdravoj trudnoći (npr. umor, otežano disanje, nazalna kongestija, mučnina/povraćanje), o čemu treba misliti prilikom uzimanja anamneze i testiranja pacijentkinja koje su afebrilne.

Kada govorimo o vremenu porodjaja mnoge studije su pokazale da je značajno povećan broj preterminskog porodjaja a kada se radi o načinu porodjaja da je povećan broj carskog reza.

Međutim zaključak nekoliko studija je da nije dokazana korist planiranog prevremenog porodjaja u slučaju teških respiratornih infekcija majke meta centrična studija Aloteja i saradnika je pokazala da 17% porođaja je izvršeno pre 37. nedelja trudnoće i 65% rođenih carskim rezom. Većina prevremenih porođaja bila je jatrogena; samo 6% je bilo spontanih prevremenih porođaja.

Vreme porođaja treba da bude individualizovano i da se planira prema stanju majke, komorbiditeta, gestacijske starosti tako da su preporuke u vezi vremena planiranja porođaja sledeće:

- u slučaju Covid-19 pozitivnih pacijenata sa slabo izraženom kliničkom slikom bolesti ili u slučaju da su asimtomatski čije su trudnoće stare 39 nedelja gestacije i više indikovano je indukovati porodjaj
- u slučaju Covid-19 pozitivnih pacijentkinja sa lakšim obikom bolesti a koje nemaju medicinske/ akušerske indikacije za hitan porodjaj, idealno je da se porodjaj sprovede nakon stizanja negativnih rezultata testa ili ukidanja izolacije, na taj način se mogućnost prenosa infekcije na novorodjnče minimizira
- u slučaju Covid-19 pozitivnih pacijentkinja sa lakšim obikom bolesti, a koje imaju medicinske/ akušerske komplikacije (prevremeno prsnuće plodovih ovojaka, preeklampsija) vreme porodjaja se planira prema protokolima za za određeni medicinski / akušerski poremećaj.
- za hospitalizovanog pacijenta sa COVID-19 sa upalom pluća, ali koji nije intubiran, u starosti trudnoća od 32-34 n.g. prevremeni porodjaj preporučuje se samo u slučaju pogoršanja opšteg stanja majke
- većina autora se slaže i ne podržava porođaj pre 32. nedelje, iako stanje majke se može pogoršati tokom druge nedelje bolesti, obzirom na morbiditet i mortalitet pretrminske (mlađe od 32. gestacione nedelje) novorodjenčadi
- za hospitalizovanog pacijenta koji je intubiran i kritično bolestan planiranje vremena porodjaja je poseban izazov i odliuke se donose od slučaja do slučaja
- za starost trudnoće od 32-34. nedelje gestacije mišljenja nisu jedinstvena tako da jedna grupa autora preporučuje porodjaj ako je pacijen u stabilnom opštem stanju, dok druga grupa autora preporučuje prevremeni porodjaj samo za pacijente sa hipoksemičnom respiratornom insuficijencijom ili kritičnim pogoršanjem bolesti
- u period vijabilnosti i <30 do 32. nedelje, sve dok stanje majke stabilno ili se poboljšava, preporučuje se kontinuirana podrška i nega majke sa intenzivnim praćenjem fetusa kako bi se izbegle komplikacije vezane za prematuritet

Kada govorimo načinu sprovodjenja porodjaja infekcija COVID-19 nije indikacija za promenu načina porođjaja. Carski rez ne smanjuje rizik neonatalne infekcije i preporuka je da se izvodi u slučaju postojnja akušerskih indikacija, ali se preporučuje u slučajevima akutne dekompenzacije intubiranih paijenata i kritično bolesnih majki. Prednost se uvek daje prirodnom načinu porodjaja uz kontinuirani CTG monitoring. Opšte uzevši, ne treba odlagati porodjaj kod pacijentkinja koje su asimptomatske ili imaju blagu kliničku sliku a čija trudnoća je stara 39 ng.

Za pacijente kod koji je neophodno indukovanje porodjaja aplikacija balon katetera je prva preporuka za započinjanje indukcije. Može se aplikovati u kombinaciji sa primenom misoprostola ili oksitocina.

Preporuka je da se obavesti kompletna medicinska ekipa koja učestvuje u porodjaju da se poradja Covid -19 pozitivna pacijentkinja da bi se korišćenjem svih mera prevencije smanjio rizik kontaminacije prostora i infekcije osoblja.

Kada se govori o anesteziji u toku porodjaja nema dokaza da je neuraksijalna blokada kontraindikovana kod pacijentkinja koje su COVID-19 pozitivne. Preporučuje se aplikacija neuraksijalne blockade pre ili početkom porođaja da bi se smanjio broj opšte intratrahealne anestezije.

Takođe kada se govori o nezi novorodjenčeta i uspostavljanja kontakta sa majkom nema zabrana za sprovodjenje kontakta koža na kožu, za dojenje ili negu novorodjenčeta u posebno pripremljenim prostorijama ukoliko majke nose hiruške maske i sprovode adekvatnu higijenu ruku.

Literatura

1. Allotey J, Stallings E, Bonet M, et al. Clinical manifestation, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy; living systematic review and meta-analysis. BMJ. 2020.
2. Yanes-Lane M, Winters N, Fregonesa F,et al. Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: A Systematic review and meta-analysis. PLoS One. 2020;15:eo241536.
3. Society for Maternal-Fetal Medicine. Management Considerations for Pregnant Patients With COVID-19 (Accessed on October 27, 2020).
4. Donders F, Lonnee-Hoffmann R, Tsiakalos A, et al. ISIDOG Recommendations Concerning COVID-19 and Pregnancy. Diagnosis (Basel) 2020;10.
5. Tolcher MC, McKinney JR, Eppes CS, et al. Prone Positioning for Pregnant Womwn With Hypoxemia Due to Coronavirus Disease, 2019 (COVID-19). Obstet Gynecol. 2020;136:259.
6. Webster CM, Smith KA, Manuck TA, Extracorporeal membrane oxygenation in pregnant and postpartus women: a ten-year case series. Am J Obstet Gynecol. 2020;2:100108.
7. Walker KF,O'Donoghue K, Grace N, et al. Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such transmission: a Systematic review and critical analysis. BJOG. 2020;127:1324.
8. Boelig RC, Manuck EA, et al. Labor and delivery quidance for COVID-19.Am J Obstet Gynecol. 2020;2:100110.
9. Ashokka B, Loh MH, Tan CH, et al. Care of the pregnant woman with coronavirus disease 2019 in labor and delivery: anesthesia, emergency cesarean delivery, differential diagnosis in the acutely ill parturient, care of the newborn, and protection of the healthcare personnel. Am J Obstet Gynecol. 2020;223:66.
10. American Academy of Pediatrics. FAQs: Management of Infants Born to COVID-19 Mothers (Accessed on October 28, 2020).
11. Salvatore CM, Han JY, Acker KP, et al. Neonatal management and outcomes during the COVID-19 pandemic: an observation cohort study. Lancet Child Adolesc Health 2020; 4:721.

Prof. dr Jelena Stamenković je rođena 03.03.1965. u Beogradu. Medicinski fakultet u Beogradu završila 1989. godine. Odbranila magistarski rad 1995. godine a doktorsku disertaciju 2004. godine. Zaposlena na Medicinskom fakultetu u Beogradu od 1999. godine. Od 2006. godine u zvanju vanrednog profesora.

Posebna oblast njenog rada je perinatologija i primena ultrazvuka u dijagnostici i terapiji fetusa. Šef je Kabineta za dijagnostiku bolesti fetusa.

Autor i koautor je u više od 100 radova, udžbenika i priručnika.

SARS-COV-2 INFECTION: ARAD'S MATERNITY WARD EXPERIENCE DURING THIS PANDEMIC

Assist. Prof. Cristian Furau[1,2]

European Society of Contraception and Reproductive Health (ESC) Board member

Boru Casiana[1,2], Furau Roxana[2], Pasare Cristina[2], Onel Cristina[1,2], Panda Bianca[2], Filimon Angelica[1,3], Burdan Dorina[1,3], Todut Oana[2], Onel Mircea[1], Furau Gheorghe[1,2]

1 Western University "Vasile Goldis" of Arad, Romania
2 Emergency Clinical County Hospital of Arad- Obstetrics and Gynecology Department
3 Emergency Clinical County Hospital of Arad- Neonate Department

This lecture briefly presents the main aspects the SARS COV 2 pandemic generated worldwide, putting an accent on the Euro Regional and national epidemiological evolution.

In the context of national and regional evolution of the infected cases, our team further analyzed the 58 confirmed COVID 19 cases admitted for continuous hospitalization in the Arad Maternity Ward. Both obstetrical and gynecological cases were divided into 3 main periods: the lockdown (mid March to mid May 2020), the relaxation period (mid May to end of July 2020) and the second wave (early August until present), the last two corresponding to a national alert state. We looked upon the patient's characteristics, reasons of presenting to the hospital, symptoms, treatment, evolution and outcome in the frame of continuous evolution of national guidelines and recommendations.

In the end of the lecture we resumed our experience and drew the conclusions on how our maternity ward was affected by the pandemic.

References

1. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320.
2. Kirtsman M, Diambomba Y, Poutanen SM, et al. Probable congenital SARS-CoV-2 infection in a neonate born to a woman with active SARS-CoV-2 infection. CMAJ. 2020; 192:E647
3. Khalil A, von Dadelszen P, Draycott T, et al. Change in the Incidence of Stillbirth and Preterm Delivery During the COVID-19 Pandemic. JAMA. 2020.
4. Rasmussen SA, Lyerly AD, Jamieson DJ. Delaying Pregnancy during a Public Health Crisis - Examining Public Health Recommendations for Covid-19 and Beyond. N Engl J Med. 2020.
5. Covid-19 and pregnancy. BMJ 2020; 369:m1672.

Through all his accomplishments, Dr. Furau has proven himself a true leader of his generation in his field of expertise and was nominated to be part of the Young Physician Leaders Program initiated by the InterAcademy Medical Panel.

He has combined the academic and research career with the clinical part and with the healthcare management and policies.

As a clinician he became a senior specialist in obstetrics&gynecology, he attended postgraduate courses obtaining complementary competences, he benefited from fellowships at Szeged and Novi Sad Hospital. He was in

charge of the Pathological Obstetrics and Delivery Room Departments with very good results and recently was appointed coordinator for the operating theater.

By being elected president of Ethical Committee at a >1400 bed hospital, director for training in residency at the Medicine Faculty, member in other committees, responsible for pilot project for maternal care in poor population and by his training in healthcare management, he shows great potential in this field.

He is a promising researcher with many articles published and awards received, an acknowledged international speaker and has very good organizing skills for medical educational events. He has developed very good international connections and he is very esteemed by his students and colleagues.

Also his communication and social skills, responsibility, ambition and commitment recommend him.

GYNECOLOGY

MEDIKAMENTOZNI PREKID TRUDNOĆE U CRNOJ GORI

Prim. Vojislav Miketić

Potpredsednik UGOSCGRS
Predsednik udruženja ginekologa i obstetričara Crne Gore
Klinika za ginekologiju i akušerstvo, Klinički Centar Crne Gore, Crna Gora

Dr Mahmut Šehović

Abortus, *lat. abruptio graviditatis* kroz istoriju ostaje jedan od najkontroverznijih činova koji na svoj i često oprečan način definišu medicina, religija, zakonodavstvo te socio-kulturološke nauke. Medicinski posmatrano je čin kojim se dovršava neželjena ili patološka trudnoća.

Prema istrazivanju objavljenom u Lancetu, 2016. god oko 56 miliona prekida trudnoće se obavi svake godine u svijetu od kojih u Južnoj Evropi , kojoj pripadaju naša država i okolne, oko 800000.

U Crnoj Gori nemamo zvanične podatke ali podaci iz 'Strategije za očuvanje i unapređenje reproduktivnog i seksualnog zdravlja Ministarstva zdravlja Crne Gore pokazuju da se ukupno godišnje obavi 1.400 abortusa kako u privatnim tako I ustanovama javnog zdravstva.

Na osnovu 'Zakona o uslovima i postupku za prekid trudnoće' koji je objavljen u "Službenom listu CG", br. 53/2009 prekid trudnoće se može izvršiti do 10 sedmica od dana začeća, na osnovu pisanog zahtjeva trudnice.

Prekid trudnoće se može izvršiti poslije isteka 10 sedmica do 20 sedmica od dana začeća, ako:

- se na osnovu medicinskih indikacija utvrdi da se na drugi način ne može spasiti život ili otkloniti teško narušavanje zdravlja žene za vrijeme trudnoće, porođaja, ili poslije porođaja;
- se na osnovu medicinskih indikacija može očekivati da će se dijete roditi sa teškim tjelesnim ili duševnim nedostacima;
- je do začeća došlo u vezi sa izvršenjem krivičnog djela;
- bi žena u toku trudnoće ili poslije porođaja mogla doći u teške lične ili porodične prilike.

U Crnoj Gori kao i u razvijenim zemljama svijeta koriste se dvije metode izbora za prekid trudnoće: medikamentozni i instrumentalni. U razvijenim zemljama svijeta medikamentozni abortus ima prednost kod pacijenktinja pa je tako 92% namjernih pobačaja u Švedskoj izvedeno ovom metodom (podaci iz 2016.god), u Engleskoj I Francuskoj oko 60% (2016), a u USA 39% (2017. godina).

Medikamentozni abortus u odnosu na invazivni tretman ima svoje prednosti i mane.

Prednosti: zaobilaženje hiruškog tretmana I anestezije, prirodniji je, nalik menstruaciji, za neke žene je emocionalno prihvatljiviji metod, nudi više privatnosti i autonomije pacijenta, može se izvesti u kućnim uslovima, ne nosi rizik za povredu grlića/materice, ima prednost kod uterinih malformacija, prethodnih hiruških intervencija na grliću, i kod BMI > 30.

Nedostaci su krvarenje, grčevi, produženo trajanje u odnosu na hiruški tretman, neželjeni efekti lijeka kao sto je dijareja itd. Efikasnost je oko 95% (zavisno od studija), a neke studije pokazuju efikasnost i do 99% kod žena koje nisu rađale. U Crnoj Gori se medikamentozni prekid trudnoće primjenjuje u Kliničkom centru Crne Gore od 2017. godine.

Na nacionalnom nivou ne postoji zvaničan protokol za medikamentozni abortus ali se vodimo preporukama FIGO, RCOG odnosno WHO (Clinal practice handbook for safe abortion).

Prema RCOG (Royal college of obstetricians and gynaecologists) preporučuju se sljedeći režimi za rani medikamentozni abortus: za trudnoću starosti 63 ili manje dana gestacije, mifepristone 200 mg oralno a potom 24-48h kasnije misoprostol, 800 mikrograma vaginalno,bukalno ili sublingvalno, za trudnoću starosti 49 ili manje dana gestacije, mifepristone 200 mg oralno a potom 24-48h kasnije misoprostol,u dozi od 400 mikrograma.

Prema FIGO preporukama za inkompletni pobačaj u slučaju medikametoznog tretmana kao metode izbora se daje jedna doza misoprostola od 400 mikrograma sublingvalno ili 400/800 mikrograma per oralno.

Prvi podaci o medikamentoznom prekidu trudnoće u Crnoj Gori datiraju od 2017.god. Prema podacima iz Kliničkog centra Crne Gore medikamentozna terapija u toku pobačaja upotrijebljena je ukupno 64 puta u 2017.godini. Ako uzmemo da je prosječan broj prekida trudnoće 1400 na nacionalnom nivou, procentualno je to manje od 5%.

Raspolažući podacima iz naše ustanove, koja je jedina u kojoj se indikuje medikamentozni prekid trudnoće, 2017.god je ukupno izvršeno 297 invazivnih prekida trudnoće kiretažom što znači da je u prvoj godini zastupljenost medikamentoznog abortusa procentualno 17,7 %.

U dijagnozama kod medikamentoznog pobačaja najzastupljenija je Missed Ab (56%), Abortus arteficialis (31%), te Abortus incompletus (5%) te Blighted ovum(8%).

Starosna struktura pacijentkinja govori da su to najčešće žene u svojim tridesetim godinama.

Prekid trudnoće se prema gestacionoj starosti najčešće dešavao u 8/9 nedjelji gestacije (45%), 6/7 gestacionoj nedjelji (31%), u 17% slučajeva trudnoća je bila mlađa od 6 nedjelja gestacija, a u 6% slučajeva starija od 10 nedjelja gestacije.

U 2018.god je bilo ukupno 190 medikamentoznih prekida trudnoće u prvom trimestru, što je nešto niže od 15% svih prekida trudnoće na nacionalnom nivou (nezvanični podaci).

U Kliničkom centru Crne Gore u 2018.god bilo je ukupno 258 invazivnih prekida trudnoće što će reći da je procentualno medikamentozni prekid trudnoće indikovan kod 42% pacijentkinja.

Zabilježeno je i 6 slučajeva ponovljene terapije misoprostola nakon medikametoznog prekidatrudnoće. U 7 slučajeva primjene medikamentoznog prekida trudnoće kod trudnica koje su imale bar jedan carski rez.

Od dijagnoza 2018. god najzastupljenija je Missed Ab u 45% slučajeva dok je Ab arteficialis zastupljen kod 37% pacijentkinja.

U trećini slučajeva su u pitanju pacijentkinje u svojim dvadesetim godinama, a najveću grupu predstavljaju žene u tridesetim godinama.

Gestaciona starost prekinutih trudnoća je 6.odnosno 7. nedjelja u 42 % slučajeva, 8/9 nedjelja gestacije kod 38%, manje ili jednako od 6. nedjelja gestacije kod 12% pacijentkinja dok je kod 10% trudnoća starosti 10 i više gestacionih nedjelja.

U 2019.god zabilježeno je 276 slučajeva medikamentoznih prekida trudnoće što je oko 20% svih prekida trudnoće na nivou države (nezvanični podaci). U Kliničkom centru su izvršena 243 invazivna prekida trudnoće što će reći da je u našoj ustanovi od prošle godine medikamentozni prekid trudnoće prvi metod izbora kod prekida, bilo patološke bilo fiziološke trudnoće i to kod 53 % pacijentkinja. 44% medikamentoznog prekida trudnoće bio je pod dijagnozom Missed Ab, a 42% pod dijagnozom Abortus arteficialis.Blighted ovum dijagnostikovan je kod 10% tretiranih

trudnica a Abortus incompletus kod 4%. Kod 14 pacijetkinja zabilježen je invazivni tretman zbog rezidue nakon medikamentoznog prekida trudnoće odnosno u 5% slučajeva.

Zabilježene su 3 ponovoljene terapije ambulantno i 3 terapije kod maloljetnih osoba uz saglasnost roditelja. Najučestalija gestacijska starost trudnoće je 6/7 nedjelja gestacije (47%), 8/9 gn u 29% slučajeva, te 6 nedjelja i manje u 15% trudnica kod kojih je primjenjen medikamentozni prekid trudnoće.

U aktuelnoj 2020. god je do septembra zabilježeno 180 prekida trudnoće medikamentoznim putem ambulantno u Kliničkom centru Crne Gore.

Medikamentozni prekid trudnoće je danas i u našoj zemlji zauzeo primat kao metoda izbora prekida trudnoće.

Iz priloženih podataka zaključuje se da imamo trend rasta medikamentoznog prekida trudnoće kao metode izbora, da su žene koje se odlučuju na ovakav korak obično u kasnim dvadesetim ili tridesetim godinama, da je indikacija prvenstveno patološka trudnoća a zatim i arteficijalni abortus odnosno neželjena trudnoća.

S obzirom da se medikamentozni prekid trudnoće trenutno sprovodi samo u Kliničkom centru Crne Gore,ono što predstoji je edukacija na nacionalnom nivou i formiranje protokola i vodiča za medikamentozni prekid trudnoće tj nacionalnih smjernica koje će moći da prate i Opšte bolnice u našoj zemlji u kojima se takođe planira dostupnost medikamentoznog prekida trudnoće uz pravnu i zakonodavnu podršku.

Literatura

1. Lyra J, Cavaco-Gomes J, Moucho M, Montenegro N. Medical Termination of Delayed Miscarriage: Four-Year Experience with an Outpatient Protocol. Rev Bras Ginecol Obstet. 2017 Oct;39(10):529-533.
2. Barceló F, De Paco C, López-Espín JJ, Silva Y, Abad L, Parrilla JJ. The management of missed miscarriage in an outpatient setting: 800 versus 600 µg of vaginal misoprostol. Aust N Z J Obstet Gynaecol. 2012 Feb;52(1):39-43.
3. Lui MW, Ho PC. First trimester termination of pregnancy. Best Pract Res Clin Obstet Gynaecol. 2020 Feb;63:13-23.
4. Kulier R, Gülmezoglu AM, Hofmeyr GJ, Cheng LN, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev. 2004;(1):CD002855.

Miketić Momčila Vojislav, rođen 15.04.1965. god.- Travnik, SFRJ-BIH. 1983. godine završio II Gimnaziju u Sarajevu, BIH, SFRJ. 1984. god upisao Medicinski fakultet Univerziteta u Sarajevu, diplomirao 1989. god sa srednjom ocjenom 8,5. 1994-1998. godina, Medicinski fakultet Beograd, Specijalista Ginekologije i akušerstva. Postdiplomske magistarske studije 1998-2002. god iz oblasti Humana reprodukcija, Medicinski fakultet Univerziteta u Beogradu na temu: Poređenje Nifedipina i Betamimetika u tretmanu prijevremenog porođaja. Postdiplomske subspecijalističke studije 2001/2002 g . iz Perinatologije, IGA, Medicinski fakultet u Beogradu, tema: Komparacija 4 testa za određivanje zrelosti fetalnih pluća. 2007/2008g završio doktorske studije iz oblasti Humana reprodukcija na Medicinskom fakultetu Univerziteta u Kragujevcu. Zvanje primarijus stekao 2010 godine.

Profesionalno radno iskustvo: 1989-1990.god Pripravnički staž KC BIH; 1990-1998. god Institut Dr Simo Milošević. H. Novi; 1999- GAK KCCG, Podgorica; 2004 - Sekretar Ginekološko akušerske sekcije Crne Gore; 2007 - Stručni saradnik na Medicinskom fakultetu Univerziteta Crne Gore; 2008 - Predjednik Udruženja ginekologa i akušera Crne Gore; 2015 - Načelnik odjeljenja patologije trudnoće GAK KCCG; 2016- Direktor GAK KCCG.

SIGMOID VAGINOPLASTY IN PATIENTS WITH VAGINAL AGENESIS: TECHNIQUE AND OUTCOMES

Prof. Miroslav Đorđević

Chief of board for postgraduate and specialist studies in pediatric surgery,
Co-director of surgery in Belgrade University Children's Hospital
School of Medicine, University of Belgrade, Serbia

Many techniques are used for creation of the neovagina, though the rectosigmoid segment seems to be the most natural substitute. The aim of the study was to evaluate outcomes of sigmoid vaginoplasty in patients with vaginal agenesis.

35 patients with vaginal agenesis (Mayer–Rokitansky–Kuster–Hauser syndrome), aged 15 to 20 years, underwent rectosigmoid vaginoplasty between January 2010 and October 2019. Length of the isolated segment of the sigmoid colon was 9 to 12 cm, and a stapling device was used for colorectal anastomosis. Simultaneous abdominal and perineal approaches were used to create a perineal cavity for neovagina. Perineal skin flaps were designed and harvested for anastomosis with sigmoid neovagina, to prevent introital stenosis and to achieve good esthetic results. Standardized questionnaires were used to assess a patient's satisfaction after surgery.

Follow-up ranged from 12 to 119 months (mean 46 months). Good aesthetic result was achieved in 33 cases. Minor aesthetic revision of introitus was performed in two patients. Totally 28 patients (80%) have become sexually active during follow-up, and 7 of them reported transitory dyspareunia and mucus production. Totally 92% of patients reported satisfaction with surgical outcome. Bleeding and pain occurred 5 years after surgery in one case, and biopsy revealed inflammatory changes of the neovagina (diversion neovaginitis).

Rectosigmoid vaginoplasty presents an excellent option for patients with vaginal agenesis, with low rates of complications. Creation of perineal flaps for introitoplasty prevents introital stenosis. Majority of patients are satisfied with the achieved outcomes.

References

1. Cao L, Wang Y, Li Y, Xu H. Prospective randomized comparison of laparoscopic peritoneal vaginoplasty with laparoscopic sigmoid vaginoplasty for treating congenital vaginal agenesis. Int Urogynecol J. 2013 Jul;24(7):1173-9.
2. Bhaskar V, Sinha RJ, Mehrotra S, Mehrotra CN, Singh V. Long-term outcomes of sigmoid vaginoplasty in patients with disorder of sexual development - our experience. Urol Ann. 2018 Apr-Jun;10(2):185-190.
3. Özkan Ö, Özkan Ö, Çinpolat A, Doğan NU, Bektaş G, Dolay K, Gürkan A, Arıcı C, Doğan S. Vaginal reconstruction with the modified rectosigmoid colon: surgical technique, long-term results and sexual outcomes. J Plast Surg Hand Surg. 2018 Aug;52(4):210-216.
4. De la Torre L, Cogley K, Calisto JL, Santos K, Ruiz A, Zornoza M. Vaginal agenesis and rectovestibular fistula. Experience utilizing distal ileum for the vaginal replacement in these patients, preserving the natural fecal reservoir. J Pediatr Surg. 2016 Nov;51(11):1871-1876.
5. Djordjevic ML, Stanojevic DS, Bizic MR. Rectosigmoid vaginoplasty: clinical experience and outcomes in 86 cases. J Sex Med. 2011 Dec;8(12):3487-94.

Dr Miroslav L Djordjevic is a Professor of Urology and Surgery at the School of Medicine, University of Belgrade, Serbia. The main field of his multidisciplinary work is urogenital reconstructive surgery, encompassing treatment of all anomalies of the genital system, regardless of gender or age. Professor Djordjevic has been multiply awarded for his comprehensive scientific work. He is the Editor of many leading Journals and Books, and a member of all relevant international associations in the field of urology and genital reconstructive surgery. Professor Djordjevic has been invited lecturer and Visiting Professor on many universities all around the world. As a member of humanitarian societies he actively participated in humanitarian missions over the world. Last but not least, he is the founder and leader of Belgrade Center for Genital Reconstructive Surgery, which is chosen as a fellowship program center by 20-30 foreign colleagues every year. From 2019, Professor Djordjevic joined Urology Department, Icahn School of Medicine at Mount Sinai in New York, United States.

POSTGRADUATE EDUCATION ON SEXUAL AND REPRODUCTIVE HEALTH CARE OF GIRLS AND ADOLESCENTS

Dr. Katarina Sedlecky

Institute for Mother and Child Health Care of Serbia „Dr Vukan Čupić“, Family Planning Centre, Belgrade

Dr. Zoran Stanković

Gynaecology and Obstetrics Clinic „Akugin“; St Medica Hospital, Belgrade

Education and training for sexual and reproductive health (SRH) care is different from other medical professional disciplines for many reasons. First of all, SRH is a relatively new concept, as it has been developed since the Fifth International Conference on Population and Development (Cairo, 1994). Furthermore, SRH care demands a multidisciplinary and comprehensive approach, with a focus on prevention, education and counselling, instead of treating diseases. In addition, SRH care professionals need to be continuously updated regarding the newest developments in different fields from contraception to sexually transmitted infections (STI), from sexual health to screening and vaccination, from epidemiology to health policies (1).

First National Programme for Safeguarding and Improving Sexual and Reproductive Health of the Citizens of the Republic of Serbia, entered into force on January 7, 2018 (2). Programme was developed using human rights approach and in accordance with the international documents and standards, including: The Global strategy for women's, children's and adolescents' health (2016-2030), Action plan for sexual and reproductive health: towards achieving the 2030 Agenda for Sustainable Development in Europe – leaving no one behind. The National programme identified the main challenges and areas that needs future improvements in sexual and reproductive health of the Serbian population: rate of modern contraception use, counselling services, age appropriate sexuality education, clinical guidelines and protocols, maternal health, gender-based violence, etc. The Program recognized that special attention should be given to particularly vulnerable population groups, such as Roma, people living on the poverty line, from rural areas, women with disabilities, but also to youth. National Programme set as the main goal to preserve and promote sexual and reproductive health of the population of the Republic of Serbia, with respect to the right to make informed decisions related to sexuality and reproduction, independently of an individual's personal characteristics. To improve implementation of the National Programme, the Ministry of Health decided to develop the Action plan. Three priority areas were identified:

- Awareness and information;
- Youth;
- Marginalized groups.

The need to focus on SRH care of young people is recognized in the new concept of health achieved through life course approach (3). The SRH care starts with screening of pregnant women and newborns, continues with vaccinations of children, and sexuality education during childhood and adolescence. Preventive activities in the field of SRH for youth include HPV vaccinations, chlamydia trachomatis screening, providing effective contraception and cervical cancer screening. The cycle ends, but also begins again with preconception and antenatal care, which indicates that

investing in health is a continuous process, that determines the heath status not only of current but also future generations.

Certainly, the state of SRH largely depends on the attitudes of doctors and their education to work in that field. European professional organisations like the European Society of Contraception and Reproductive Health (ESC), European Association of Paediatric and Adolescent Gynaecology and the European Board and College of Obstetrics and Gynaecology (EBCOG) are striving to develop and adopt standards of training of health professionals in various areas of SRH care which would be recognized and used in all countries of the continent (4).

The challenge is, however, that in a number of countries, including Serbia and Republic Srpska, these educational opportunities are insufficiently recognized and used. In order to better understand the organisation of SRH service delivery across Europe, as well as the situation regarding education and training of relevant health workers, a survey was conducted among relevant opinion leaders who were country representatives in the Board of the ESC. This investigation demontrated that pregraduate education of health care professionals who provide SRH (gynaecologist in all countries, general practitioners and midwifes/nuses in some countries) is still insufficient in many European countries, including Serbia and Republic Srpska, while postgraduate education is not properly regulated. It is encouraging, however, that most countries have recognized the need to adopt uniform recommendations and guidelines for the work of health professionals, including Serbia (5).

First National guidelines for contraceptive provision have been recently published in Serbia, but due to unfavorable epidemiological situation this document has not been presented to the professional public (6). This guidelines are distributed by mail to 200 health institutions, and are posted on the websites of the Institute for Mother and Child of Serbia, the Ministry of Health and the Institute of Public Health of Serbia.

These clinical guidelines contain all the necessary information on the basic principles of contraceptive counseling and the contraceptive methods available in our country. Characteristics of SRH care of adolescents, postpartum and perimenopausal women are especially emphasized.

At the European level, the criteria for the education of doctors, primarily gynaecologists but also paediatricians, which make them competent to work in the field of paediatric and adolescent gynaecology are defined.

Rationale is that physical and psychological wellbeing of children and adolescents is crucial for their future general and reproductive health. Gynaecological conditions can be common and disruptive, with rare conditions requiring specialist multidisciplinary management. Inappropriate provision of care can result in poor outcomes and adverse long term consequences. SRH care in the field of paediatric and adolescent gynaecology should be patient focused, because children and adolescents should receive the best evidence based specialist treatment in order to preserve their future reproductive potential. Surgical procedures for paediaatric and gynaecology conditions should primarily be based on minimal invasive techniques. Appropriate information for children, their parents or guardians should be available. An easy access, non-judgemental service should be available where the welfare of the child is the primary focus. Age-appropriate sex and contraceptive education should be available. Vaccination against human papilloma virus should be promoted and offered to all adolescents. National prevention programmes should be encouraged.

Children and adolescents with gynaecological problems should be seen in appropriate and designated clinical environments. All services should have a non-threatening reception area. All services should have age appropriate displays and posters to provide patient information. Clinical networks should be established to allow for the multidisciplinary management of rare and complex conditions, the setting of standards and the development of clinical, educational and referral pathways. Disorders of sex development should be classified and managed accordingly. Processes should be put in place to ensure a comprehensive and seamless transition of care of adolescents with gynaecological conditions to adult care. All professionals involved in managing children with gynaecological problems should be competent in child protection procedures. The safeguarding of children is paramount. Clinicians providing this service should be competent in medical and surgical interventions required.

Training in paediatric an adolescent gynaecology (PAG) should be provided in recognised centres. Trainers should be members of or work in close collaboration with national PAG Societies. Training should be based on well established curriculum and training programme (5). The period of the fellowship should last for two years. At the end of the training program the supervisor makes final evaluation. After completing this, trainee fulfils requirements and is ready to be approved by competence committee by national standards (exam, certificate, approval).

References

1. Improving the Quality of care for reproductive, maternal, neonatal, child and adolescent health in the WHO European region. A Regional Framework to Support the Implementation of Health 2020. Copenhagen: World Health Organization; 2016.
2. Decree on the National Programme for Sexual and Reproductive Health and Rights. „Gazette of RS “, no. 120/2017.
3. Promoting health through the life-course: WHO’s work in countries in the life-course. Geneva: World Health Organization; 2017.
4. European Board and College of Obstetrics and Gynaecology. Standards of care for women’s health in Europe; 2014.
5. Sedlecky K, Rašević M, Bitzer J. Education and training of health care workers for contraceptive service delivery in 21 countries across Europe. Sex Reprod Healthc. 2020 Jun;24:100498.
6. Sedlecky K, Živanović A, Kapamadžija A, Mitrović-Jovanović A, Simić D, Pantić-Aksentijević S. National Clinical Guidelines for Contraception. Belgrade: Ministry of Health of the Republic Srbija; 2020.

Katarina Sedlecky je lekar, specijalista ginekologije i akušerstva, doktor medicinskih nauka, savetnik u Republičkom centru za planiranje porodice Instituta za zdravstvenu zaštitu majke i deteta Srbije. Uža naučna oblast: planiranje porodice, dečija i adolescentna ginekologija, reproduktivno zdravlje mladih. Rukovodilac Nacionalnog vodiča dobre kliničke prakse „Vodič za bezbedni prekid trudnoće“ – štampan 2013. godine; Rukovodilac Radne grupe za izradu „Kliničkih smernica za kombinovanu hormonsku i intrauterinu kontracepciju“ – smernice publikovane 2006. godine sa pozitivnom recenzijom Evropskog udruženja za kontracepciju i reproduktivno zdravlje; Rukovodilac Radne grupe Ministarstva zdravlja Republike Srbije koja je sačinila Nacionalni program za očuvanje i unapređenje seksualnog i reproduktivnog zdravlja i prava, usvojen januara 2018. godine; Rukovodilac Radne grupe Ministarstva zdravlja Republike Srbije koja je sačinila Nacionalne kliničke smernice za propisivanje savremene kontracepcije (2017/2018); Član istraživačkog tima u okviru projekta Ministarstva za demografiju i populacionu politiku „Poboljšanje kvaliteta zaštite reproduktivnog zdravlja mladih u Beogradu“, realizacija u toku (2019.g.); Član Ekspertskog tima Evropskog udruženja za kontracepciju i reproduktivno zdravlje za izradu edukativnih programa za profesionalce u oblasti zaštite seksualnog i reproduktivnog zdravlja,

a koji je sačinio ESC Advanced Teach the Teachers Course on Modern Contraception; Član Ekspertske grupe Evropskog udruženja za kontracepciju i reproduktivno zdravlje „Non-hormonal contraception“. Članstvo u profesionalnim udruženjima: Ginekološko-akušerska sekcija Srpskog lekarskog društva; Udruženje ginekologa i akušera Srbije, Crne Gore i Republike Srpske, član Predsedništva; Udruženje za dečiju i adolescentnu ginekologiju Srbije; The European Society of Contraception and Reproductive Health, Secretary general 2010-2014.

Zoran Stanković je Naučni saradnik; IFEPAG, zaposlen u AKUGIN Beograd, Specijalistička ordinacija iz ginekologije i akušerstva. Uža naučna oblast: Dečja i adolescentna (pedijatrijska) ginekologija - reproduktivno zdravlje.

Usavršavanja: 1999. Mesto ginekologa u dijagnostici i tretmanu seksualno zlostavljanih devojčica. 2004. Položio međunarodni ispit iz dečje i adolescentne ginekologije (IFEPAG) u Atini i postao član FIGIJ (Međunarodna federacija za dečju i adolescentnu ginekologiju).

2005. Stipendija Francuske vlade u okviru kontinuirane edukacije iz pedijatrijske ginekologije i endokrinologije. 2005. Salzburg, seminar o zaštiti dravlje majke i deteta. 2006. Ženeva, Stipendija SIOP 2007. Singapur . 2013. Hong Kong – ultrazvuk; 2016. Firenca – laparaskopije. 2019 Milano – laser u lečenju endometrioze.

DAGS, dečja i adolescentna ginekologija Srbije – presednik Udruženja; EURAPAG-član predsedništva od 2011; FIGIJ član.

GLOBAL OVERVIEW OF COMMERCIALLY AVAILABLE HPV TESTS: 2020 UPDATE

Prof. Mario Poljak

President of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)
Head of Laboratory for Molecular Microbiology and Slovenian HIV/AIDS Reference Centre
Institute of Microbiology and Immunology
Faculty of Medicine, University of Ljubljana, Slovenia

Molecular tests for detection of human papillomaviruses (HPV) play a crucial role in the prevention of cervical cancer, including recently announced elimination efforts. HPV testing is a recommended approach for cervical cancer screening of women over 30 and for management of those with precancerous cervical lesions. In addition, they are widely used in epidemiological studies, HPV surveillance and vaccination impact monitoring.

To provide an updated 2020 inventory of commercial molecular HPV tests available on the global market data were retrieved from internal files, and a detailed search using Medline/Pubmed, Web of Science, Scopus, Google Scholar, Google and Bing, without language or period restrictions, was performed in September 2019 and again in January 2020.

We identified 254 distinct commercial HPV tests and at least 425 test variants available on the global market in 2020, which represents a 31% and 235% increase in the number of distinct tests and variants, respectively, in comparison to the previous inventory performed in 2015. Although the proportion of commercially available HPV tests with at least one peer-reviewed publication has increased over the past decade, 60% of the HPV tests on the global market are still without a single peer-reviewed publication. Furthermore, 82% of tests lack any published analytical and/or clinical evaluation, and over 90% are not evaluated in line with consensus requirements that ensure safe use in clinical settings.

Significant challenges and scope for improvement still exist for both the HPV scientific community and the manufacturers of HPV tests. The latter must put more effort into validating their products, in agreement with standardised procedures, including all steps of HPV testing and various clinical specimens. High throughput capacity as well as point-of-care HPV tests are needed, both with affordable prices.

References

1. Poljak M, Kocjan BJ, Oštrbenk A, Seme K. Commercially available molecular tests for human papillomaviruses (HPV): 2015 update. J Clin Virol. 2016;76 Suppl 1:S3-S13.
2. Jaworek H, Kubanova K, Koudelakova V, Slavkovsky R, Drabek J, Hajduch M. Pitfalls of commercially available HPV tests in HPV68a detection. PLoS One. 2019;14(8):e0220373.
3. Jaworek H, Koudelakova V, Drabek J, Vrbkova J, Zborilova B, Oborna I, et al. A Head-to-Head Analytical Comparison of Cobas 4800 HPV, PapilloCheck HPV Screening, and LMNX Genotyping Kit HPV GP for Detection of Human Papillomavirus DNA in Cervical and Cervicovaginal Swabs. J Mol Diagn. 2018;20(6):849-58.
4. Poljak M, Oštrbenk A, Seme K, Šterbenc A, Jančar N, Vrtačnik Bokal E. Three-year longitudinal data on the clinical performance of the Abbott RealTime High Risk HPV test in a cervical cancer screening setting. J Clin Virol. 2016;76 Suppl 1:S29-S39.
5. Bihl MP, Tornillo L, Kind AB, Obermann E, Noppen C, Chaffard R, Wynne P, Grilli B, Foerster A, Terracciano LM, Hoeller S. Human Papillomavirus (HPV) Detection in Cytologic Specimens: Similarities and Differences of Available Methodology. Appl Immunohistochem Mol Morphol. 2017;25(3):184-89.

Mario Poljak, MD, PhD, specialist in clinical microbiology, is a Professor of Microbiology and Immunology and Head of Laboratory for Molecular Microbiology at Institute of Microbiology and Immunology at Faculty of Medicine, University of Ljubljana, Slovenia.

He was President of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) from 2016-2018 and member of ESCMID Exective Committee from 2012-2020. ESCMID has 9,000+ members from all European countries and all continents and is organising the largest conference in the field of infection in the World - ECCMID - with 15,000+ delegates.

He is author of 390 original research or review articles published in PubMed-cited journals. His papers have been cited more than 12,000 times (Hirsch index = 53).

As invited speaker he gave more than 350 lectures at international and national scientific and professional meetings.

CHRONIC POSTOPERATIVE PAIN: NEW ICD DEFINITION

Prof. Nebojša Lađević

Vice President of Serbian Society of Anesthesiologysts and Intesivists (UAIS)
Director of Center for Anesthesiology and Reanimatology, Clinical Center of Serbia
School of Medicine, University of Belgrade, Serbia

Chronic postoperative pain (CPOP) is a major health problem which affects millions of patients every year (1). The number of surgical procedures is large and continues to grow in all economic environments. It was estimated that between 266.2 and 359.5 million operations took place in 2012, and surgical volume increased 33.6% over 8 years (2). Also, it is estimated that 10 – 50% of patients underwent surgery develop CPOP, and pain is severe in 2 – 10% of them (3,4). Although CPOP is a serious health issue that directly interferes with the quality of life of affected patients and results in occurrence of disability (5), the first paper on CPOP was published by Crombie et al. only 20 years ago (6,7). Definition was serious problem when investigating CPOP.

Finally, the World Health Organization (WHO) released its new the International Classification of Diseases, 11th Revision (ICD-11) in June 2018, according to which CPOP is defined as chronic pain developed after a surgical procedure and persisting beyond the healing process, i.e. at least 3 months after surgery; pain is either localized to the surgical field, projected to the innervation territory of a nerve situated in this area, or referred to a dermatome (after surgery/injury to deep somatic or visceral tissues); other causes of pain including infection, malignancy etc. need to be excluded as well as pain continuing from a pre-existing pain problem (8).

Depending on the type of surgery, CPOP is often neuropathic pain (on average 30% of cases with a range from 6% to 54% and more) (8,9). Neuropathic pain resulting from surgical trauma is still the most common expression of CPOP (10). Differentiation of neuropathic from non neuropathic causes of postoperative pain is essential for the design of effective strategies to prevent and treat the conditions (11).

References

1. Kraychete DC, Sakata RK, Lannes Lde O, Bandeira ID, Sadatsune EJ. Postoperative persistent chronic pain: what do we know about prevention, risk factors, and treatment. Braz J Anesthesiol. 2016(66):505-12.
2. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. Lancet. 2015;(385): S11.
3. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006; 367(9522):1618-25.
4. Johansen A, Romundstad L, Nielsen CS, Schirmer H, Stubhaug A. Persistent postsurgical pain in a general population: prevalenceand predictors in the Tromsø study. Pain. 2012;153(7):1390-6.
5. Joshi GP, Ogunnaike BO. (2005). Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. Anesthesiology Clinics of North America. 2005;23:21-36.
6. Crombie IK, Davies HT, Macrae WA. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. Pain. 1998;76:167-71.
7. Macrae WA. Chronic post-surgical pain: 10 years on. Br J Anaesth 2008; 101: 77–86.
8. WHO. ICD-11 2018;
9. Treede RD, Rief W, Barke A, Aziz Q, Bennett M, Benoliel R, et al. A classification of chronic pain for ICD-11. Pain. 2015;(156):1003-7.
10. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain. 2013;(154):95-102.
11. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367:1618-25.

Prof. dr Nebojša Lađević, Medicinski fakultet, Univerzitet u Beogradu.

Direktor Centra za anesteziologiju i reanimatologiju Kliničkog centra Srbije, Beograd, Srbija. Predsednik Udruženja anesteziologa i intenzivista Srbije.

Predsednik Srpskog udruženja za terapiju bola. Zamenik Urednika časopisa Serbian Journal of Anaesthesia and Intensive Therapy. Član Etičkog odbora Srbije. Specijalista anesteziologije i ranimatologije. Specijalista medicine bola.

NOVI PRISTUPI U LEČENJU URINARNE INFEKCIJE KOD ŽENA

Doc. Ivana Likić Lađević

Načelnik drugog hirurškog odeljenja, Klinika za ginekologiju i akušerstvo, Klinički Centar Srbije
Medicinski fakultet, Univerzitet u Beogradu, Srbija

Infekcije urinarnog trakta spadaju, uz respiratorne, među najčešće infekcije. Ove infekcije predstavljaju značajan zdravstveni problem za pacijente, takođe i veliko opterećenje za zdravstveni sistem.

Urinarne infekcije se češće javljaju kod žena, što se objašnjava anatomskom građom i lakšim ulaskom bakterija kroz mokraćni kanal - uretru.

U SAD se preko 7 000 000 ambulantnih pregleda obavi zbog urinarnih infekcija, takođe, zbog njih se ordinira 15% ambulantno prepisanih antibiotika.

Najčešće izolovani uropatogen je *E. Coli*. Druge *Enterobacteriaceae* i *Enterococcus* spp. se takođe izoluju u značajnom procentu kod pacijenata sa urološkim obojenjima.

Ono što poslednjih godina posebno zabrinjava je dramatičan porast antimikrobne rezistencije, naročito na antibiotike širokog spektra, kao što su cefalosporini II i III generacije i fluorohinoloni. Beleži se i značajan porast *ESBL* (*extended spectrum β lactamase*) produkujućih bakterija, onih koji pokazuju osetljjivost isključivo na karbapeneme, a gotovo nerešiv problem predstavlja pojava fekalnih bakterija sa *ESBL carba* enzimom.

Imajući, dakle, u vidu multirezistentne sojeve bakterija, koji se, nažalost, sve više sreću kao izazivači urinarnih infekcija, na značaju dobija njihovo racionalno lečenje, odnosno racionalna upotreba antibiotika. Racionalnost nipošto ne treba poistovetiti sa štednjom. Racionalnost podrazumeva lečenje simptomatskih urinarnih infekcija, delotvornom terapijom, koja u isto vreme najmanje pogoduje razvoju multirezistentnih sojeva.

Simptomi urinarnih uinfekcija uključuju fizičke simptome, kao što su suprapubični pritisak i bol, učestali nagon na mokrenje, osećaj pečenja i bola pri mokrenju. Neretko, uz fizičke simptome, javljaju se i psihički simptomi, strah od ponovne infekcije i fizičkih simptoma koji je prate, a zatim i strah od E. coli, kao najčešćeg uropatogena, koji veliki broj pacijenata vezuje za povećan rizik od „propadanja bubrega".

Simptomatsku urinarnu infekciju možemo smatrati za skup simptoma i znakova koji su izazvani prisustvom bakterija u urinarnom traktu. Najčešći put širenja bakterija kroz urinarni trakt je kanalikularni, odnosno urinarni put širenja. Hematogeni put (*Staphilococcus aureus, Candida albicans, Salmonella spp., Micobacterium tuberculosis*...) je znatno ređi, dok limfogeni i per continuitatem imaju vise akademski značaj, nego praktični.

Urinarne infekcije se mogu klasifikovati na više načina. One se mogu podeliti na nekomplikovane i komplikovane infekcije, takođe mogu se klasifikovati i na osnovu predominantih urinarnih simptomima. U nekomplikovane urinarne infekcije spadaju nekomplikovana infekcije donjeg urinarnog trakta (*cystitis*) i nekomplikovani pijelonefritis.

U komplikovane infekcije spadaju: kompliklovani pijelonefritis, urosepsa, prostatitis, orfi-epididimitis.

Cistitis spade u najčešću infekciju urinarnog trakta. Infekciju mokraćne bešike karakteriše učestali nagon na mokrenje (polakiurija), otežano mokrenje (dizurija), nezadrživi nagon na mokrenje, bol pri kraju mokrenja, nekada se javlja i prisustvo krvi u urinu (hematurija). Ukoliko se upala mokraćne bešike proširi na gornji urinarni trakt, dolazi do pijelonefritisa, a uz ranije navedene smetnje javlja se i povišena temperatura, jeza, groznica, slabinski bol.

Kod infekcija urinarnog trakta u sedimentu urina beleži se povišen broj leukocija (Le > 10), zatim leukocitna esteraza, prisustvo nitrita i proteina. Uočava se i povećan broj bakterija. Ranije signifikanti broj kolonija bakterija u mL urina od > 10^5, danas se više ne uzima kao relevantan, odnosno i manji broj kolonija bakterija u mL urina može biti smatran za signifikantni, ukoliko ga prate simptomi urinarne infekcije. Na primer > 10^3 kol/ml uropatogena (srednji mlaz urina) – kod akutnog nekomplikovanog cistitisa; > 10^4 kol/ml uropatogena (srednji mlaz urina) – kod akutnog nekomplikovanog pijelonefritisa; > 10^5 kol/ml uropatogena (srednji mlaz urina) kod žena, ili >10^4 kod muškaraca – komplikovana infekcija urinarnog trakta.

Najčešći uropatogen je *E.coli*, prisutna kod 70-95% infekcija donjeg urinarnog trakta, odnosno kod 50-60% ako su u pitanju infekcije gornjeg urinarnog trakta. Zatim *Staphylococcus, Proteus, Klebsiella, Enterococcus faecalis*.

Ranije pomenuta rezistencija *E. coli*, kao najčešćeg uropatogena, predstavlja sve veći problem. Na tabeli 1 vidi se zastupljenost rezistentnih sojeva *E. coli* po pojedinim regionima.

Tabela 1. Zastupljenost rezistentnih sojeva *E. coli* po pojedinim regionima

U svakodnevnoj kliničkoj praksi kriterijumi za postavljanje dijagnoze su: klinički simptomi, laboratorijske analize (krv, urin, prostatični eksprimat), zatim dokazano prisustvo mikroorganizama (UK, specifični testovi), naravno uz poštovanje standarda uzimanja i obrade uzoraka.

Svakako najčešća urinarna infekcija je upala mokraćne bešike – *cystitis*. Kao klinički entitet sreće se isključivo kod žena. Simptomatologija, ranije navedena: učestali nagon na mokrenje, osećaj pečenja i bola pri mokrenju, pritisak, odnosno bol u donjem delu trbuha se dosta lako prepoznaju i od strane samog pacijenta.

Neretko se lečenje cistitisa sprovodi od strane lekara primenom rezervnih antibiotika (cefalosporini II i III generacije, fluorohinoloni) , a u trajanju od 7 dana, nekada i duže.

Danas se zna da je terapija cistitisa u trajanju od 3 dana (*short term*) podjednako efikasna. Često i *single dose* terapija, odnosno jednokratna primena antibiotika, može da dovede do izlečenja.

Što se odabira antibiotika tiče, opšti stav je da bi trebalo izbegavati rezervne antibiotike. Najnoviji stav Evropskog udruženja urologa je primena fosfomicina 3gr jednokratno, zatim nitrofurantoin 2x100mg tokom 5 dana, pivmecillinam 3x400mg tokom 3 dana, kao terapijske opcije prve linije. Ova preporuka se bazira na njihovoj visokoj efikasnosti, retkoj rezistenciji uzročnika na ovaj antibiotik, retkim neželjenim efektima i prihvatljivoj ceni. Nije za zanemarivanje i visoka komplijansa pacijenata na ordiniranu terapiju, pre svega u slučaju fosfomicina, zbog jednokratnog doziranja.

Takođe, najnoviji vodiči Evropskog i Američkog udruženja urologa izričito navode potrebu za ograničenom upotrebom antibiotika, prevashodno fluorohinolona i cefalosporina kod nekomplikovanih infekcija i asimptomatske bakteriurije. Terapija asimptomatske bakterijurije je indikovana u trudnoci. Takođe je obavezna kod intervencija na urogenitalnom traktu uz moguće otvranje mukoze. Skrining na asimptomatski bakterijuriju u trudnoći treba planirati između 12 i 16 nedelje gestacije.

Literatura

1. European Association of Urology, Guidelines, 2015 edition.
2. Lecompte F, et al. Single dose treatment of cystitis with fosfomycin trometamol (monuril): analysis of 15 comparative trials on 2048 patients. Giorn It Ost Gin. 1997;19: 399-404.
3. Warren JW, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acutenpyelonephritis in women. Infectious Disease Society of America (IDSA). Clin Infect Dis. 1999;29(4):745-58.
4. Rubin RH, et al. Evaluation of new anti-infective drugs for the treatment of urinary tract infections. Infectious Diseases Society of America and the Food and Drug Adminisatration. Clin Infect Dis. 1992;15(Suppl 1):S216-227.

Rođena 1967. godine u Beogradu, gde je završila osnovnu i srednju školu, kao i medicinski fakultet. Od 1995. godine zaposlena na Klinici za ginekologiju i akušerstvo Kliničkog centra Srbije. Specijalista ginekologije i akušerstva od 1997. godine, magistar i doktor medicinskih nauka. U zvanje docenta na Medicinskom fakultetu u Beogradu izabrana 2017. godine. Član je Konzilijuma za ginekološku onkologiju i načelnik II hirurškog odeljenja Klinike za ginekologiju i akušerstvo KCS.

MÜLLERIAN DUCT ANOMALIES – DIAGNOSTIC PROCEDURES

Prof. Aleksandra Dimitrijević

Director of Clinic for Gynecology and Obstetrics, Clinical Center Kragujevac
School of Medical Sciences, University of Kragujevac, Serbia

Congenital (congenital) malformations of the uterus are structural defects that occur during embryonic development that are present at birth. When they exist as isolated defects, they can significantly reduce the reproductive potential, and in complex cases, especially if they are associated with obstructive anomalies of the vagina, they can also seriously endanger a woman's health.

The exact diagnosis of congenital anomalies of the uterus and their differentiation was in the past, and so it is today, a controversial area both because of the limitations of certain diagnostic methods and because of disagreements over diagnostic criteria.

Congenital malformations of the uterus are structural defects that occur during embryonic development that are present at birth and they are the result of errors in the formation, differentiation, fusion and / or resorption of Müller (paramesonephric) canals.

The incidence of Müller-type anomalies in the general population has not been precisely determined, and in numerous studies conducted so far it has varied in a very wide range from 0.06% to as many as 38% of women.

The arcuate uterus is the most common anomaly in the general population, and the septate uterus is the most common in the population of subfertile women.

The importance of detecting and classifying anomalies of the Müller tract lies in the fact that these are structural defects of the wall and cavity of the uterus that change its shape to such an extent that they can be a potential cause of numerous reproductive problems.

In modern clinical practice, sonohysterography (SHG), three-dimensional transvaginal ultrasound (3D TVS ultrasound) and hystero-laparoscopy (simultaneous application of hysteroscopy and laparoscopy) are used with the greatest success in the diagnosis of uterine anomalies. 3D ultrasound devices in the analysis of the structure of the uterus is becoming more frequent, especially when it comes to newer generation devices, which do not lag behind in accuracy in terms of MR.

References

1. Bhagavath B, Ellie G, Griffiths KM, Winter T, Alur-Gupta S, Richardson C, Lindheim SR. Uterine Malformations: An Update of Diagnosis, Management, and Outcomes. Obstet Gynecol Surv. 2017 Jun;72(6):377-92.
2. Li Y, Phelps A, Zapala MA, MacKenzie JD, MacKenzie TC, Courtier J. Magnetic resonance imaging of Müllerian duct anomalies in children. Pediatr Radiol. 2016 May;46(6):796-805.
3. Friedman MA, Aguilar L, Heyward Q, Wheeler C, Caldamone A. Screening for Mullerian anomalies in patients with unilateral renal agenesis: Leveraging early detection to prevent complications. J Pediatr Urol. 2018 Apr;14(2):144-9.
4. DI Spiezio Sardo A, Spinelli M, DA Cunha Vieira M, Zizolfi B, Nappi C, Bifulco G. Hysteroscopic treatment of Müllerian duct anomalies. Minerva Ginecol. 2016 Apr;68(2):175-85.

Prof. Dr Aleksandra Dimitrijević, rođena je u Kragujevcu, 1970. Medicinski fakultet Univerziteta u Beogradu završila je 1996. god.

Magistarsku tezu odbranila na Fakultetu medicinskih nauka u Kragujevcu 2005. god, a doktorsku disertaciju na istom fakultetu 2010. god. Od 2017. god na Fakultetu medicnskih nauka Univerziteta u Kragujevcu vanredni je profesor za užu naučnu oblast Ginekologija i akušerstvo. Od 1998. god zapošljena u Klinici za ginekologiju i akušerstvo KC Kragujevac, specijalizaciju iz Ginekologije i akušerstva završila na Medicinskom fakultetu Univerziteta u Beogradu 2003. god.

Trenutno na funkciji direktora Klinike za Ginekologiju i akušerstvo od oktobra 2015. god.

Autror je više radova od međunarodnog i nacionalnog značaja.

PATIENT BLOOD MANAGEMENT IN OBSTETRICS AND GYNECOLOGY

Prim. Ljubinka Nikolić

Head of department of internal medicine and hematologic laboratory with transfusiology

Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Serbia

Blood transfusion (BT) has changed mortality rate rapidly and nowhere is that change seen more clearly than in Obstetrics and Gynecology. In the era before BT mortality rate in postpartal hemorrhage women (PPH) was ≈50-60%, and after introducing BT mortality rate decline to <5 /100 000 live births. Considering tese data, BT is life-saving procedure, and, by WHO Blood Transfusion has been identified as one of the 8 essential components for reducing maternal mortality rate in PPH. Beside positive effects of BT, physicians reported adverse reactions to blood transfusion, and based on reporting data was created Hemovigilance reporting system in each country. National Hemovigilance Systems are part of International Hemovigilance Network (IHN). The task of these systems is to collect and assess information on unexpected effects, with aims to identify critical steps in transfusion practice and to target areas for improvement. Transfusion is a complex multistep process. Precisely, process from donor to patient is described in 282 steps of which 72 belong to Blood Services and 210 to Hospital Blood Banks. At each of these steps mistakes may be made that can lead to adverse reactions. The most frequently reactions are due to administration of Whole Blood (WB) or Packet RBC which contain both plasma and WBC. Analyzing reporting data by IHN it was concluded that the majority of reactions has caused by plasma proteins and by content of leukocyte. Administration of leucodepleted RBC component significantly has been reduced nonhemolytic transfusion reactions. To improve safety of patients, reporting of all adverse transfusion reactions is mandatory by the law (the EU legislation). Despite adverse reactions, over ordering of blood is a common practice for elective surgeries. Over ordering of blood has been assessed by ratio Crossmatch/Transfusion (C/T ratio). Optimal ratio is described as < 2.0. Considering high C/T ratio it was obviously that should find a mechanism to maximize usage of blood and minimize wastage. The first maximal surgical blood ordering schedule (MSBOS) was published in 1976. The goal of the MSBOS is to promote efficient use of blood. The majority of surgical procedures do not require crosshatch (xm), only to perform blood group and antibody screening - T&S (G&S). The MSBOS guidelines repeatedly shown to decrease unnecessary cross-matching and wastage of blood. Next activity in lowering C/T ratio is introducing the electronic crossmatch. The electronic crossmatch has now replaced the serologic crossmatch for the vast majority of patients who have had at least two negative samples for alloantibodies. The electronic crossmatch is major advance in transfusion medicine – called the remote electronic blood release system (EBRS). Of concern are the patients who have RBC-Ab potentially difficult to crossmatch. Such patients are at risk for having a surgical start before enough blood is available. Operative environment such as recently developed surgical procedures, hemostatic drugs and preoperative conditions of patients can change; therefore MSBOS should be evaluated regularly, according to the changes. MSBOS decrease delays in starting surgical cases, decrease excess ordering of laboratory tests and helps in the decision of ordering and transfusing blood which reduces blood wastage. In one word:MSBOS promotes the goals of Patient Blood Management programs (PBM).

The term PBM was first used in 2005 by Professor James Isbister, an Australian hematologist, who realized that the focus of transfusion medicine should be changed from blood products

to the patients. PBM is a multimodal, multidisciplinary patient-centered approach adopted to minimize the use of allogeneic blood components with the aim of improving clinical outcomes of patients. The first attempt to minimize the use of allogeneic blood in elective surgery is Autologous Blood Donation. PBM has three main objectives (pillars): 1) improving red cell mass, including pharmacological correction such as erythropoiesis-stimulating agents (ESA) and iron and vitamin supplements and time surgery with optimization of Hb 2) minimizing blood loss by optimizing surgical and anesthetic techniques, treatment with tranexamic acid (TXA) and autologous blood salvage; and 3) optimizing the tolerance of anemia by promoting maximum pulmonary and cardiac function, optimize ventilation, optimize oxygenation and the use of a restrictive transfusion threshold. The last published is: Patient blood management in obstetrics: prevention and treatment of postpartum hemorrhage. A NATA consensus statement (2019). This Consensus was created in collaboration of the: NATA (Network for the Advancement of Patient Blood Management, Hemostasis and Thrombosis), FIGO (International Federation of Gynecology and Obstetrics), EBCOG (European Board and College of Obst. and Gynaec.) ESA (European Society of Anesthesiology). According to this consensus: It is recommended to optimize Hb during the antenatal period with Oral Iron in first and second trimester, and with IV iron if oral iron is not tolerated (>14 gestation week). In 3rd trimester is recommend the administration of IV iron to cover individually calculated total iron deficiency at Hb level 60-90 g/L. In PPH Blood type should be identified and antibody screening should be performed, and the blood bank should be contacted if bleeding is not rapidly controlled. It is recommended the administration of tranexamic acid (1 g by intravenous route) as soon as possible within the first 3 hours after PPH onset. This dose can be repeated after 30 min if bleeding continues (WOMAN Trial). Once the hemorrhagic episode is controlled, women should receive intravenous iron for the treatment of moderate-to-severe post partal anemia (PPA) (Hb 60-90 g/L). IV iron has proved to be effective in obstetric hemorrhage, in association with other surgical and medical therapies (TXA) in reducing blood loss and the need for allogeneic blood transfusions. PPH management protocols must include the immediate issue of group O, RhD-negative and K-negative RBC units. In blood banks, by blood bank policy, is O-ccddee K- RBC always available. Unfortunately, O- K- blood is not compatible in all patients. In this situation, it is essential to perform extended erythrocyte phenotyping for Rh (CcDEe), Dufy (Fya,Fyb) , MNSs, Kidd (Jka,Jkb) blood group system. Extended erythrocyte phenotyping is needed for: women who are candidates for monoclonal antibody therapy (CD20, C38, CD47, Mabtera, Dorzalex) and kidney transplantation, for women with RBC antibodies, and for pregnant women who are candidates for Intra Uterine Transfusion. Administration of Compatible phenotyped blood according to patient pfenotype doesn't mean the same blood group, but Blood Group with minimal risk of sensitization and adverse reactions for particular patient. This is a real Personalized Therapy. In an era of cost reduction and pressure to reduce tests and procedures that are not beneficial to patient care, PBM is an important approach. Furthermore, by standardizing care and reducing unnecessary testing and costs, this change in practice are according to the goals of campaign Choosing Wisely.

Avoid transfusion whenever is possible; Use all types of autologous transfusion when the patient's clinical condition allows; Use pharmacological ESA (Fe, B12, Folic acid, EPO), to correct anemia; Use pharmacological agents to control bleeding (Tranexamic acid, Desmopresin); Optimize surgical and anesthetic techniques. Mandatory transfuse at Hb level <60 g/L, and always use leukodepleted blood components.

References

1. Muñoz M, Stensballe J, Ducloy-Bouthors AS, Bonnet MP, De Robertis E, Fornet I, Goffinet F, Hofer S, Holzgreve W, Manrique S, Nizard J, Christory F, Samama CM, Hardy JF. Patient blood management in obstetrics: prevention and treatment of postpartum haemorrhage. A NATA consensus statement. Blood Transfus. 2019 Mar;17(2):112-136.
2. Franchini M, Liumbruno GM. Implementation of a patient blood management programme in obstetrics: let's do it! Blood Transfus. 2019 Mar;17(2):87-88.
3. Zdanowicz JA, Surbek D. Patient blood management in obstetrics - Review. Transfus Apher Sci. 2019 Aug;58(4):412-415.
4. Althoff FC, Neb H, Herrmann E, Trentino KM, Vernich L, Füllenbach C, Freedman J, Waters JH, Farmer S, Leahy MF, Zacharowski K, Meybohm P, Choorapoikayil S. Multimodal Patient Blood Management Program Based on a Three-pillar Strategy: A Systematic Review and Meta-analysis. Ann Surg. 2019 May;269(5):794-804.
5. Abraha I, Montedori A, Di Renzo GC, Angelozzi P, Micheli M, Carloni D, Germani A, Palmieri G, Casali M, Nenz CMG, Gargano E, Pazzaglia M, Berchicci L, Tesoro S, Epicoco G, Giovannini G, Marchesi M; Umbria PBM Group. Diagnostic, preventive and therapeutic evidence in obstetrics for the implementation of patient blood management: a systematic review protocol. BMJ Open. 2018 Oct 15;8(10):e021322.

Ljubinka Nikolić – born 3 September 1958.

Education: 2018 - PhD Thesis in progress: „Inflammatory response after the preterm delivery in women with inflammatory parodontal diseases", School of Medicine, University of Belgrade; 2016 – Subspecialization in clinical transfusiology, School of Medicine, University of Belgrade; 2001 - Master's Degree: „Evaluation of the single trophoblastic markers in diagnosis of germ line malignant tumors of testis", School of Medicine, University of Belgrade; 2000 – received the honor of primarius MD; 1993 – specialization in transfusiology, School of Medicine, University of Belgrade; 1977-1983: graduate studies in medicine, School of Medicine, University of Belgrade.

Positions: 2001 – Head of the Laboratory for Hematology and Transfusion, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia; 1988 – 2001 – Laboratory for Hematology, National Institute for Oncology and Radiology of Serbia; 1987 – National Institute for Transfusiology of Serbia.

Languages: English, Romanian and Russian in conversation.

Membership in scientific and other organizations: Serbian Medical Society (Transfusiology Department and Clinical Pharmacology Department); European Society for Medical Oncology; International Society for Blood Transfusion; Serbian society for Thrombosis and Haemostasis.

PREKANCEROZNE LEZIJE GRLIĆA MATERICE

Tanja Milić-Radić

Klinika za ginekologiju i akušerstvo
Univerzitetski klinički centar Republike Srpske

Cervikalna intraepitelna neoplazija (CIN) predstavlja prekancerogenu promjenu na grliću materice, koja vremenom može prijeći u karcinom grlića materice. Prema Svjetskoj zdravstvenoj organizaciji cervikalne intraepitelne neoplazije dijele se na 3 stepena. CIN najčešće nastaje kao posljedica infekcije HPV virusom, koja se prenosi polnim putem. Ukoliko PAPA test otkrije prisustvo abnormalnih ćelija na grliću materice, sljedeća pretraga koju je potrebno uraditi jeste HPV tipizacija, kolposkopija i u zavisnosti od kolposkopskog nalaza pristupa se daljem liječenju po protokolu za premaligne lezije.

Cilj rada je prezentovanje dijagnostikovanih premalignih lezija, cervikalne intraepitelne neoplazije, u jednogodišnjem periodu u Klinici za ginekologiju i akušerstvo (KGA) Univerzitetskog kliničkog centra Republike Srpske (UKC RS).

U KGA UKC RS provedena je retrospektivna studija o učestalosti CIN lezija tokom 2018. godine koja je obuhvatila 282 žene, kod kojih je histopatološki verifikovano prisustvo premaligne lezije. Korišteni su podaci iz operacionog protokola KGA UKCRS, te Zavoda za patologiju UKCRS (PH nalaz). Ispitanice su podijeljene u odnosu na starosnu dob u sledeće grupe: 20-29 god, 30-39 god, 40-49 god, 50-59god, te >60 godina, te u odnosu na stepen displazije CIN I, CIN II i CIN III.

Kod ukupno 282 pacijentkinje utvrđen je jedan od tri stepena CIN lezija. Kod 162 pacijentkinje ili 57,45% je dijagnostikovan CIN I, kod 63 pacijentkinje ili 22,37% je dijagnostikovan CIN II, a kod 57 pacijentkinja ili 20,20% je dijagnostikovan CIN III. Prema navedenim podacima, CIN 1 lezija se u posmatranom periodu najčešće javljala u starosnoj dobi 40-49 godina, CIN II u starosnoj dobi 30-59 godina, a CIN III u starosnoj dobi 30-39 godina.

Postoji značajan porast broja dijagnostikovanih prekanceroznih lezija, u poređenju sa prethodnim periodom, što može biti posljedica učinkovitijih dijagnostičkih procedura, s obzirom da je u UKC RS uvedena i HPV tipizacija kao dijagnostička procedura. Uvođenje novih dijagnostičkih procedura u vidu primjene biohemijskih markera za detekciju prekanceroznih lezija iz PAP-a brisa moglo bi olakšati donošenje odluke o terapiji. Potrebno je sprovođenje organizovanog plana za prevenciju karcinom grlića materice, koji bi kroz određeni vremenski period imao za cilj njegovu eradikaciju.

INFERTILITY & IVF

OHSS: PREVENCIJA I TRETMAN

Prof. Snežana Vidaković

Načelnik odeljenja minimalno invazivne hirurgije i odeljenja asistirane reproduktivne tehnologije,
Klinika za ginekologiju i akušerstvo, Klinički Centar Srbije
Medicinski fakultet, Univerzitet u Beogradu, Srbija

Sindrom ovarijalne hiperstimulacije jeste najteža komplikacija in vitro fertilizacije. Iako poznat od uvođenja ove procedure u lečenje infertiliteta, zbog svoje težine i životne ugroženosti pacijentkinja, zaslužuje stalnu pažnju. Svaka pacijentkinja, bez faktora rizika, može razviti OHSS jer hiperstimulacija postoji u svakom protokolu stimulacije.

Patofiziološke promene posledica su oslobađanja vazoaktivnih substanci iz hiperstimulisanih jajnika (28). To dovodi do ekstravazacije tečnosti iz vaskularne mreže u treći prostor sa posledičnom hipovolemijom, hemokoncentracijom, smanjenom perfuzijom organa i hiperkoagulabilnim stanjem. hCG se smatra ključnim medijatorom za nastanak patofizioloških promena (3). „Rani“ OHSS nastaje kao posledica egzogenog hCG-a kao trigera, a „kasni“ oblik nastaje kao posledica endogenog hCG-a iz trofoblasta (24).

hCG posreduje u oslobađanju vaskularnog endotelijalnog faktora rasta (VEGF) koji povećava permeabilnost krvnih sudova. Drugi mehanizam koji se uključuje u nastanak OHSS-a je aktivacija ovarijalnog sistema renin-angiotenzin (RAS) od strane hCG-a. RAS je uključen u regulaciju vaskularne permeabilnosti, oslobađanje prostaglandina, angiogenezu i proliferaciju endotela (1,26).

Promene su klasifikovane u 4 stadijuma u zavisnosti od težine simptoma. Blagi oblik OHSS-a praćen je lakšim osećajem nelagodnosti, blagom dispnejom, uvećanjeem jajnika i eventualno mučninom i dijarejom, bez značajnih laboratorijskih pomeranja. U srednje teškom obliku se javlja leukocitoza i hematokrit >41% sa pojavom ascitesa. U trećem stadijumu teškog oblika OHSS-a se javlja i hidrotoraks, teška dispneja, oligo/anurija, venska tromboza, sinkopa, sa daljim pogoršanjem laboratorijskih nalaza i povišenjem enzima jetre. Kritični stadijum podrazumeva pojavu anurije sa akutnom bubrežnom insuficijencijom, aritmiju, tromboembolijske komplikacije, efuziju perikarda i sepsu sa daljim pogoršanjem laboratorijskih analiza.

Za rešavanje svakog problema ili komplikacije bitno je prepoznavanje pacijentkinja u visokom riziku za njen nastanak, kako se može predupredi i kakav je terapijski pristup.

Prepoznavanje rizične grupe pacijentkinja za nastanak OHSS-a je bitan preduslov za smanjenje šansi za nastanak komplikacije. Značajno visok rizik pokazuju žene sa PCOS, mlađe pacijentkinje sa niskim BMI (60% < 35 godina), kao i žene sa prethodnim OHSS-om (14). Žene crne rase takođe pokazuju češću pojavu OHSS-a. Pokazatelji ovarijalne rezerve, koje procenjujemo pre uvođenja žene u proceduru, je sledeći parametar koji ukazuje na postojanje povišenog rizika. U proceni se rukovodimo vrednostima anti-mullerian hormona (AMH) i brojem antralnih folikula (AFC). Cut-off za AMH od 3,36 ng/ml se pokazao kao dobar prediktor rizika. U više studija je pokazano da je AMH pouzdaniji od godina starosti i BMI (11,13). Drugi pokazatelj, sličnog stepena pouzdanosti kao AMH, je broj antralnih folikula (27). Iskustva su pokazala da je veći broj folikula od 24 u korelaciji sa pojavom OHSS-a (8,6% vs 2,2%). Ovarijalni odgovor takođe ukazuje na prisustvo povećanog rizika. U praćenju ovarijalnog odgovora procenjujemo broj rastućih folikula i vrednosti estradiola u serumu. Multifolikularni razvoj se ponaša kao nezavisan pokazatelj u predikciji OHSS-a. Više od 25 folikula u razvoju ukazuje na povećan rizik, kao i veliki broj aspiriranih ćelija ≥24. Koncentracija

estradiola u serumu je značajno povezana sa rizikom od OHSS-a. Srednja vrednost estradiola kod pacijentkinja sa hiperstimulacijom je u publikovanim studijama iznosila >3.500 pg/ml.

Analiza protokola sa GnRH agonistima ili antagonistima je pokazala značajnu prednost antagonista. Nastanak teških oblika OHSS-a je značajno manja u grupi antagonista u odnosu na agoniste (5,1 vs 8,9), a bez uticaja na stopu živorođenosti. Verovatno objašnjenje je u redukciji estradiola u cirkulaciji kod protokola sa antagonistima.

Zbog povišene aktivnosti vaskularnog endotelijalnog faktora rasta (VEGF) pod uticajem hCG-a povećana je aktivnost trombocita i oslobađanje vazoaktivnih substanci koje dodatno potenciraju vazodilataciju i kapilarni permeabilitet. Poznavajući ove činjenice u prevenciju je uključen aspirin koji može da ublaži ove promene. Studije su pokazale da aspirin pokazuje povoljan efekat kada se koristi u dozi od 100mg od prvog dana stimulacije sam ili u kombinaciji sa prednizolonom (10-30 mg) (7).

Kao efikasan lek u prevenciji hiperstimulacije se pokazao metformin. Smanjujući intraovarijalni hiperandrogenizam metformin smanjuje broj ne-periovulatornih folikula i na taj način redukuje sekreciju estradiola (17). Jedna od prvih randomiziranih studija koja je ispitivala uticaj metformina pokazala je značajno smanjenje pojave OHSS-a (3,8% vs 20,4%). Isti efekat su potvrdile druge studije bez uticaja na stopu trudnoća, živorođenosti ili spontanih pobačaja (16). Takođe je pokazano da metformin ne utiče na hiprstimulaciju kod mršavih žena. Za najbolji efekat je preporučena doza metformina od 1000-2000 mg dnevno dva meseca pre početka stimulacije.

Pokušaj da prekidom davanja gonadotropina kod najave OHSS-a (coasting) nije pokazao uspeh. Zaustavljanje stimulacije dovodi do smanjenog broja aspiriranih oocita bez efekta na hiperstimulaciju (15,21).

Završna maturacija oocita se najčešće postiže davanjem hCG-a koji imitira preovulatorni LH skok. Modifikacija doze i davanje 5.000 IJ umesto 10.000 IJ nije pokazala staistički značajnu razliku u pojavi OHSS-a. Promena trigger-a i upotreba GnRH agonista za završnu maturaciju je pokazala statistički značajnu razliku u pojavi hiperstimualcije (19). Više studija je pokazalo da primena agonista kao trigger-a skoro potpuno eliminiše pojavu OHSS-a.

Obzirom da se koloidni rastvori vezuju i deaktiviraju vazoaktivne substance odgovorne za nastanak OHSS-a, u prevenciji je predložena primena infuzija albumina. Drugi mehanizam koji može biti od pomoći je što albumin povećava onkotski pritisak u vaskularnoj mreži što smanjuje prelazak tečnosti u treći prostor i hipovolemiju. Studije nisu dokazale pozitivan efekat albumina uz postojanje rizika za prenos virusnih infekcija kao što su hepatitis ili HIV ili mogućnost anafilakse (29). Hidroksietil skrob (HES) (Voluven) je nejonski derivat skroba koji je predložen kao alternativa. Zbog brojnih neželjenih efekata povučen je iz upotrebe u EU odlukom EMA 2018. godine.

Kabergolin je lek koji se potvrdio u prevenciji OHSS-a. Deluje kao antagonista dopamina i značajno smanjuje vaskularni permeabilitet. Efekat je potvrđen kod umerenih oblika OHSS-a ali ne i kod teških (30). Uključivanje kabergolina se preporučuje od dana trigger-a u dozi od 0,5 mg u toku 8 dana.

Isptivanja ukazuju da kalcijum inhibira sekreciju RAS-a i posledično smanjuje aktivnost VEGF kao jednog od ključnih medijatora u OHHS-u. Studije su rađene sa primenom 10% kalcijum glukonata, 10 ml u 200 ml normalnog fiziološkog rastvora i rezultati su pokazali povoljan efekat na pojavu OHSS-a u odnosu na primenu samo standardnog fiziološkog rastvora (23% vs 7%). Druge studije su pokazale da je kalcijum efikasan u prevenciji isto kao i kabergolin (26,29).

Klinička primena „freeze all" protokola je započela pre 15-ak godina da bi se odložila eventualna trudnoća i izbegao kasni oblik OHSS-a. Podaci pokazuju da su rezultati uspeha IVF (stopa implantacije, kliničkih trudnoća i živorođenosti) iste, ako ne i bolje po jednom broju studija (31).

Kombinacija protokola sa antagonistima, GnRH agonistom kao trigger—om i „freeze all" protokola danas predstavlja metodu izbora za pcijentkinje u visokom riziku za nastanak OHSS. Ovaj „segmentisani" pristup skoro u potpunosti eliminiše pojavu hiperstimulacionog sindroma (32).

Simptomatski OHSS srednjeg i teškog stepena predstavljaju stanje hipovolemije i hiponatremije sa posledičnim promenama homeostaze u organizmu. Obavezna je nadoknada tečnosti da bi se održala normalna perfuzija. Teška hipovolemija je praćena visokim rizikom za nastanak tromboembolizma pa je obavezna antikoagulantna terapija (33). Paracenteza, jednokratna ili ponavljana, se pokazala kao dobar pristup u tretmanu OHSS-a.

Literatura

1. Herr D,Bekes I,C. Wulff C. Local Renin-Angiotensin system in the reproductive system. Frontiers in Endocrinology. 2013;4:50.
2. Schwentner L, Wockel A,Herr D,Wulff C. Is there a ¨ role of the local tissue RAS in the regulation of physiologic and pathophysiologic conditions in the reproductive tract? Journal of the Renin-Angiotensin-Aldosterone System. 2011;12(4):385-93.
3. Nastri C.O,Teixeira D.M,Moroni R.M,Leitao V.M,Martins W-P. Ovarian hyperstimulation syndrome: pathophysiology, staging, prediction and prevention. Ultrasound in Obstetrics & Gynecology. 2015;45(4):377-93.
4. Goldsman M.P,Pedram A,Dominguez C.E,Ciuffardi I,Levin E,Asch R.H. Increased capillary permeability induced by human follicular fluid: a hypothesis for an ovarian origin of the hyperstimulation syndrome, Fertility and Sterility. 1995;63(2):268-72.
5. Tollan A,Holst N,Forsdahl F,Fadnes H.O,Oian P,Maltau J.M. Transcapillary fluid dynamics during ovarian stimulation for in vitro fertilization, The American Journal of Obstetrics and Gynecology. 1990;62(2):554-8.
6. Bates D.O, Harper S.J. Regulation of vascular permeability by vascular endothelial growth factors, Vascular Pharmacology. 2002;39(4-5):225–3.
7. Naredi N, Talwar P, Sandeep K. VEGF antagonist for the prevention of ovarian hyperstimulation syndrome: current status, Medical Journal Armed Forces India. 2014;70(1):58-63.
8. Schwentner L, Wockel A, Herr D, Wulff C. Is there a ¨ role of the local tissue RAS in the regulation of physiologic and pathophysiologic conditions in the reproductive tract? Journal of the Renin-Angiotensin-Aldosterone System. 2011;12(4):385-93.
9. ASRM, Ovarian hyperstimulation syndrome. Fertility and Sterility. 2008;90(5), suppl:S188-S193.
10. Joint SOGC-CFAS Clinical Practice Guideline, The diagnosis and management of ovarian hyperstimulation syndrome. Journal of Obstetrics and Gynaecology Canada. 2011;2068:1156-62.
11. Dewailly D, Andersen C.Y, Balen A et al. The physiology and clinical utility of anti-Mullerian hormone in women. Human Reproduction Update. 2014;20(3):370–85.
12. Orvieto R. Ovarian hyperstimulation syndrome- an optimal solution for an unresolved enigma. Journal of Ovarian Research. 2013;6(1):77.
13. Aflatoonian A,Oskouian H,Ahmadi S,Oskouian L. Prediction of high ovarian response to controlled ovarian hyperstimulation: anti-Mullerian hormone versus small antral ¨ follicle count (2–6 mm). Journal of Assisted Reproduction and Genetics.2009;26(6):319-25.
14. Papanikolaou E.G,Humaidan P,Polyzos N.P,Tarlatzis B. Identification of the high-risk patient for ovarian hyperstimulation syndrome. Seminars in Reproductive Medicine. 2010:28(6):458-62.
15. Revelli A,Casano S, Salvagno F,Delle Piane L. Milder is better? advantages and disadvantages of 'mild' ovarian stimulation for human in vitro fertilization. Reproductive Biology and Endocrinology. 2011;9:25.
16. Elia E.M,Quintana R,Carrere C. Metformin decreases the incidence of ovarian hyperstimulation syndrome: an experimental study. Journal of Ovarian Research. 2013;6(1):62.
17. El-Faissal Y. Approaches to complete prevention of OHSS. Middle East Fertility Society Journal. 2014:19(1):13-5.
18. Franik S, Kremer J.A, Nelen W.L, Farquhar C. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. Cochrane Database of Systematic Rev. 2014;2:Article ID CD010287.
19. Kol S, Humaidan P. GnRH agonist triggering: recent developments. Reproductive BioMedicine Online. 2013;26(3):226-30.
20. Fatemi H.M,Popovic-Todorovic B,Humaidan P. Severe ovarian hyperstimulation syndrome after gonadotropinreleasing hormone (GnRH) agonist trigger and 'freeze-all' approach in GnRH antagonist protocol. Fertility and Sterility. 2014;101(4):1008-11.

21. D'Angelo A,Brown J,N.N. Amso. Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome. Cochrane Database of Systematic Reviews. 2011;2(6):Article ID Cd002811.
22. D'Angelo A. Ovarian hyperstimulation syndrome prevention strategies: cryopreservation of all embryos. Seminars in Reproductive Medicine. 2010;28(6): 513-8.
23. Roque M. Freeze-all policy: is it time for that? Journal of Assisted Reproduction and Genetics. 2015;32(2):171-6.
24. Mathur RS, Akande AV, Keay SD, Hunt LP, Jenkins JM. Distinction between early and late ovarian hyperstimulation syndrome. Fertil Steril 2000;73:901-07.
25. Practice Committee of American Society for Reproductive Medicine. Ovarian hyperstimulation syndrome. Fertil Steril 2008;90:S188-S193
26. Herr D, Bekes I, Wulff C. Local Renin-Angiotensin system in the reproductive system. Frontiers in Endocrinology. 2013;4:150.
27. Jayaprakasan K, Chan Y, Islam, R. Prediction of in vitro fertilization outcome at different antral follicle count thresholds in a prospective cohort of 1,012 women, Fertility and Sterility, 2012;98(3):657-63.
28. Tummon I, Gavrilova-Jordan L, Allemand M.C. Polycystic ovaries and ovarian hyperstimulation syndrome: a systematic review. Acta Obstetricia et Gynecologica Scandinavica,2005;84(7):611-6.
29. Youssef M.A, Al-Inany H.G, Evers J.L, Aboulghar M. Intra-venous fluids for the prevention of severe ovarian hyperstimulation syndrome. Cochrane Database of Systematic Reviews, 2011;(2):Article ID CD001302.
30. Leitao V.M.S, Moroni R.,Seko L.M.D, Nastri C.O, MartinsW.P. Cabergoline for the prevention of ovarian hyperstimulation syndrome: systematic review and meta-analysis of randomized controlled trials. Fertility and Sterility, 2014;101(3):664-75.
31. Aflatoonian A, Oskouian H, Ahmadi S, Oskouian L. Can fresh embryo transfers be replaced by cryopreservedthawed embryo transfers in assisted reproductive cycles? A randomized controlled trial. J Assist Reprod Genet. 2010;27:357-63.
32. Devroey P, Polyzos NP, Blockeel C. An OHSS-free Clinic by segmentation of IVF treatment. Hum Reprod. 2011;26:2593-7.
33. Rova K, Passmark H, Lindquist PG: Venous thromboembolism in relation to in vitro fertilization: an approach to determining the incidence and increase in risk in successful cyles. Fertil Steril. 2012:97:95-100.

FREEZE ALL STRATEGY – THE FUTURE OF IVF AND THE OPTION ACCEPTABLE DURING THE CORONAVIRUS PANDEMIC?

Prof. Vesna Kopitović

Ferona Fertility Clinic Novi Sad, European Center for Peace and Development (ECPD), Belgrade University for Peace Established by the United Nation, Serbia

Prof. Aleksandra Trninić Pjević[1], Assist. Prof. Stevan Milatović[2]

1 Gynecology Specialist Clinic "Ferona" Novi Sad
2 The Clinical Centre of Vojvodina, Clinic for Gynecology and Obstetrics, Novi Sad

The freeze-all (FA) strategy implies the elective cycle segmentation aimed at intentional segmentation of the IVF cycles into a single cycle in which the ovarian aspiration is carried out prior to initiating ovarian hyper stimulation, fertilization and cryopreservation of all obtained embryos without any intention of performing embryo transfer procedures in a stimulated cycle intended for subsequent cycles. This concept was first described and proposed as criteria for eliminating the risk of ovarian hyperstimulation syndrome development (OHSS) as one of the most dangerous entities of reproductive medicine and risk factors for developing OHSS in IVF cycles when GnRH antagonists can rapidly suppress LH levels, that can trigger final oocyte maturation in GnRH antagonist leading to elective all cryopreservation embryos and thus successfully prevent the development of OHSS without adversely affecting cumulative cycle outcome - a concept described as an OHSS Free Clinic through segmentation of IVF cycles by Devroey et al.

The objective of the present study is to evaluate the specifics for successful segmentation of IVF cycles by analyzing the relevant literature and surveying the prevailing attitudes, and trying to answer the question whether the use of in-vitro-fertilization in future should be the only option. Given that we are currently facing the coronavirus pandemic, we have also tried to provide an answer about patient acceptance of this concept and eventual deferred embryo transfer.

A literature review of traditional medicine research offers studies that deal with perinatal outcomes in IVF population showing discretely weaker parameters in terms of preterm birth and low birth weight compared with spontaneously conceived children, and the differences that persisted after excluding the influences of maternal characteristics. On the other hand, the first large-scale study on perinatal outcomes after FET procedures, such as the Nordic cohort study from the CoNARTaS group, found that children conceived by FET are at lower risk for having a low birth weight, very preterm birth, but at higher risk for postterm birth, fetal macrosomia and perinatal mortality rate, as compared to spontaneously conceived children and IVF children born after fresh embryo transfer. On the other hand, numerous studies have obtained superior perinatal outcomes of the FET cycle, as to which they approached and equated with spontaneously conceived pregnancies. In a recent meta-analysis of Zhao et al. on this particular topic, she concluded that perinatal outcomes after FET cycle were better compared with that after IVF-ICSI / ET. An analysis of 13 cohort studies including 126,911 women showed that in women conceiving after FAT cycle compared to those after IVF cycle there was a 14% higher risk for preterm birth, a 48% higher risk for low body weight, with no significant differences in stillbirth and perinatal mortality, while FET cycles were associated with higher caesarean section rates. Previously mentioned studies provide further evidence for the significance of non-physiological milieu in conventional stimulation not only for the receptivity of the endometrium, and the consequent negative impact on implantation,

but also for more subtle mechanisms of placentation and further pregnancy. The key problem in gaining wider acceptance of this concept is certainly the absence of studies which indiscriminately use this approach, since most studies were non-randomized and examined the safety aspect of this procedure in terms of OHSS prevention in a certain subpopulation of IVF patients.

Embryo cryopreservation with subsequent thawed embryo transfer is a reliable, safe, effective and a routine clinical procedure without which practice of IVF cannot be imagined today, and must be considered an integral part of in-vitro-fertilization and as such recognized by the financial control bodies responsible for financing the procedures. Segmented IVF cycles has proven to be reliable, safe, and efficient procedures in certain clinical situations that show promising results both in terms of the success rates across IVF cycles and perinatal outcomes. However, the circumstances in which this concept is routinely applied represent specific clinical situations. The non-selective application of this concept to all patients is currently not supported by adequate scientific evidence in accordance with the postulates of evidence-based medicine. The routine use of the FA concept as the "gold standard" for the future of IVF will certainly require further substantial research, adequately designed, prospective, randomized, and primarily relying on outcome parameters in terms of success and safety of the procedure expressed as live birth rate and better health outcomes for children. The new expectations for the ART procedure will also affect the development of this procedure. Thus, it would not be wrong to say that the basic expectation of IVF procedures is not only pregnancy but a healthy term infant, and that the fertilization with single euploid blastocyst transfer is considered by many to be a new IVF treatment paradigm to achieve this goal, whereas in the current constellation this is also achieved through cycle segmentation. Moreover, legal and ethical considerations will almost certainly follow, since in this concept of a genetically tested, frozen and only then embryo transfer, numerous dilemmas arise that go beyond well-known and unacceptable challenges, such as sex selection.

In addition to the previously specified economic indicators, cost-benefit analysis have yet to provide a basis for judgment on the cost-effectiveness of the proposed concept, as well as to respond to the numerous organizational, personnel and structural challenges that such a practice would produce. There is no doubt that the progress of ART in our environment, the introduction of PGS programs, as well as the development of oncofertility have set an adequate basis for mastering many challenges, but considering routine cryopreservation of all embryos and cycle segmentation, which has undoubtedly became standard in many centers, it requires recognition and refunding cryopreservation techniques as standard IVF treatment.

Given the conditions in our country, the coronavirus disease pandemic has undoubtedly contributed to the use of this strategy in all patients with inclusion criteria but less prone to the embryo transfer and anxious about entering pregnancy given the exceptional circumstances, such as those of Covid-19. In addition to the fear caused by possible negative effects on subsequent pregnancy outcomes which may have serious consequences for the fetus, and the medical justification for using the freeze - all strategy in all patients opting for it in the period of coronavirus disease, it has also been supported by the lack of sufficient literature on pregnancy and childbirth during corona and contracting COVID -19.

References

1. Roque M, Nuto Nóbrega B, Valle M, Sampaio M, Geber S, Haahr T, Humaidan P, Esteves SC. Freeze-all strategy in IVF/ICSI cycles: an update on clinical utility. Panminerva Med. 2019;61(1):52-7.
2. Roque M. Freeze-all policy: is it time for that? J Assist Reprod Genet. 2015;32(2):171-6
3. Maheshwari A, Bhattacharya S, Bowler U, Brison D, Child T, Cole C, et al. Study protocol: E-freeze - freezing of embryos in assisted conception: a randomised controlled trial evaluating the clinical and cost effectiveness of a policy of

freezing embryos followed by thawed frozen embryo transfer compared with a policy of fresh embryo transfer, in women undergoing in vitro fertilisation. Reprod Health. 2019;13;16(1):81.

4. Choucair F, Younis N, Hourani A. IVF laboratory COVID-19 pandemic response plan: a roadmap. Middle East Fertil Soc J. 2020;25(1):31.
5. Adiga SK, Tholeti P, Uppangala S, Kalthur G, Gualtieri R, Talevi R. Fertility preservation during the COVID-19 pandemic: mitigating the viral contamination risk to reproductive cells in cryostorage. Reprod Biomed Online. 2020; 15:S1472-6483(20)30518-6.

Prof. Vesna Kopitović, MD, PhD. Date and place of birth: 21.03.1966. Novi Sad, Vojvodina, Yugoslavia. Nationality: Serbian. Civil status: Female, married to Aleksandar, one son 29 years old.

MEDICAL SCHOOL: Faculty of Medicine, Novi Sad, University of Novi Sad, Medical doctor, MD (average mark 9, 73, max 10.0).

OB/GYN RESIDENCY: Department of Gynecology and Obstetrics, University Clinical Center, Novi Sad, Serbia.

QUALIFICATIONS: postgraduate studies at the Faculty of Medicine, University of Novi Sad, , 1990-1992, Group of Neuroendocrinology; specialist in Ob/Gyn since 1995; Master of Medical Sciences, 15.04.1994. University Novi Sad; PhD thesis in Sterility, 25.12.2004. PhD, University Novi Sad; Assiociate Professor Ob/Gyn, 2005; Specialist in Fertility and Sterility since 2006; Professor Ob/Gyn, 2014; 2012 - 2016 a member of the Government of the Autonomous Province of Vojvodina, as Ministry of Health, Social Policy and Demography, simultaneously employed at the Clinical Center of Vojvodina as a specialist obstetrician gynecologist.

MAJOR INTEREST: Infertility and ART, Endoscopic surgery.

EDUCATION – GRANT: Nominated in front of Scientific commite of ESGE for Educational Grant for 2004, donated by the Storz company. Spent three months in Italy in 2004, in Verona and Bari with Prof Steffano Bettocchi and Prof Luca Minelli. The education has been in the field of Gynecological Endoscopy. In 2008 completed the workshop „Train the Trainers“ in Leuven, Belgium in front of the EAGE president Dr Rudi Campo, and has completed several traininig courses in Europe with dr Yves Van Belle. Organizer of more than 50 Workshops, Symposiums and Congresses in Serbia through the continuing medical education, particularly in the field of gynecological endoscopy and the field of human reproduction. Organized and held training courses and practical work for more than 100 gynecologists at the University Clinical Center of Novi Sad in endoscopy field. Lecturer and invited speaker in Serbia and abroad for more than 80 events.

BIBLIOGRAPHY: Publications: 120; Book chapters: 10; Editor of the textbook 2; Mentor in 15 completed and defended graduate student work; Mentor in 10 Master thesis and 3 Doctoral dissertations; Projects: 9 (domestic and international); Erasmus plus from 2017 – 2020 “ART-REM ”.

THE INFLUENCE OF INFERTILITY ETIOLOGY AND INFERTILITY THERAPY ON GENETICS, EPIGENETICS AND FERTILITY OUTCOMES

Prof. Svetlana Spremović Rađenović

Head of department of gynecological endocrinology
Clinic for Gynecology and Obstetrics, Clinical Center of Serbia
School of Medicine, University of Belgrade, Serbia

About 10% of women in reproductive age face the problem of infertility. IVF/ICSI procedures contribute to 1.5% of all live births, while non IVF therapy procedures (ovulation induction or controlled hyperstimulation with or without IUI. contribute to about three times more neonates, in numbers 4,6%. (1). The risks for adverse outcomes in either IVF (2, 3) or non IVF fertility treatment procedures is increased (4). Preeclampsia is more frequent in both groups, gestational diabetes in anovulatory women, problems with placenta previa and placental abruption in IVF group, low birth weight in anovulatory women, maternal morbidity is increased in IVF group, especially linked with hemorrhage after delivery and placental problems. The common feature for all of these adverse outcomes are placental defects and disturbed placentation (5, 6, 7).

The most common causes of infertility are: PCOS which accounts for about 30-40 % of the total number of infertile women, followed by endometriosis, which accounts for about 27% and in the end, unexplained infertility, accounts for about 18%. Genetics and epigenetics of these diseases, together with influences of applied therapy, affect implantation, placentation and final outcome in relation to short term and long term consequences on mother and neonate (8).

There are a few candidate genes in PCOS women: LHCGR gen, critical for normal menstrual function, FSHR and INSR gens, which are related to reproductive hormone function and have been associated with metabolic syndrome and insulin resistance, potential cause for miscarriage and gestational diabetes in pregnancy (9, 10). A number of genes have been performed for endometriosis, with single nucleotide polymorphisms that lead to cell invasion, migration and implantation failure of trophoblast tissue. Epigenetic modifications: heritable alterations that result from non-coding mechanisms of gene regulation dependent from methylation of DNA and from enhancer and promotor regions: that means from regulatory patterns of gene expression.

Only 33% of embryos are implanted, and this is related, to some extent, to the etiology of infertility and is presented into the graph. The lowest rate of delivery is recorded in the patients suffering from endometriosis. Alterations in epigenome are recorded throughout the menstrual cycle and are related to hormonal variations. The data points to the substantial role of epigenome in endometrial function. Assays to study the receptive transcriptome during the window of implantation in IVF cycles, are created and linked with bioinformatics prediction analyses. Procedure makes possible to do personalized embryo transfer and has improved the outcomes from 33- 38 to 49-50% (11). Thus, other factors might be contributing to the failed implantation outcomes. Epigenetics of implantation could be related to the etiology of infertility, which was not considered in the assays. Some mi RNA, both in endometriosis and in PCOS, influence through pathways such is inflammation and hormone metabolism, both very important in mechanisms of implantation.

How does etiology of infertility influence on placentation? In women suffering from PCOS, hyperandrogenism and elevated lipid concentration reduced spiral arteries impedance, and

triggers the series of events which leads through defective placentation to small for date babies. In patients suffering from endometriosis imbalance of endocrine and inflammatory markers lead to defective placentation; consequences include preeclampsia, placenta previa, greater risk for preterm birth and postpartum hemorrhage. Unexplained infertility: variability in pregnancy outcomes is based in the allostatic load (a measure of chronic physiologic stress). Allostatic load is determined a priori from the body mass index(BMI), waist/hip ratio, systolic blood pressure, dehydroepiandrosterone sulfate, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, C reactive protein- homeostatic model assessment score is associated with increased risk of adverse effects in pregnancy and does not affect clinical pregnancy rate (12). It seems to be that epigenetic influence of fertility treatments on placentation is very present and important in IVF and non IVF fertility treatments. A sustained high hormonal environment in controlled superovulation cycles altered hormonal milieu in which trophoblastic function can be changed. Placenta could be reprogrammed, leading to sustained increased production of estradiol and progesterone from syncytiotrophoblast throughout all pregnancy. And also, altered hormonal milieu leads to early degenerative changes of trophoblast, tubulogenesis, dysfunction of tubular cells and altered placentation. In women with high risk for OHSS, all freeze technology with delayed embryo transfer is a big step forward, that has brought better treatment outcomes and higher delivery rate, and great relief for both, doctors and patients, from danger which OHSS brings to all. This procedure allows to pregnancy to begin in normal hormonal milieu, and if the embryo transfer (ET) is done in the presence of corpus luteum, the problems with implantation, miscarriage and latter preeclampsia are in great percentage overcome (13). Although GD has been commonly associated with PCOS, women with unexplained infertility have 45% greater risk for developing GD, comparable to risk of PCOS women, which is 52%.

Infertility etiology and maternal outcomes: Relative risk for tip 2 diabetes depends of habits, but in women suffering from gestational diabetes in pregnancy, doubles after 5 years from delivery and amounts 9.34. Although GD has been commonly associated with PCOS, women with unexplained infertility have 45% greater risk for developing GD, comparable to risk of PCOS women, which is 52%. Preeclampsia as the state of chronic inflammation, increases the risk of developing hypertension in pregnancy, which influence on hypertensive illness in later life. Hypertension in average, occurs 7,7 years earlier than in women without history of preeclampsia. Chronic inflammation per se produces oxidative stress, and is the risk factor for hyperlipidemia, the other promoting factor for hypertensive illness in later life.The risks for heart diseases, stroke and venous thromboembolism increases nearly two fold in women suffering from endometriosis. The risk of cardiovascular death is also two fold increased (14).

Hypo perfusion and oxidative stress in fetal life are the etiologic factors for low birth weight, and are etiologic factors for endothelial dysfunction in childhood (15). In the young individuals born from IVF/ICSI procedures, antioxidant treatment improves nitric oxide bioavailability and vascular responsiveness in the pulmonary and systemic circulation accordingly, ART induced vascular dysfunction in young individuals is reversible and is subject of redox regulation better understanding of adverse outcomes will bring improvements.

Fertility treatment is aimed to achieve pregnancy- the delivery rate is the first measure of success

Successful outcome means healthy mother and healthy child.

Adverse outcomes are more frequently recorded in treated infertile women, but in absolute numbers, this risks are small

The knowledge about influence of genetics and epigenetics of infertility etiology and influences of treatment will help us to improve pregnancy outcomes.

References

1. Faddy MJ, Gosden MJ, Gosden RG, A demographic projection of the contribution of the assisted reproductive technologies to world population growth. Reproduc Biomed Online 2018;(36):455-58.
2. Jacson S Hong C, Wang ET, Alexander C, Gregory KD; Pisarska MD. Pregnancy outcomes in very advanced maternal age pregnancies: the impact of assisted reproductive technology. Fertil Steril 2015;103(1):76-80.
3. Qin J, Liu X, Wang H, Gao S. Assisted reproductive technology and the risk of pregnancy related complications and adverse pregnancy outcomes in singleton pregnancies- a metaanalysis of cohort studies. Fertili Steril. 2016;(105):73-85.
4. Wang ETRL, Ramos L, Vyas N, Bhasin G, Simmons CF, Pisarska MD. Maternal and fetal outcomes associated with infertility. J Matern Feftal Neonatal Med. 2018;20:1-4.
5. Wang ET, Oyimek JA, Greene N, Ramos L, Vyas N, Kilpatrick SJ, Pisarska MD. Impact on fertility treatment on severe maternal morbidity. Fertil Steril. 2016;106:423-426.
6. Kroener L, Wang ET, Pisarska MD. Predisposing factors to abnormal first trimester placentation and the impact on fetal outcomes SeminReprod Med 2016;34:27-35.
7. Zhao, L., Zheng, X., Liu, J. et al. The placental transcriptome of the first-trimester placenta is affected by in vitro fertilization and embryo transfer. Reprod Biol Endocrinol. 2019; 17:50.
8. Pisarska M, Chan LJ, Lawrenson K, Gonyales LT< Wang TE. Genetics and epigenetics of infertility and treatments to outcomes. J Clin Endocrinol Metabol. 2019; 104:1871-86.
9. Steiner, N., Ates, S., Shaulov, T. A comparison of IVF outcomes transferring a single ideal blastocyst in women with polycystic ovary syndrome and normal ovulatory controls. Arch Gynecol Obstet. 2020; 302:1479–86 .
10. Schulte MM, Tsai JH, Moley KH, Obesity and PCOS: The effects of metabolic derangements on endometrial receptivity at the time of implantation. Rep Sci. 2015: 22:6-14.
11. Sebastian-Leon1 P, Garrido N, Remohí J, Pellicer A, Diaz-Gimeno A. Asynchronous and pathological windows of implantation: two causes of recurrent implantation failure. Hum Rep. 2018; 33:626-35.
12. Riggan, K.A., Gilbert, A. & Allyse, M.A. Acknowledging and Addressing Allostatic Load in Pregnancy Care. J. Racial and Ethnic Health Disparities 2020.
13. . Wei D, Yu Y, Sun M, Shi Y, Sun Y, Deng X, Li J Wong Z, Zhao S, Zhang H, Legro SR, Chen ZJ. The effects of supraphysiological estradiol on pregnancy outcomes differes between women with PCOS and ovulatory women. J Clin Endocrinol Metab. 2018; 103:2735-42.
14. Banker M, Mehta V, Sorathiya D, Dave M, Shah S. Pregnancy outcomes and maternal and perinatal complications of pregnancies following in vitro fertilization/intracytoplasmic sperm injection using own oocytes, donor oocytes, and vitrified embryos: A prospective follow-up study. J Hum Reprod Sci. 2016;9(4):241-49.
15. Miettrola S, Hartikainen AL, Vaarasmaki M, Bloigu A, Roukonen A, Jirvelin MR, Pouta A, Offspring's blood pressure and metabolic phenotype after exposure to gestational hypertension in utero. Eur Jour Epidemiol. 2013 ;28: 87-98.
16. Rimoldi SF, Sartori C, Rexhaj E, Bailey DM< de Marchi SF, Mc Eneny J, Arx R Cerny D, Du-plain H, Germond M, Allemann Scherrer U. Antioxidants improve vascular function in children conceived by assisted reproductive technologies: a randomized double blind placebo controlled trial. Eur J Prev Cardiol. 2015; 22(11)1399- 407.

Svetlana Spremovic-Radjenovic – Head of the Department of Gynecological Endocrinology, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia (KCS). Professor of Gynecology and Obstetrics, Faculty of Medicine, University of Belgrade. Member of the team for the Assisted Reproduction in Clinic of Gynecology and Obstetrics KCS. Specialist in gynecology and obstetrics since 1993; General Endocrinology Subspecialist since 2004; Master's degree at the Faculty of Medicine, University of Belgrade in the field of endocrinology in 1991. She received her PhD from the Faculty of Medicine, University of Belgrade in 1995 in the field of neuroendocrinology. Completed an International Course in Hysteroscopy, Cyprus 2004, organized by the European Society of Endoscopic Surgery. Completed a laparoscopic suturing course in Leuven in 2008, organized by the European Society of Endoscopic Surgery

Member of the American Association of Endocrinologists: ~ Endocrine Society ~; Member of the International Association of Gynecological Endocrinology (ISGE); Member of Serbian Medical Society and Human Reproduction Association; President of the Serbian Association for Gynecological and Reproductive Endocrinology (SAGRE) from 2018.

Author and coauthor of the publications in peer-reviewed, internationally recognized journals, chapters in textbooks, books and monographs

INDUKCIJA I STIMULACIJA OVULACIJE U POSTUPCIMA INTRAUTERINIH INSEMINACIJA: LETROZOL ILI KLOMIFEN CITRAT?

Doc. Jelena Stojnić

Klinika za ginekologiju i akušerstvo, Klinički Centar Srbije
Medicinski fakultet, Univerzitet u Beogradu, Srbija

Poslednjih godina se dešava „veliki povratak" intrauterinih inseminacija (IUI) kao postupka u tretmanu infertiliteta. Nakon zanemarivanja opcije IUI i primene u vidu usputnog tretmana do uključivanja u postupke IVF/ICSI, koji je tretiran kao jedina prava opcija terapije infertiliteta, svedoci smo polake , ali sigurne promene stava i prakse.

Postupci intrauterinih inseminacija su pokazali poboljšanje stope kliničkih trudnoća, ali i smanjivanja neželjenih efekata (multiple trudnoče, sindrom OHSS) najviše zahvaljujući savremenim protokolima stimulacije ovulacije, obavezne obrade semena, aplikovanju stop injekcije hCG i boljem vremenu intervencije, kao i primeni podrške lutealnoj fazi.

Prosečna stopa uspeha IUI je oko 13% po ciklusu odnosno 10-20% prema većini studija (Bahadur i sar., 2016), a stopa preterane upotrebe IVF iznosi oko 25-50%. Mnoge pacijetkinje žele IUI metodu koja je komfornija, sa primenom tableta mesto injekcija, ređim monitoringom i potrebom za dolaženjem, manje invazivna odnosno bez aspiracije i anestezije, manje stresogena i opterećujuća, i koja ne remeti životni ritam i obaveze u velikoj meri, manje finansijski zahtevna, ali očekuju da ima određen procenat uspešnosti u odnosu na IVF (stopa uspeha oko 35% kod žena do 35 godina).

Postavlja se pitanje uspešnosti IUI u odnosu na politiku čekanja ekspektativnu i spontanog pokušavanja kod parova. U opštoj populaciji onih koji pokušavaju koncepciju 84% će ostvariti nakon godinu dana, a 92% nakon 2 godine. Kokhranova baza pokazuje značajno bolje podatke sa stimulisanim ciklusima IUI u odnosu na spontane IUI cikluse, OR 2,33, 95% CI 1,46-3,71 na 415 žena (Veltman-Velhurts, 2016). Stopa živorođenja od 11% za stimulasane IUI cikluse je poređena sa 2,2% za one sa ekspektativnim pristupom sa OR 5,6 (95% CI 1,8-17,4), (Woodward i sar., 2016).

Svedoci smo da farmaceutske kompanije, proizvođači opreme, pa čak i sami ginekolozi, favorizuju metodu IVF u odnosu na IUI naglašavajući razliku u uspehu metode, ali zanemarujući individualizovan princip u lečenju infertiliteta i konkretne okolnosti svakog slučaja, kao i psihiološki efekat vezan za lečenje infertiliteta.

Svaka od etapa u postupcima IUI je pretrpela promene u cilju povećavanja uspeha metode i smanjivanje neželjih efekata. Stope multiplih trudnoća su bile jedna od ranijh problema sa IUI postupcima, što je novijim pristupom svedeno na minimum (Peeraer i sar., 2015; Veltman-Velhurst i sar., 2016).

Indikacije za IUI, prema savremenom gledištu bi obuhvatale: nepoznat faktor infertiliteta, subfertilnost muškarca, ovulatorna disfunkcija-anovulacija, cervikalni faktor, kompetentnost bar jedne tube, endometrioza nižeg gradusa, kao i oni sa verskim ubeđenjima protiv ART.

Inseminacije bez obrade semena se često povezuju sa pelvičnim infekcijama, pa uklanjanje semene plazme je neophodno zbog izbegavanja efekta prostaglandinana indukciju uterine kontrakcije. (Bahadur i sar., 2017). Obrada semena je neophodni deo intervencije i obavlja se centrifugom semena u kulturi medijuma ili obrada prema gradijentu. IUI se obično izvodi sa 0,2 do 0,5 mililitara suspenzije sperme, ubacuuje se putem katetera u kavum materice. Pitanje mirovanja

posle intervencije je još uvek stvar debata, i mnoge studije pokazuju veću stopu kliničkih trudnoća nakon 20 nedelje gestacije u slučaju ustajanja odmah posle intervencije (Scholten i sar., 2014).

Većina studija navodi vreme inseminacije od 32 do 36 sati nakon stop injekcije, ali pitanje primene stop injekcije zavisi od veličine folikula, kao i primenjenog preparata za stimulaciju ovulacije. U intervencijama koje su rezultovale trudnoćom, primećeno je da je u ciklusima sa klomifen citratom optimalna prosečna veličina folikula 20mm, dok u ciklusima sa gonadotropinima (HMG, humani menopauzalni gonadotropini) optimalna veličina 18mm. (Bahadur i sar., 2017). Primećeno je da rezultati IUI postupka ne zavise od vrste katetera koji je upotrebljen.

Prevremeni skok LH se javlja u 25 do 30% stimulisanih IUI ciklusa i vodi prekidu i obustavi ciklusa, češći je kod starijih pacijetkinja i javlja se na manjim dimenzijama folikula folikula (Klein i sar., 2002; de Koning J i sar., 2001). Primena GnRh antagonista ovo uspešno rešava, ali povećava troškove postupka.

Više od 4 decenije, primena Klomifen citrata (CC clomiphene citrat) je prvi izbor u indukciji ovulacije u slučaju anovulatornog infertiliteta, a u stimulaciji ovulacije (superovulacija) kod slučajeva infertiliteta nepoznate etiologije, endometrioze, muškog subfertiliteta, cervikalnog faktora. Takozvana „pilula plodnosti" je najčešće korišćeno sredstvo i prvi izbor u postupcima intrauterinih inseminacija za izazivanje ili stimulaciju ovulacije kod anovulatornih ili oligoovulatornih žena.

Klomifen citrat ima nisku cenu, primenjuje se oralno i povezan je sa niskim rizikom od nastanka multiplih trudnoća i pojave težih oblika ovarijalnog hiperstimulacionog sindroma (OHSS). (Fouda, Sayed, 2011). Klomifen kao rezultat postiže ovulaciju u 60-85% i 10-20% je stopa trudnoća po ciklusu (Pourali i sar., 2017). Klomifen je selektivni modulator estrogenskih receptora (SERM), nesteroidni estrogen koji se vezuje za multipla mesta u reproduktivnom traktu i može imati i ulogu agonsite i antagoniste. Klomifen se vezuje za estrogene receptore u hipotalamusu i inhibira negativnu povratnu spregu estrogena na oslobadjanje gonadotropina. Međutim, mnoge studije su pokazale nepovoljni efekat klomifena, na receptivnost endometrijuma, endocervikalnu sluznicu, ovarijume i sam fetus.

Anti-estrogeni efekat klomifena na endometrijum može voditi do nepovoljne stope trudnoća i i značajnog procenta ranih spontanih pobačaja (biohemijskih trudnoća) zbog smanjenja broja receptora za estrogene. Klomifen ima dug poluživot od 5 do 7 dana i samim tim se akumulira u telu i tkivima (Thomas i sar., 2019). Neželjeni efekti koji se javljaju pri administraciji leka su retki i obuhvataju bolove u mišićima i kostima, klimakterične simptome, glavobolju, mučninu i gastrointestinalne simptome. Rezistancija na klomifen odnosno izostanak reakcije se viđa 15-20%, najčešće u slučajevima PCOS (Liu A i sar., 2014; Yun Hyon B i sar., 2015).

Letrozol pripada trećoj generaciji inhibitora aromataze i u upotrebi za indukciju i stimulaciju ovulacije je već deceniju, a prvobitno je cela grupa razvijena za terapiju hormon zavisnog karcinoma dojke. Ima potpuno drugačiji mehanizam dejstva od klomifena i nema dugotrajni antiestrogenski efekat u tkivima jer ne smanjuje broj receptora estrogenskih. Ima kratak poluživot , oko 45 sati i brzo se eliminiše iz organizma (Pourali i sar., 2017).

Inhibitori aromataze blokiraju konverziju androgena u estrogene u ovarijalnim folikulima, perifernim tkivima i mozgu i samim tim dovode do povećanja depoa androgena u folikulima., koji su na raspolaganju kao prekursori estrogena. Ovo dovodi do pada u cirkulišućim i lokalnim estrogenima i porastu intraovarijalnih androgena. Pad estrogena dovodi putem negativne povratne sprege do oslobadanja i rasta FSH, koji rezultira rastom folikula. Za razliku od Klomifena, povratna sprega kod inhibitora aromataze je intaktna, rast folikula je normalan i procesi selekcije

domin antnog folikula , kao i atrezija manjih folikula su očuvani, i zato je reakcija u stimulaciji obično monofolikularna (Kar, 2013).

I mehanizam povećanja intraovarijalnih androgena verovatno učestvuje u dejstvu povećavajući folikularnu senzitivnost na FSH, stimulišući IGF I, koji opet sinergistički sa FSH povećava rast folikula. U odnosu na klomifen, inhibitori aromataze ne smanjuju broj estrogenih receptora u tkivima, ostavljaju intaktnu osovinu hipotalamus-hipofiza i imaju kratki poluživot, pa samim tim rezultauju većom debljinom endometrijuma, ne menjau cervikalni mukus, rezultuju monofolikularnim rastom i boljom folikulogenezom (Legro i sar., 2012).

Kliničkim iskustvom su kod primene letrozola ustanovljene prednosti in dukcije ovulacije i stimulacije u slučajevima PCOS kao prvi metod izbora, PCOS rezistantnih na Klomifen citrat, pacijetkinja sa sniženom ovarijalnom rezervom koje su u programu intrauterinih inseminacija.

Većina studija do sada je pokazala da letrozol ima isti ili približan učinak u odnosu na klomifen citrat za Kontrolisanu stimulaciju ovulacije za IUI postupke (sa indikacijama neobjašnjenog infertiliteta, srednje endometrioze ili muškog faktora) u pogledu stope kliničkih trudnoća po ciklusu, kumulativne stope trudnoća, pobačaja ili stope živorođene dece (Badawy i sar., 2010; Abu Hashim i sar., 2012; Ibrahim i sar., 2012; Akbari i sar., 2012; Zadehmodares i sar., 2012).

Studija Pourali i sar., 2017. godine je poredeći efekte letrozola ili klomifen citrata uz dodatak gonadotropina u protokolima IUI da je debljina endometrijuma znatno viša u Letrozol grupi, zatim veći stopa kliničkih trudnoća,ali i značajno veću učestalost OHSS u klomifen grupi, bez razlike u stopi spontanih abortusa. Finansijski troškovi u obe grupe su bez značajnih razlika. U navedenoj studiji nije bilo značajne razlike u broju folikula većih od 16mm, ali su neke studije pokazale značajno veći broj ovih folikula u Klomifen grupi, verovatno jer su studije obuhvatale veće učešće pacijetkinja sa PCOS (Badawy i sar.,2009.; Casper i sar., 2006.). Uz veći broj folikula zrelih u Klomifen grupi, većina ovih studija je pokazala komparabilne stope trudnoća kod obe terapijske opcije, što mnogi pripisuju efektu endometrijuma i njegove receptivnosti. (Fouda i sar., 2011).

Moramo imati na umu i da su mnogi objavili da se sa brojem zrelih folikula povećava i uspeh IUI, pa je procenat kliničkih trudnoća iznosio 6,2% u slučaju jednog folikula, 12,9% kod dva folikula i 30% sa tri folikula veća od 16 mm (Sikandar i sar., 2005), što broj folikula čini značajnim prognostičkim faktorom u slučaju IUI.

Dodatak gonadotropina pored klomifena i letrozola popravlja stopu kliničkih trudnoća, ali povećava učestalost OHSS sindroma, stopu multiplih trudnoća i troškove terapije i postupka (Yun BH i sar., 2015). Koncept minimalne stimulacije je upotreba malih doza gonadotropina uz klomifen ili letrozol, različitog trajanja, je pokazala bolje rezultate u odnosu na protokole stimulacije samo gonadotropinima u smislu kliničkih trudnoća, ali i manji procenat komplikacija u vidu multiplih trudnoća i OHSS.

Pojava učestalosti OHSS sindroma se više navodi kod primene klomifen citrata u odnosu na letrozol (Yun HB i sar., 2015; Thomas i sar., 2019;), odnosno najčešće zbog monofolikularnog odgovora i nižih vrednosti estradiola kod letrozola.

Multiple trudnoće se često navode kao razlog protiv IUI sa stimulacijom ovulacije. Stopa multiplih trudnoća u postupcima IUI se navodi sa 0,3% nakon razvijanja jednog folikula i 2,8% nakon multifolikularnog rasta. Rizik multiplih trudnoća se povećava za 6, 14 i 10%, zavisno da li imamo 2, 3 ili 4 folikula u stimulisanom ciklusu (Bahadur i sar., 2017).

Pitanje bezbednosti upotrebe klomifen citrata i letrozola je još uvek stvar debata. Pored, 40 godina upotrebe klomifena pitanje kongenitalnih anomalija je još uvek kontradiktorno, a za letrozol nema dovoljno podataka ni studija.

Studija koja je poredila 514 beba rodjenih nakon terapije letrozolom sa 36 000 beba rađenih nakon Klomifena je pokazala da nema povećanog rizika za kongenitalne anomalije nakon letrozola (Tubaldi i sar., 2006). Forman i sar., 2007. su poredeći ishode 112 beba rođenih nakon terapije letrozolom sa 271 bebe nakon klomifena i 94 bebe iz spontanih trudnoća, pokazali učestalost kongenitalnih malformacija sa 0%, 2,6% klomifen i 3,2% iz spontanih trudnoća.

Biljan i sar., 2005. objavili izveštaj koji je izazvao veliko uznemirenje, gde su poredeći 150 beba nakon terapije letrozolom sa 36 000 beba iz nisko rizičnih trudnoća , prijavili povećanu učeštalost anomalija srca i koštanog sistema nakon primene letrozola, ali uz opštu incidencu anomalija 3do 4%, koja nije uvećana odnosno na nivou je opšte populacije.

Multicentrična studija Reefhuis i sar., 2011. u okviru Nacionalne studije o kongenitalnim anomalijama su istraživali vezu klomifena i kongenitalnih anomalija kod 25 000 porođenih pacijetkinja, sa korišćenim klomifenom 2 meseca pre koncepcije i zaključili značajno povećan rizik za nastanak kongenitalnih anomalija srca i to septalni defekti, ventikularni septalni muskularni defekti i koarktacija aorte.

Davies i sar., 2012. su izvestili o kongenitalnim malformacijama nakon IVF/ICSI i prijavili povećan rizik kongenitalnih malformacija nakon uputrebe klomifen citrata, nakon kontrole pridruženih faktora rizik od 3.19, bez specifikacije tipa anomalija.

Tulandi i kolege, 2006. godine u okviru kanadske multicentrične studije su poredli neonatalne ishode 397 beba nakon upotrebe klomifena i 514 beba nakon letrozola. Učestalost kongenitalnih anomalija i hormozomopatija u letrozol grupi je 2,4% i 4,8% u klomifen grupi sa dominacijom kardijalnih anomalija sa 1,8% prema 0,2 % u letrozol grupi. Ventrikularni septalni defekt sa 0,2% u letrozol grupi je mnogo manje zastupljen nego 1,8% u klomifen grupi. Zaključili su da nema značajne razlike u incidenci major i minor malformacija, nezavisno da li korišćen letrozol ili klomifen., kao i da su kongenitalne srcane malformacije ređe nakon primene letrozola.

Za sada, većina studija je pokazala istu ili približnu efikasnost stimulacije ovulacije i postizanje trudnoće sa upotrebom letrozola u odnosu na klomifen citrat, uz preporuku letrozola kao prvog leka izbora za pacijetkinje sa hroničnom anovulacijom i gojaznošsu, odnosno kod PCOS sindroma. što se tiče bezbednosti oba preparata, postoji potreba za velikim studijama, randominiziranim, koje bi pokazala i efikasnost i bezbednost.

Literatura

1. Bahadur G, Homburg R, Muneer A, et al. First line fertility treatment strategies regarding IUI and IVF require clinical evidence. Hum Reprod. 2016.
2. Veltman- Velhurst SM, Hughes E, Ayeleke RO, et al. Intra-uterine insemination for unexpained subfertility. Cochrane Database syst Rev. 2016;2:CD001838.
3. Woodward B, Tomlinson M, Kirkman-Brown J. Replacing IUI with IVF for initial treatment of unexplained infertility: why this NICE recommendation is a cause of concern. Hum Fertil. 2016.
4. Peeraer K, Dobrock S, De Loecker P, et al. Low-dose human menopausal gonadotrophin versus clomiphene citrate in subfertile cuoples treated with IUI: a randomized controlled trial. Hum Reprod. 2015;30:1079-88.
5. Bahadur G, Homburg R, Al-Habib A. A New dawn for Intrauterine inssemination: Efficient and Prudent Practice will Benefit Patients, The Fertility industry and the Healthcare Bodies. J Obestet Gynecol Indian. 2017; 67(2):79-85.
6. Scholten I, Custers IM, Moolenaar LM, et al. Long-term follow up of couples initially randomized between immobilization and immediate mobilization subsequent to IUI. Reprod Biomed Online. 2014;29(1):125-30.
7. Klein NA, Harper AJ, Houmard Bs, et al. Is the short follicular phase in older women secondary to advanced or accelerated dominant follicle development? J Clin Endocrinol Metabol. 2002;87:5746-50.

8. De koning J, Lambalk CB, Helmerhorst FM, et al. Is GnRh self-primimg an obligatory feature of the reproductice cycle? Hum Repro. 2001;16:209-14.
9. Fouda UM, Sayed MA. Extended letrozole regimen versus clomiphene citrate for superovulation in patients with unexplained infertility undergoing intrauterine insemination: A randomized controlled trial. Reprod Biol Endocrin. 2011;9:84.
10. Pourali L, Sedigheh A, Tavakolizadeh S, Sileimani H, Sani FT. Clomiphene citrate verus letrozole with gonadotropins in intrauterine insemination cycles: A randomized trial. Int J Reprod Biol Med. 2017;15:49-54.
11. Thomas S, Woo I, Ho J, Jones T, Paulson R, Chung K, Bendikson K. Ovulation rates in stair-step protocol with letrozole vs clomiphene citrate in patients with polycystic ovary syndrome. Contra Reprod Med. 2019;4:20.
12. Liu A, Zhebg C, Lang J, Chen W. Letrozole versus Clomiphene citrate for unexplained infertility: A systematic review and meta-analysis. J Obstet Gynecol Res. 2014;40:120516.
13. Yun Hyon B, Chon SJ, Park JH, Seo SK, Choo SH, Choi YS, et al. Minimal stimulation using gonadotropin combined with clomiphene citrate or letrozolr for intrauterine insemination. Yonsei Med J. 2015;56 (2):490-6.
14. Kar S. Current evidence supporting "letrozole" for ovulation induction. J Hum Reprod Sci. 2013; 6(2):93-8.
15. Legro RS, Kunselman AR, Brzyski RG, Casson PR, Diamond MP, Schlaff WD, et al. The pregnancy in polycystic ovary syndrome II (PPCOS II) trial: rationale and design of double-blind randomized trial of clomiphene citrate and letrozole for the treatment of infertility in women with polycystic ovary syndrome. Contemp Clin Trial. 2012; 33:47081.
16. Badawy A, Elsanashar A, Totongy M. Clomiphene citrate or aromatase inhibitors combined with gonadotropins for superovulation in women undergoing intrauterine insemination: A prospective randomized trial. J Obstet Gynecol. 2010; 30:617-21.
17. Abu Hashim H, El Rakhawy M, Elaal I. randomized comparison of superovulation with letrozole vs. clomiphene citrate in an IUI program for women recently surgically treated minimal to mild endometriosis. Acta Obstet Gynecol Scand. 2012; 91:338-45.
18. Ibrahim MI, Moustafa RA, Abdel-Azeem AA. Letrozole versus Clomiphene citrate for superovulation in Egyptian women with unexplained infertility: a randomized controlled trial. Arch Gynecol Obstet. 2012;286:1581-7.
19. Akbari S, Ayazi Roozbahani M, Ayazi Roozbahani F. Comparing of Letrozole verusu Clomiphene citrate combined with gonadotropins in intrauterine insemination cycles. Iran J Reprod Med. 2012;10:29-32.
20. Badawy A, Elnasar A, Totongy M. Clomiphenee citrate or aromatase inhibitors in women with unexplained infertility undergoing intrauterine insemination: a prospective randomized trial. Fertil Steril. 2009; 92: 1355-9.
21. Zadehmodares S, Niyakan M, Sharafy SA, Yazdi MH, Jared F. Comparison of treatment outcomes of infertile women by Clomiphenee citrate and letrozole with gonadotropins underwent intrauterine insemination. Acta Med Iran. 2012;50:18-20.
22. Casper RF, Mitwally RF. Review: aromatase inhibitors for ovulation induction. J Clin Endocrinol Metab. 2006;91(3):760-71.
23. Sikandar R, Virk S, Lakhani S, Sahab H, Rizvi J. Intrauterine insemination with controlled ovarian hyperstimulation in the treatment of subfertility. J Coll Physicians Surg Pak. 2005;15(12):782-5.
24. Tulandi M, Martin J, Al-Fadhi R, Kabli N, Forman R, Hitkari J, et al. Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. Fertil Steril. 2006;85(6):1761-5.
25. Forman R, Gill S, Moretti M, Tulandi T, Koren G, Casper R. Fetal safety of letrozole and clomiphene citrate for ovulation induction. J Obstet Gynecol Can. 2007; 29(8):668-71.
26. Biljan MH, Hemmings R, Brassard N. The outcome of 150 babies following the treatment of letrozole and gonadotropins. Fertil Steril. 2005;84(Suppl1):s95.
27. Reefhuis J, Honein MA, Schieve LA, Rasmussen SA. National Birth defects Prevention Study. Use of clomiphene citrate and birth defects. National Birth Defects prevention Study, 1997-2005. Hum Reprod. 2011; 26:451-7.
28. Davies MJ, Moore VM, Willson KJ, Van Essen P, Prist K, Scott H, et al. Reproductive technologies and the risk of birth defects. N Engl J Med. 2012; 366:1803-13.

Jelena Stojnic has completed her Bachelor's at Medical School University of Belgrade (1996). She became Master of Science Degree at Belgrade Medical School (2001) with thesis "Non invasive ultrasound screening in the first trimester of pregnancy". Her PhD (2015) was "Perinatal outcome of pregnancies after IVF/ICSI procedures"at University of Belgrade. At Academic special studies in Gynecology and Obstetrics (2002) was trained at Belgrade Medical School.

She has an overall 20 years of clinical experience, working as reproductive gynecologist at Clinic for Gynecology and Obstetrics,

Clinical Centre of Serbia, at the ART department. At 2020. was appointed as a Chief of Infertility and ART Department.

At the Medical faculty, University of Belgrade, she works as an Associate Profesor of Gynecology and Obstetrics, first elected at 2018. She has about 30 representative publications in CC/SCI expanded and JCR indexed journals and is active participant in more than 30 international congresses with total number of publications about 100.

At Clinic for Gynecology and Obstetrics she is a member of Endometriosis Therapy Board and ART Consortium for Goverment funded ART procedures approval.

She is member of ESHRE (European society of Human Reproduction and Embriology), Society of Human Reproduction of Serbia, Society of Reproductive endocrinology in Serbia.

She was awarded with “Zarko Pilic” award from Ultrasound Society of Serbia, for the best publication from Ultrasound in Infertility as a young author at 2002.

Her major research interest is in infertility and ART and include the ovarian stimulation and poor responders, basic aspects aspects of folliculogenes and ovarian tissue cryopreservation and perinatal outcome of pregnancies following ART, endometriosis and infertility, fertility after cancer therapy.

MINIMALLY INVASIVE SURGERY

HYSTEROSCOPIC MYOMECTOMY

Assist. Prof. Milan Dokić

Secretary General of Section for Gynecology and Obstetrics of Serbian Medical Society
Clinic for Gynecology and Obstetrics, Clinical Center of Serbia
Faculty of Medicine, University of Belgrade, Serbia

Myoamas – fibroids are the most common pelvic tumors in women. About 15-20% of uterine myomas are submucous type. According to the localisation, types of myoma in uterus could be: subserous, intramural, submucous, submucous – pendular, myoma nascence, intraligamentary, parasitic and cervical myoma. The way of treatment – myomectomy could be done by:

- Hysteroscopy
- Laparoscopy
- Laparotomy

Choice of access depends on:

- myoma size,
- myoma type (localization),
- number of myomas,
- medical equipment and conditions (appliances, instruments, op. room) and
- knowledge and skill of the operator and the entire op. team.

For preoperative preparation, we usually use some of these medicaments: GnRh analogues (Busereline or Gosseline), Vasopressin and oral contraceptives.

The aim of preoperative treatment is:

- reduction of myoma size – shorter duration of intervention,
- better demarcation – thinner endometrium,
- less bleeding.

Also, some surgens perform cervical preparation wihr PGE2 or laminaria. Antibiotic prophylaxis and thromboprofilaxis is recomanded.

Hysteroscopic myoemctomy should do only specialist of gynaecology with experience in MIC. All myomectomies have to be performed in well equipped op. room. That inculde:

- instruments,
- well trained staff and
- possibility to do laparoscopy or laparotomy in case of complication.

Types of submucosous myoma:

- Type 0 - completely in the cavity
- Type 1 – myoma is dominantly in the cavity, less than 50% is intramural
- Type 2 – most of the myoma is intramural ≥ 50%

The most convenient for hysteroscopy is submucousus myoma type 0 up to 40 mm in diameter!

Instruments & equipment for hystreroscopy and myomectomy:

- Hysteroscope (resectoscope)
- Source of light + fiber-optic cable

- Irrigation system
- Video system (camera, monitor, recording system)

The main types of hysteroscope are rigid or flexible. Hysteroscopes are produced in different diameters - 2 mm to 9 mm, different angles: 0˚, 12˚ or 30˚ and with or without irrigation system (Hamou pump). Some of hysteroscopes are for diagnostic only (no sleeve for instruments as scissors, forceps, electrode...). The most common is office hystereoscope because if small diameter and practical use for interventions such as polypectomy, septum resection and remove myomas. The most apropriate instrument for hysteroscopic muyomectomu is operative hysteroscop – resectoscope. Resectoscope is the most useful for myomectomy and is about 8-12 mm in diameter. Usually, for small submucous myomas, office hysteroscope is adeqat tool because it provides:

- Cutting myoma by scissors or by electrode
- Morselation (morselation in utero)

Bigger myomas (up to 40 mm) should be removed by sliceing myoma with loop of resectoscope. Loop of resectoscope use monopolar or bipolar current for cuting. Myoma is removed in pices - slices like „chips“.

As the curettage, we expect complications during hysteroscopy such as perforatrion of uterus wall, uterus bleeding and infections. Specific type of complications are cosed:

- Complications with non electrolyte medium and monopolar current
- Hiponatremy : brain edema (somnolence, vomitus, headache, coma), lung edema (dyspnoea), cardiopulmonary symptoms, neuromuscular symptoms, fatal outcome

If the los of medium is 1500 ml or more – IMMEDIATELY STOP with HYSTEROSCOPY!

- Complications with electrolyte medium and bipolar current

When the los of medium is 2500 ml or more, symptoms are:

- Cardiopulmonary symptoms
- Lung edema (dyspnoea)

There are significant les complications with electrolyte medium!

References

1. Piecak K, Milart P. Hysteroscopic myomectomy. Prz Menopauzalny. 2017 Dec;16(4):126-8.
2. Ciebiera M, Łoziński T, Wojtyła C, Rawski W, Jakiel G. Complications in modern hysteroscopic myomectomy. Ginekol Pol. 2018;89(7):398-404.
3. Vitale SG, Sapia F, Rapisarda AMC, Valenti G, Santangelo F, Rossetti D, et al. Hysteroscopic Morcellation of Submucous Myomas: A Systematic Review. Biomed Res Int. 2017;2017:6848250.
4. Friedman JA, Wong JMK, Chaudhari A, Tsai S, Milad MP. Hysteroscopic myomectomy: a comparison of techniques and review of current evidence in the management of abnormal uterine bleeding. Curr Opin Obstet Gynecol. 2018 Aug;30(4):243-51.
5. Vilos GA, Allaire C, Laberge PY, Leyland N; SPECIAL CONTRIBUTORS. The management of uterine leiomyomas. J Obstet Gynaecol Can. 2015 Feb;37(2):157-78.

LAPAROSCOPIC BURCH, CONDITION AND PERSPECTIVES

Prof. Miroslav Kopjar

President of Croatian Society for Gynecological Endoscopy, Croatia

Assist. Prof. Rajko Fureš[1], Dr. Dora Fureš[2]

1 Institute of Gynecology, Obstetrics and Minimally Invasive Gynecological Surgery. Faculty of Dental Medicine and Health Osijek, Josip Juraj Strossmayer University of Osijek, Croatia
2 Faculty of Medicine, University of Split, Republic of Croatia

It is indisputable that even in modern times, new possibilities are being sought in terms of minimally invasive gynecological surgery related to the treatment of stress urinary incontinence. It is undisputed that the laparoscopic Burch colposuspension is certainly equivalent to an open Burch colposuspension. We can objectify this, regarding the subjective cure rate (76-95%.). Recent research confirms that Burch laparoscopic colposuspension is an effective treatment for stress urinary incontinence. It is certain that the success of the surgery itself is significantly influenced by the experience of the surgeon and the surgical technique itself. It is undisputed that laparoscopic colposuspension according to Burch is the operative method of choice for women undergoing pelvic floor defects and retropubic surgery. Certainly, Burch laparoscopic surgery is very significant as this avoids the potential complications of sling surgery. Based on our experience with Burch laparoscopic surgery at Zabok General Hospital, in the future we will strive to reaffirm this surgery, in the interest of patients with stress urinary incontinence. The laparoscopic approach related to Burch surgery is certainly one of the very high quality options in the treatment of patients with stress urinary incontinence, and the current and future generations of urogynecologists provide a very high quality alternative in the treatment of our patients.

References

1. Prezioso D, Iacono F, Di Lauro G, Illiano E, Romeo G, Ruffo A, Russo N, Amato B. Retraction Note: Stress urinary incontinence: long-term results of laparoscopic Burch colposuspension. BMC Surg. 2016:28;16(1):26.
2. Hill AJ, Jallad K, Walters MD. Laparoscopic Burch Colposuspension Using a 3-Trocar System: Tips and Tricks. J Minim Invasive Gynecol. 2017;24(3):344.
3. Gümüş İ, Kalem MN, Kalem Z, Surgit O, Köşüş A. The Effect of Stress Incontinence Operations on Sexual Functions: Laparoscopic Burch versus Transvaginal Tape-O. Gynecol Minim Invasive Ther. 2018;7(3):108-113.

Prof. dr. sc. Miroslav Kopjar was from 1978 to 1983 the head of the Department of Gynecological Urology OB Varaždin, from 1989 to 2002 the head of the Department of Gynecology and Obstetrics of the General Hospital Zabok. From 1992 to 1994 he was the director of the Zabok Medical Center, and from 1994 to 2001 he was the director of the Zabok General Hospital.

Prof. Kopjar completed his medical studies at the Faculty of Medicine in Zagreb, and specialized in gynecology and obstetrics at the Varaždin Hospital and the Clinic for Women's Diseases and Obstetrics in Petrova from 1972 to 1976. He acquired the title of primarius in 1988. He became a Master of Science in 1987, and a Doctor of Science in 1996 at the Faculty of Medicine, University of Zagreb. From 2003 until today, he is a professor at the International University of Dubrovnik

- Libertas, and is an assistant professor at the Department of Gynecology and Obstetrics, Faculty of Medicine, University of Zagreb.

He transfers his acquired knowledge to other colleagues, which is shown in his participation and organization of professional and scientific conferences and postgraduate studies where he critically evaluates the advantages and disadvantages of laparoscopic and hysteroscopic operations (MIGK) so that he still holds the position of President of the Croatian Gynecological Endoscopic Society. society. He is a permanent court expert.

Under the leadership of Dr. Kopjar, the Zabok Medical Center grew into a general hospital. Trained personnel were also brought in, which enabled the establishment of all departments necessary for the recognition of the status of a general hospital. In 2000, he organized the Croatian postgraduate course of the 1st category in gynecological endoscopy at the General Hospital in Zabok and at the Faculty of Medicine in Zagreb, which continues to this day (to date, 18 international postgraduate courses of the 1st category "Kurt Semm" have been organized). with the participation of numerous domestic and foreign eminent experts, in which symposia on minimally invasive gynecological surgery are traditionally held every year. With his initiative, the Croatian Society for Gynecological Endoscopy has so far organized four world congresses in minimally invasive gynecological surgery (the last in 2016 in Opatija).

For his selfless professional work he received numerous awards and recognitions, among which we emphasize: the Charter of the Croatian Medical Association for his contribution to medical science and profession, and for the development of health care in the Republic of Croatia, 1994; Homeland War Memorial, 1995; Supporting member of the Croatian Academy of Medical Sciences, 1997; Ladislav Rakovac Award, 1997; Krapina-Zagorje County Plaque, 1997; Order of Danica Hrvatska with the figure of Katarina Zrinska, 1999; Certification in advanced operative laparoscopy - Accreditation Council for Gynecologic Endoscopy, New York Academy of Sciences, USA, 1999; included in the "2000 outstanding scientists of the 21st century" International Biographical Center, Cambridge, England, 2001; "Great mind of the 21st century" (in the field of medical science), American Biographical Institute, USA, 2001.

He is a long-term lecturer at numerous postgraduate studies at the Faculty of Medicine, University of Zagreb, such as: Perinatology, Ultrasound in Clinical Medicine, Department of Gynecology and Obstetrics, Maternal and Child Protection, Telemedicine, Anesthesiology, Intensive Care and Intensive Care, Emergency and Intensive Care in Obstetrics and Gynecology (in English) where he was also appointed mentor.

Longtime member of the Main Board of the HLZ, Current Chairman of the Commission for International Cooperation. Since 2002 he has been a full member of the Croatian Academy of Medical Sciences. Prof. dr.sc. honey. International University of Dubrovnik "Libertas".

In his social work he performed numerous duties, including that of the Mayor of the City of Zlatar, and today he is a councilor in the City Council of the City of Zlatar and in the Krapina-Zagorje County Assembly where he is the President of the Economy Committee.

Subspecialty: Gynecologic Oncology. 2010. Primarius. 2000. - Active participant in numerous conferences and meetings. Lecturer of international postgraduate course gynecological endoscopy first category "Kurt Semm" since 2000.

TOTAL LAPAROSCOPIC HYSTERECTOMY, CONDITION AND PERSPECTIVES

Assist. Prof. Rajko Fureš

Head of the Institute of Gynecology, Obstetrics and Minimally Invasive Gynecological Surgery.
Faculty of Dental Medicine and Health Osijek, Josip Juraj Strossmayer University of Osijek, Croatia

Prof. Miroslav Kopjar[1], Dr. Dora Fureš[2]

1 President of Croatian Society for Gynecological Endoscopy, Croatia
2 Faculty of Medicine, University of Split, Republic of Croatia

Minimally invasive gynecological surgery is integrated into the concept of total laparoscopic hysterectomy. It is certain that total laparoscopic hysterectomy has established itself in the routine hysterectomy method for almost forty years. It is indisputable that today, laparoscopic hysterectomy is one of the most common and performed surgeries in women, since it is a minimally invasive gynecological surgical procedure. Certainly advances in technology and science, and in the field of laparoscopic hysterectomy, are making major strides. It is undisputed that laparoscopic hysterectomy, including total laparoscopic hysterectomy, have their future, which will largely be based on robotic surgery, given its minimally invasive component. The future of minimally invasive gynecological surgery is inextricably linked to the further development and advancement of total laparoscopic hysterectomy techniques.

Refereces

1. Laursen KR, Hyldgård VB, Jensen PT, Søgaard R. Health care cost consequences of using robot technology for hysterectomy: a register-based study of consecutive patients during 2006-2013. J Robot Surg. 2018;12(2):283-94.
2. Bijen CB, Vermeulen KM, Mourits MJ, Arts HJ, Ter Brugge HG, van der Sijde R, Wijma J, Bongers MY, van der Zee AG, de Bock GH. Cost effectiveness of laparoscopy versus laparotomy in early stage endometrial cancer: a randomised trial. Gynecol Oncol. 2011;121(1):76-82.
3. Farag S, Frazzini Padilla P, Smith KA, Flyckt R, Sprague ML, Zimberg SE. Fallopian tube perfusion in ex-vivo and in-vivo laparoscopic hysterectomy specimens: potential application for uterine transplantation. Hum Reprod. 2018;33(12):2232-40.

I was born in Martinišće, Croatia in 1966. 2006 - 2009 Assistant Director for Medical Affairs, Hospital Zabok. 2011 – Head of the Department of Gynaecology and Obstetrics Hospital Zabok. 1992 Doctor of Medicine – Faculty of Medicine, University of Zagreb. 1999 Specialist in gynecology and obstetrics – Hospital Sisters of Mercy, Zagreb. 1998 Thesis: “tumor marker CA 125 in ovarian cancer”, Faculty of Science, University of Zagreb. 2008 Postgraduate studies – “Menagement in health”, Faculty of Medicine, University of Zagreb. 2010. Doctoral dissertation - “The value of protein Bcl-2, nm23 and HER-2 as a prognostic indicator in breast cancer.” Faculty of Science, University of Zagreb. 2015 title scientific assistant professor in the scientific field of biomedicine and health, scientific field of clinical medical sciences, scientific branch of gynecology and obstetrics, in the Department of Gynecology and Obstetrics, Faculty of Medicine within the University of Osijek. 2010. Subspecialty: Gynecologic Oncology. 2010. Primarius. 2000. - Active participant in numerous conferences and meetings. Lecturer of international postgraduate course gynecological endoscopy first category “Kurt Semm” since 2000.

THE ROLE OF MINIMALLY INVASIVE SURGERY IN THE TREATMENT OF ENDOMETRIOSIS IN INFERTILE PATIENTS

Prof. Mladenko Vasiljević

Faculty of Medicine, University of Belgrade
Clinic of Obstetrics and Gynecology "Narodni Front" Belgrade

Endometriosis is a bening, estrogen-dependent disease found in three to 10% of reproductive age women. The management of endometriosis involves medical and surgical methods. Excisional techniques have an advantage over ablative techniques in the management of ovarian endometriosis, but they also decrease ovarian reserve as a result of simultaneous healthy ovarian tissue removal. Surgical management of deep infiltrating endometriosis significantly decreases pain, but is also associated with higher rates of complications. Patients who undergo surgical management of stage III and IV endometriosis should be referred for In Vitro Fertilization and embryo transfer. The recurrence rate of endometriomas after surgical management is significant. Medical treatment with GnRH analogues postoperatively does not prevent recurrence, but can prolong the disease-free interval

Prof. Dr. Mladenko Vasiljević, Full Professor at the Faculty of Medicine, University of Belgrade; Master and Doctor of Medical Sciences; Obstetrician Gynecologist with a subspecialty in Fertility and Sterility; Division Head for the Department of Infertility at the "Narodni Front" Clinic for Obstetrics and Gynecology in Belgrade. Areas of interest include fertility and sterility, IVF-ET, ultrasound, minimally invasive and open surgical techniques in obstetrics and gynecology. Published over 400 research papers.

DEVELOPMENT AND IMPLEMENTATION OF LAPSERB – LAPAROSCOPIC COLORECTAL SURGERY PROGRAMME IN SERBIA – IS IT USEFUL METHOD FOR LAPAROSCOPIC GYNAECOLOGICAL SURGICAL TRAINING?

Assist. Prof. Miljan Ćeranić

Clinic for digestive surgery of First surgical clinic, Clinical Center of Serbia
School of Medicine, University of Belgrade, Serbia

The National Training Programme in laparoscopic colorectal surgery (S-MICRAS-LAPSERB) in Serbia was set up to introduce standardized and structured training in laparoscopic colorectal surgery.

This study aims at retrospective analysis of prospectively collected data for patients undergoing colorectal resections.

We look at short-term clinical and pathological outcome of patients within laparoscopic colorectal resections performed in National training program.

The development of the project can be divided into two periods. From November 2015 to April 2018, we performed training of the surgeon who will be trainers. In that period, it was 2 supervised workshops lasting two days each. During the second workshop, it was presentation video materials of the surgeons who were candidates for trainers. Laparoscopic colorectal resections were performed only in hospitals that would become training centers.

An assessment based structured training program (LAPSERB) started in April 2018. Series of hands on supervised workshops, were conducted for different hospitals using the structured training by single trainer. Training process involved: up to 20 cases under direct supervision in the base hospital, teaching and training of the team with anesthesiologists, radiologists and pathologists.

This study demonstrates successful and safe adoption of laparoscopic technique for colorectal resections. Standardization of operative technique and structured training remains the key in success for the safe adoption of laparoscopic colorectal surgery and to develop advanced laparoscopic competency in gynaecological surgeons.

References

1. Coleman MG, Hanna GB, Kennedy R; National Training Programme Lapco. The National Training Programme for Laparoscopic Colorectal Surgery in England: a new training paradigm. Colorectal Dis. 2011;13(6):614-6.
2. Mackenzie H, Miskovic D, Ni M, Tan WS, Keller DS, Tang CL, Delaney CP, Coleman MG, Hanna GB. Risk prediction score in laparoscopic colorectal surgery training: experience from the English National Training Program. Ann Surg. 2015;261(2):338-44.
3. La Torre M, Caruso C. Resident training in laparoscopic colorectal surgery: role of the porcine model. World J Surg. 2012;36(9):2015-20.

Miljan Ćeranić, Klinički centar Srbije, Beograd, Klinika za digestinu hirurgiju – Prva hirurška. Od januara 2011 Projekat Ministrastva za nauku i tehnologiju „Uloga preoperativnog odredjivanja stadijuma bolesti, prognostičkih, terapijskih markera, objektiviziranje funkcionalnih rezultata u odluci o strategiji lečenja karcinoma rektuma, a u cilju unapredjenja onkoloških rezultata i kavaliteta života.“ broj 41033.

Kao stipendista Franucuske vlade za oblast onkologije u martu i aprilu 2005. godine boravio je na stručnom usavršavanju na odeljenju za digestivnu onkološku hirurgiju Instituta Gustave Roussy, Villejeuf, Francuska. Dr Dominique Elias, koji je šef digestivne hirurgije ove prestižne onkološke bolnice.

Bio je učesnik ESTRO kursa „Evidence and research in rectal cancer« koji je održan u Beogradu od 20-22. maja 2010. godine i učesnik ETHICON ovog kursa „Biosurgery Innovation Wet Lab Meeting“koji je održan u Zagrebu, 17.06.2011. godine. Završio je Internacionalni kurs Ultrasonographic imaging of pelvic floor disorders koji je održan u Treviso-u, Italija 23-25. novembra 2011. godine. Završio je „Advanced course in laparoscopic colorectal surgery“ Rijeka, Hrvatska, 18-19. sep. 2014. godine. Završio je „THD and gatekeeper: Mini invasive surgery for the treatment of hemorrhoids and faecal incontinence“ 26-26 marta 2015. Roma, Italy. 2016. „ Mini Fellow Ship laparoscopic colorectal surgery –Prof Yves Panis of Hôpital Beaujon” Paris, France. „Advanced Master Class In Minimally Invasive Colorectal Surgery“, koji je održan u Lisabonu, Portugal od 19-21. februara 2018. Godine. „Laparoscopic Colorectal Training Programme for Serbia (LAPSERB)“ 22. November 2018. godine. „Laparoscopic CME Course“ Norderstedt, Germany on Monday 17 – Tuesday 18 December 2018.

MINIMAL INVASIVE TRATMENT OF UTERINE FIBROIDS

Ass. Rastko Maglić

Klinika za ginekologiju i akušerstvo Narodni Front
Medicinski fakultet, Univerzitet u Beogradu, Srbija

Myomas (fibromas) are the most frequently encountered benign tumour in women over 35 years. The ACOG (American College of Obstetrics and Gynaecology) well defines criteria for selecting cases for treatment. The modalities are depending on type, size, symptoms and weather the patient is in childbearing age, or finished her childbearing - divided in hysteroscopy or laparoscopy/ laparotomy approach. Hysteroscopy is reserved for type 0,1, 2 and 3 fibromas. Laparoscopy/ laparotomy for type 4,5,6 and 7 fibromas based on their location in the myometrium. This group can have either myomectomy or hysterectomy depending on the childbearing and personal preference. Hysteroscopy can be done though office hysteroscopy for myomas smaller than 1,5 cm, and through resectoscopy for all other sizes, with a cut-off value of 6 cm and no more than 4 myomas in the uterine cavity.

Developments in suture materials (barbed sutures) and sutturing techniques increases the quality of minimal invasive myomectomy. Today minimal invasive surgery is the gold standard for both myomectomy and hysterectomy because of the quality of uterine suturing, less risk of uterine rupture in pregnancy and short time of recovery/rapid discharge from the hospital. Only in case of exceptionally large myomas laparotomy still has its place because in these cases the operating time can be extended and surgery very demanding for both the surgeon and the anaesthesia. Laparoscopic morcellation remains a controversial point for minimal invasive surgery. Several new minimal invasive techniques are in development including ultrasound ablation, RF ablation, intrauterine hysteroscopic morcellators etc.

References

1. Carranza-Mamane B, Havelock J, Hemmings R; REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY COMMITTEE; SPECIAL CONTRIBUTOR. The management of uterine fibroids in women with otherwise unexplained infertility. J Obstet Gynaecol Can. 2015;37(3):277-85.
2. Faridi P, Fallahi H, Prakash P. Evaluation of the Effect of Uterine Fibroids on Microwave Endometrial Ablation Profiles. Annu Int Conf IEEE Eng Med Biol Soc. 2018;2018:3236-9.
3. Kho KA, Brown DN. Surgical Treatment of Uterine Fibroids Within a Containment System and Without Power Morcellation. Clin Obstet Gynecol. 2016;59(1):85-92.
4. Bhave Chittawar P, Franik S, Pouwer AW, Farquhar C. Minimally invasive surgical techniques versus open myomectomy for uterine fibroids. Cochrane Database Syst Rev. 2014;(10):CD004638.

Rastko Maglić je specijalista ginekologije i akušerstva, magistar medicinskih nauka, klinički asistent. Uža naučna oblast: Ginekologija i akušerstvo. Završio je Jugoslovensku školu ultrazvuka i bazični kurs iz laparoskopske hisrurgije i napredni Workshop_ Laparoskopija u ginekološkoj onkologiji. 2006. godine je prisustvovao naprednom kursu Advanced Minimaly Invasive Operating Techniques in Gynecology u Nemačkoj. Bio je predavač u školi za unapređenje reproduktivnog zdravlja Centra za KME Medicinskog fakulteta u Beogradu i Centru za KME Medicinskog fakulteta u Novom Sadu u okviru bazičnog kursa laparoskopske hirurgije.

LAPAROSKOPSKA HIRURGIJA U URGENTNIM STANJIMA

Ass. dr Srđan Mijatović

Generalni sekretar Udruženja endoskopskih hirurga Srbije (SAES)
Načelnik I hirurškog odeljenja, Urgentni Centar, Klinički Centar Srbije
Medicinski fakultet, Univerzitet u Beogradu, Srbija

Dr Ljudmila Jablan, dr Nikola Radmanović

Laproskopska odnosno minimalno invazivna hirurgija predstavlja predstavlja hiruršku tehniku kod koje se napravi nekoliko manjih incizija u koži te se kroz njih uvedu optički i radni instrumenti te se uz minimalnu traumu trbušnog zida pristupa abdominalnim i pelvičnim organima. Obzirom na svoje pogodnosti među kojima su kraći postoperativni oporavak, manja trauma na trbušnom zidu, u brojnim studijama pokazan manji inflamatorni odgovor u odnosu na otvorene operacije i takodje bolji estetski efekat minimalno invazivna hirurgija bi mogla postati zlatni standard u operativnom lečenju različitih oboljenja. Međutim sve češće postavljeno pitanje je mesto minimalne invazivne hirurgije u tretmanu urgentnih stanja, u ovom slučaju akutnog abdomena. Naime, na konferenciji međunarodnih udruženja o formiranju konsenzusa Societa` Italiana di Chirurgia Endoscopica e nuove tecnologie (SICE), Associazione Chirurghi Ospedalieri Italiani (ACOI), Societa` Italiana di Chirurgia (SIC), Societa` Italiana di Chirurgia d'Urgenza e del Trauma (SICUT), Societa` Italiana di Chirurgia nell'Ospedalita` Privata (SICOP), i European Association for Endoscopic Surgery (EAES) 2006 I 2011 postavljene su smernice za operativno lečenje određenih urgentnih hirurških stanja među kojima su akutni holecistitisi, apendicitisi, divertikulitisi, pankreatitisi, uklještene hernije, kod trauma, ginekološka oboljenja i neodređeni abdominalni bol. Predstavljajući rezultate operativnog lečenja pojedinih urgentnih stanja na Klinici za Urgentnu hirurgiju Kliničkog Centra Srbije želimo da više približimo ideju da minimalno invazivna hirurgija nije rezervisana samo za elektivne slučajeve ali takođe prednosti i mane koje postoje u minimalno invazivnoj hirurgiji u navedenim situacijama.

Literatura

1. Samsonov VT, Ermolov AS, Gulyaev AA, Yartsev PA, Levitsky VD, Rogal MM. Laparoscopy in emergency abdominal surgery. Khirurgiia. 2019;(9):32-Balén E, Herrera J, Miranda C, Tarifa A, Zazpe C, Lera JM. El papel de la laparoscopia en la cirugía abdominal urgente [The role of laparoscopy in emergency abdominal surgery]. An Sist Sanit Navar. 2005;28 Suppl 3:81-927.
2. Mandrioli M, Inaba K, Piccinini A, Biscardi A, Sartelli M, Agresta F, et al. Advances in laparoscopy for acute care surgery and trauma. World J Gastroenterol. 2016;;22(2):668-80.
3. Balén E, Herrera J, Miranda C, Tarifa A, Zazpe C, Lera JM. El papel de la laparoscopia en la cirugía abdominal urgente [The role of laparoscopy in emergency abdominal surgery]. An Sist Sanit Navar. 2005;28 Suppl 3:81-92.
4. Guterman S, Mandelbrot L, Keita H, Bretagnol F, Calabrese D, Msika S. Laparoscopy in the second and third trimesters of pregnancy for abdominal surgical emergencies. J Gynecol Obstet Hum Reprod. 2017 May;46(5):417-22.

OBSTETRICS

UTERUS AFTER DIFFERENT TECHNIQUES OF CESAREAN SECTION

Prof. Tihomir Vejnović

Vice President of the Diczfalusy Foundation, Clinic for Gynecology and Obstetrics, Clinical Center of Vojvodina, Faculty of Medicine, University of Novi Sad, Serbia

Ass. Vejnovic Aleksandra, Dr. Karadeglija Bojan

Department of Gynecology and Obstetrics, Clinical Center of Vojvodina, Clinic of Gynecology and Obstetrics, Faculty of Medicine, University of Novi Sad, Serbia

The incidence of the complications in post cesarean pregnancies is increasing. Rupture of the uterus and placenta accreta spectrum are directly associated with the uterine scar. It is becoming clear that the quality of the uterine scar is dominantly determined by the technique used to close the uterus.

To compare anatomical outcomes of the uterus after different techniques of the suturing in cesarean section (SC).

Prospective study approved by the Ethical board was done at the Clinic of Gynecology and Obstetrics – Clinical Center of Vojvodina, from October 2018- April 2019. There were 263 subjects who had undergone SC. During SC the thickness of the uterine scar was evaluated by palpation and measured with the nonius in the level of the upper and lower lips of the uterine incision. Adhesions were graded. Subjects were divided in four groups: 1. Control group – primiparas, and three groups with subjects who had previous SC done by 2. modification Vejnovic 3. double-layer uterine suture with two threads 4. single-layer uterine suture with two threads.

The lower and upper lip was thicker in control group and group 2, compared to group 3 and 4 (lower lip - 10.3, 10.55, 6.1, 7.6 mm, respectively; upper lip – 14.1, 16.2, 11.8, 12.5 mm). Palpatory there were more cases of thin wall in group 4 compared to the other groups (0%, 31.0%, 42.4%, 53.2%, respectively). There were significantly less adhesions in group 2 compared to group 3 and 4, especially those of a more severe degree (degree 2 - 6.9%, 35.5%, 27.3% respectively).

Different techniques of uterus suturing give different anatomical outcomes. Incidence of certain complications should be investigated in context of operative technique of uterus suturing.

References

1. Vejnović T, Vejnović A. New technique in obstetrics: Vejnović modification of caesarean section. Is there an impact on the frequency of placenta increta/percreta? Jatros. Medizin für die Frau 3/16. p.26-9.
2. Kremer TG, Ghiorzi IB, Dibi RP. Isthmocele: an overview of diagnosis and treatment. Rev Assoc Med Bras. 2019;65(5):714-21.
3. Vejnović T, Dan Costa S, Ignjatov A, Vejnović A. Modified Vejnovic technique. In: Ionescu C, Dimitriu M, editors. Operatia Cezariana. Bucharest: Carol Devila University, 2018.
4. Dickov I. [Analysis of the series of cases of placenta accreta at the Clinic for gynecology and obstetrics of the Clinical center of Vojvodina] [master's thesis]. [Novi Sad]: Faculty of Medicine; 2019. 39 p. Serbian.
5. Karadeglija B. [Surgical-anatomical changes during iterative cesarean section in patients operated by different techniques] [dissertation]. [Novi Sad]: Faculty of Medicine; 2019. 44 p. Serbian

Doktor medicine (Medicinski fakultet u Novom Sadu 1984.), specijalista ginekologije i akušerstva (Medicinski fakultet u Novom Sadu 1992.), subspecijalista perinatologije (Medicinski fakultet u Novom Sadu 2008.). Magistar ((Medicinski fakultet u Novom Sadu 1989.) i doktor medisinskih nauka (Medicinski fakultet u Novom Sadu 1992.). Usavršavao se na Klinici Mayo, Karolinska Institutu, Prvom Univerzitetu u Moskvi, Klinikama u Nemačkoj, Austriji, Mađarskoj, Rumuniji i dr. Objavio je veliki broj naučnih i stručnih radova od koji se 7 nalazi na SCI listi.

Dobitnik je diploma Fetal Medicine (London 2000.) i Good Clinical Practice (Segedin). Član je Medicinske Akademije Srpskog lekarskog Društva.

PROSTAGLANDIN E1 IN LABOR INDUCTION – OUR EXPERIENCE

Prim. Danko Natalić

Clinic for Gynecology and Obstetrics, Clinical Center of Montenegro, Montenegro

Induction of labor is the process of initiating contractions in pregnant women who are currently not in labour, to help them achieve delivery within 24 to 48 hours. Cervical ripening is one of the methods used for labor induction - the use of means to soften, efface, or dilate the cervix to increase the likelihood of a vaginal delivery. The two major techniques for cervical ripening are mechanical means (e.g. insertion of balloon catheters), and application of pharmacological agents (e.g. prostaglandins). Prostaglandins are one of the preferred methods for cervical ripening, including the agents dinoprostone and misoprostol.

Labor induction rate is up to 20% of all births in most countries. It is indicated when the risk of continuing the pregnancy outweighs the risks of labor induction and delivery for the mother or the foetus. Induction is contraindicated in previous uterine rupture, pelvic deformities, and abnormal foetal lie or presentation. Labour induction increases the risk of Caesarean section and surgical vaginal delivery, chorioamnionitis, cord prolapse with artificial rupture of membranes, and uterine rupture.

Misoprostol is a synthetic analogue of prostaglandin E1, which has gastric antisecretory and mucosal protective effects. The oral form is approved in many countries for the treatment and prevention of gastroduodenal ulcers. The most common side effects with a single oral dose of misoprostol are diarrhoea, abdominal pain, nausea, flatulence, and dyspepsia. Misoprostol also has uterotonic properties, by contracting smooth muscle fibres in the myometrium and relaxation of the cervix, facilitating cervical opening. The usual dose is 50 mcg orally or 25 mcg vaginally, which may be repeated every 4 hours if contractions are absent or not painful. Serious adverse effects with misoprostol for cervical ripening and labour induction are like other prostaglandins, and include uterine tachysystole, meconium staining of liquor, and rarely, uterine rupture. Other side effects include fever, chills, vomiting, and diarrhoea.

A retrospective study is used for estimating the outcome of all labor induction cases in our facility, in period between November the 1st 2019 to October the 31st 2020.

In period between the 1st November 2019. to 31st October 2020. there were 3022 deliveries in total in Gynaecology and Obstetrics Clinic, Clinical Centre of Montenegro (average number of deliveries for our centre is between 2900-3300, last 10 years). As it is mentioned before, the induction with prostaglandin E2 is common and available in our centre more than 20 years ago, in form of vaginal tablets (gel form is not in use anymore). Misoprostol became available to us last three years, at the beginning used as abortion-inducing drug, for medical termination of pregnancy, combined with mifepristone or alone.

In the last year, we had 113 inductions of labor (3.74% of all deliveries), while 1062 stimulations with oxytocin (35.1% of all deliveries). Of these, dinoprostone was used in 74 and misoprostol in 39 deliveries. The 8 patients from misoprostol group and 5 from dinoprostone group were excluded, where the indication for labor induction was fetal death. We used two protocols, for dinoprostone tablet 3 mg, applications vaginally every 4h, and for misoprostol buccal application of 25 mcg every 4/6h.

Comparing prostaglandin use only, about 65% of all inductions were with dinoprostone and 35% with misoprostol. Comparing characteristics regarding maternal age, number of deliveries in prostaglandin groups were similar. In dinoprostone group more woman needed second and third dose of medication to achieve active labor.

Comparing time from beginning the induction to delivery there was no significant difference. Apgar score (1/5min) for dinoprostone was 8.93/9.49, while for misoprostol was 9.00/9.39. Comparing caesarean section rate, in dinoprostone group it was in 13 patients (17.5%) while in misoprostol group the incidence was lower – 5 patients (12.8%) – caesarean section rate in our centre varies between 20-25% last five years. The most common reason for caesarean section after induction was non-reassuring CTG pattern or dystocia.

There were no fatal (fetal or maternal death) or serious complications (uterine rupture) in any group. The same states for side effects, they were rare, with only two patients in dinoprostone group with nausea and one with tachysystole.

Misoprostol results seem similar as dinoprostone, in terms of efficacy and safety, but there are few advantages. Dosing and terms of application are more practical. There is no need for woman to lie down for two hours after application, which is mandatory with dinoprostone. The oral/buccal application is safer, regarding premature rupture of membranes, in terms of possible medication flushing out and not achieving the goal, also does not facilitate infection in such patients (1-3).

This analysis speaks in favour regarding the use of misoprostol for cervical ripening and induction of labor, providing similar results as other prostaglandins, being more comfortable for application, lower dosing, with less side effects.

References

1. Chatsis V, Frey N. Misoprostol for Cervical Ripening and Induction of Labour: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018.
2. Alfirevic Z, Keeney E, Dowswell T, et al. Methods to induce labour: a systematic review, network meta-analysis and cost-effectiveness analysis. BJOG. 2016;123(9):1462-70.
3. Ten Eikelder ML, Mast K, van der Velden A, Bloemenkamp KW, Mol BW. Induction of Labor Using a Foley Catheter or Misoprostol: A Systematic Review and Meta-analysis. Obstet Gynecol Surv. 2016;71(10):620-30.

Danko Natalić rođenje 1973. godine u Kotoru, Crna Gora, gdje je završio osnovnu i srednju školu. 1992. godine upisao je Medicinski fakultet Univerziteta u Beogradu, gdje je 1999. stekao zvanje doktor medicine. Nakon rada u Hitnoj službi Doma Zdravlja Kotor, od 2001. godine stalno je zaposlen u Kliničkom Centru Crne Gore, Podgorica, na Klinici za ginekologiju i akušerstvo (odjeljenje Patologije trudnoće, Porodilište i Akušersko odjeljenje). 2006. godine stiče zvanje specijaliste ginekologije i sakušerstva na Medicinskom fakultetu Univerziteta u Beogradu. Od 2007. godine uključen u rad Medicinskog fakulteta u Podgorici kao saradnik za predmet ginekologija i akušerstvo i rukovodilac Savjetovališta i škole za trudnice u Domu Zdravlja Danilovgrad. Od 2008. godine potpredsjednik Udruženja ginekologa i akušera Crne Gore, predsjednik regionalne Komisije za prekid trudnoće, član Konzilijuma za kongenitalne anomalije KCCG. 2011/12. završava edukaciju iz uže specijalizacije iz Perinatologije, pri Medicinskom fakultetu Univerziteta u Beogradu. Od 2015. godine načelnik Akušerskog odjeljenja Klinike za ginekologiju i akušerstvo Kliničkog Centra Crne Gore. 2015. godine stiče zvanje Primarijus. 2018. odbrana rada uže specijalizacije iz Perinatologije na Medicinskom fakultetu Univerziteta u Beogradu.

U toku radnog staža učestvuje na brojnim stručnim i naučnim skupovima iz oblasti perinatologije, u zemlji i inostranstvu, kao i na kratkoročnim usavršavanjima. Od stečenih vještina neophodno je istaći: tretman visokorizičnih trudnoća, ultrazvuk u ginekologiji i akušerstvu, invazivne dijagnostičke procedure u perinatologiji i laparoskopske ginekološke operacije. Raspolaže znanjem engleskog i italijanskog jezika.

VENSKI TROMBOEMBOLIZAM U AKUŠERSTVU

Prof. Tatjana Ilić-Mostić

Pomoćnik direktora Centra za anesteziologiju i reanimatologiju, Klinički Centar Srbije
Medicinski fakultet, Univerzitet u Beogradu, Srbija

Venski embolizam u trudnoći i postpartalno (VETP) najčešće nastaje zbog venskog tromboembolizma, uz embolizam amnionskom tečnosti i venski vazdušni embolizam koji se javljaju u mnogo manjem procentu. VETP predstavlja najznačajniji uzrok mortaliteta trudnica. VETP može nastati prepartalno (antepartalno), intrapartalno i postpartalno, odnosno u puerperijumu. Najčešći uzrok venskog tromboembolizma je tromboza dubokih vena donjih ekstremiteta, ali je plućni embolizam moguć i iz površnih vena donjih ekstremiteta, puerperalnih ovarijalnih vena i puerperalnih septičkih pelvičnih vena.

Uzroci tromboembolizma u trudnoći i puerperijumu su rezultat povećanja venske staze, hiperkoagulabilnosti krvi i ozlede vaskulature, naročito tokom vaginalnog porođaja ili carskog reza. Poznati faktori rizika za venski tromboembolizam (VTE) u trudnoći su i gojaznost, prisustvo trombofilije, odnosno lupus antikoagulansa, deficita proteina C i proteina S, antitrombina i disfibrinogenemije. Posledična embolija pluća se može komplikovati plućnim edemom usled porasta hidrostatskog pritiska, disrupcije normalnog kapilarnog integriteta, kao i agresivnom intravenskom terapijom tečnostima.

Terapiju treba započeti odmah po uspostavljanju dijagnoze tromboze dubokih vena. Pored antikoagulante terapije u cilju redukcije nastanka posttromboflebitičkog sindroma treba elevirati nogu uz primenu elastične kompresije. Niskomolekulski heparini (LMWH) se u savremenoj terapiji smatraju lekovima izbora za profilaksu i lečenje tromboza u akušerstvu. LMWH se odlikuju većom bioraspoloživosti, prediktibilnijim odgovorom i dužim poluživotom u odnosu na nefrakcionisani heparin. Severno-američke preporuke u gradaciji stepena rizika za nastanak ponovnog VTE ističu podelu faktora rizika u one sa niskim rizikom, intermedijarnim i visokim rizikom za nastanak VTE.

Standardne profilaktičke doze LMWH mogu se zameniti takozvanim prilagođenim dozama (dose-adjusted) LMWH i u profilaktičkom režimu optimalizovati analizom anti Xa nivoa. Kod asimptomatskih trudnica sa istorijom tromboze dubokih vena anesteziolog pri porođaju ili carskom rezu mora razmotriti rizik i korist od regionalne anestezije, posebno imajući u vidu rizik nastanka hematoma.

Profilaksa, rano prepoznavanje oboljenja, dijagnostika i adekvatna terapija patogenetski različitih oblika tromboembolizma preduslov su adekvatnog zbrinjavanja u akušerstvu.

Literatura

1. Skeith L. Preventing venous thromboembolism during pregnancy and postpartum: crossing the threshold. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):160-167.
2. Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, Vazquez SR, Greer IA, Riva JJ, Bhatt M, Schwab N, Barrett D, LaHaye A, Rochwerg B. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv. 2018 Nov 27;2(22):3317-3359.
3. Fogerty AE. Management of Venous Thromboembolism in Pregnancy. Curr Treat Options Cardiovasc Med. 2018 Jul 23;20(8):69.
4. Ho VT, Dua A, Lavingia K, Rothenberg K, Rao C, Desai SS. Thrombolysis for Venous Thromboembolism During Pregnancy: A Literature Review. Vasc Endovascular Surg. 2018 Oct;52(7):527-534.
5. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 196: Thromboembolism in Pregnancy. Obstet Gynecol. 2018 Jul;132(1):e1-e17.

Prim. Prof. Univ. dr sci med. Tatjana Ilić Mostić, Viši naučni saradnik, Specijalista anesteziologije sa reanimatologijom, subspecijalista Kliničke farmakologije i Medicine bola. Godina rodjenja: 1965.

Školovanje: Medicinski fakultet, Univerziteta u Beogradu, upisala 1983/84; završila 1989. Napredovanje u službi: 1992. prvo radno mesto u Urgentnom centru KCS, do 1996. kada prelazi na Kliniku za ginekologiju i akušerstvo. Načelnik Odeljenja anestezije i reanimacije pri Klinici za ginekologiju i akušerstvo 2003.god. Pomoćnik direktora Centra za anesteziju i reanimaciju KCS, decembar 2014. god. Položen specijalistički ispit sa odličnim uspehom 1996. Magistarska teza na Katedri za kardiologiju odbranjena na Medicinskom fakultetu u Beogradu 2000. Odbranjena doktorska teza na Medicinskom fakultetu u Beogradu 2005. Odlukom Ministarstva nauke od 2017. zvanje Višeg naučnog saradnika u oblasti medicinskih nauka. Odlukom Ministarstva zdravlja Republike Srbije, od 24.09.2009. naziv – Primarijus.

Osnivač Srpskog aktiva akušerskih anesteziologa pri Sekciji za anesteziologiju, reanimatologiju i intenzivnu terapiju, Srpskog Lekarskog Društva, 2009.god. Odlukom Medicinskog fakulteta, Univerziteta u Beogradu, izabrana 2012.god. u zvanje Profesora za poslediplomsku nastavu. Završene subspecijalističke studije iz oblasti Klinička farmakologija – farmakoterapija i subspecijalističkih studija iz Medicine bola.

POROĐAJ KOD INTRAUTERUSNOG ZASTOJA U RASTU PLODA

Doc. Vesna Mandić Marković

Klinika za ginekologiju i akušerstvo Narodni Front
Medicinski fakultet, Univerzitet u Beogradu, Srbija

U grupi ranih preterminskih neonatusa u podgrupi sa prisutnim neonatalnim mortalitetom/morbiditetom i podgrupi sa acidozom/asfiksijom porođaj je češće indikovan stanjem ploda (86.7 i 63.3%%), dok je u podgrupi bez neonatalnog morbiditeta i acidoze indikacija postavljana najčešće zbog stanja majke (66.7%); 5-minutni Apgar skor je najniži u podgrupi sa prisutnim neonatalnim mortalitetom/morbiditetom; pH artrijske krvi pupčanika je niža u podgrupi sa prisutnim neonatalnim mortalitetom/morbiditetom i podgrupi sa acidozom/asfiksijom; telesna masa na rođenju najniža u podgrupi sa prisutnim neonatalnim mortalitetom/morbiditetom; a dužina hospitalizacije najkraća u podgrupi bez neonatalnog morbiditeta i acidoze. Nije uočena statistički značajna razlika u učestalosti Carskog reza i pola neonatusa. U grupi kasnih preterminskih neonatusa nije nađena statistički značajna razlika u indikacijama za porođaj, načinu porođaja i polu deteta. 5-minutni Apgaru je niži u podgrupi sa prisutnim neonatalnim mortalitetom/morbiditetom i podgrupi sa acidozom/asfiksijom; pH pupčanika i telesna masa na rođenju su niži u podgrupi sa prisutnim neonatalnim mortalitetom/morbiditetom i podgrupi sa acidozom/asfiksijom; a dužina hospitalizacije najkraća u podgrupi bez neonatalnog morbiditeta i acidoze. Nije nađena značajna razlika u indikacijama za porođaj, u vrednosti pH pupčanika, niti u polu deteta između grupa ranih i kasnih preterminskih neonatusa. Porođaj je češće završavan Carskim rezom kod ranih preterminskih neonatusa, 5-minutni Apgar skor i telesna masa su bili niže, a dužina hospitalizacije duža u grupi ranih preterminskih neonatusa.

Ne postoji konsenzus o vremenu porođaja kod IUZR, a preporučuje se individualan pristup koji treba bazirati na gestacijskoj dobi i stanju ploda. Porođaj je indikovan ukoliko postoji mogućnost smrti ploda u slučaju nastavka trudnoće i u manjog gestaciji, ali je uvek indikovana primena kortikosteroida u cilju maturacije fetalnih pluća.

GRIT studija (Growth Restriction Intervention Trial) obuhvatila je 587 preterminskih trudnoća sa IUZR između 24 i 36 ng kod kojih su sprovedeni hitan porođaj ili intenzivno praćenje. U grupi hitnog porođaja bilo je manje intrauterusne smrti ploda, ali je neonatalna smrtnost bila veća. Nije postojala razlika u neonatalnom morbiditetu, kao ni u psihomotornom razvoju nakon dve godine.

U DIGITAT studiji (Disproportionate Intrauterine Growth Intervention Trial At Term) ispitan je porođaj kod terminskih IUZR i nije nađena razlika u neonatalnom ishodu između grupa hitnog porođaja i intenzivnog monitoringa, osim što su u grupi hitnog porođaja deca rođena 10 dana ranije u odnosu na grupu monitoringa.

TRUFFLE studija (Trial of Randomized Umbilical and Fetal Flow in Europe) uključila je 503 slučajeva jednoplodnih trudnoća 26 do 32ng sa IUZR i Pi a.umbilicalis > 95-og percentila. Intrauterusna smrt je nastupila u 2.4%, gestacijska dob na porođaju je bila 30.7±2.3 ng, a telesna masa je bila 1013 ± 321 g. Carski rez je urađen kod 97%, a kod 81% porođaj je indikovan stanjem ploda. Neonatalna smrt nastupila je u 5.5%, a težak neonatalni morbiditet kod 24%. Neonatusi sa morbiditetom i mortalitetom su bili manje telesne mase na rođenju (867 ± 251 g) i rođeni ranije(29.6 ± 2.0ng). Ukupni perinatalni ishod – 8% perinatalnog mortaliteta i čak 70% bez ozbiljnog neonatalnog morbiditeta ukazuju na relativno dobar ishod ranih preterminskih trudnoća sa IUZR.

Literatura

1. Baschat AA. Planning management and delivery of the growth-restricted fetus. Best Pract Res Clin Obstet Gynaecol. 2018 May;49:53-65.
2. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics and the Society forMaternal-FetalMedicin. ACOG Practice Bulletin No. 204: Fetal Growth Restriction. Obstet Gynecol. 2019 Feb;133(2):e97-e109.
3. Lausman A, Kingdom J; MATERNAL FETAL MEDICINE COMMITTEE. Intrauterine growth restriction: screening, diagnosis, and management. J Obstet Gynaecol Can. 2013 Aug;35(8):741-748. English, French.
4. Frusca T, Todros T, Lees C, Bilardo CM; TRUFFLE Investigators. Outcome in early-onset fetal growth restriction is best combining computerized fetal heart rate analysis with ductus venosus Doppler: insights from the Trial of Umbilical and Fetal Flow in Europe. Am J Obstet Gynecol. 2018 Feb;218(2S):S783-S789.
5. Boers KE, Bijlenga D, Mol BW, LeCessie S, Birnie E, van Pampus MG, Stigter RH, Bloemenkamp KW, van Meir CA, van der Post JA, Bekedam DJ, Ribbert LS, Drogtrop AP, van der Salm PC, Huisjes AJ, Willekes C, Roumen FJ, Scheepers HC, de Boer K, Duvekot JJ, Thornton JG, Scherjon SA. Disproportionate Intrauterine Growth Intervention Trial At Term: DIGITAT. BMC Pregnancy Childbirth. 2007 Jul 10;7:12.
6. Van Wassenaer-Leemhuis AG, Marlow N, Lees C, Wolf H; TRUFFLE investigators. The association of neonatal morbidity with long-term neurological outcome in infants who were growth restricted and preterm at birth: secondary analyses from TRUFFLE (Trial of Randomized Umbilical and Fetal Flow in Europe). BJOG. 2017 Jun;124(7):1072-1078.

Vesna Mandić Marković je docent Medicinskog fakulteta Univerziteta u Beogradu, šef odseka odmakle trudnoće Patologija 1. Uža naučna oblast: Ginekologija i akušerstvo perinatologija. „The Fetal Medicine Foundation - Advanced Course in Fetal Medicine", 2002. godine, položen teoretski ispit za "Diploma in Fetal Medicine". Usavršavanja: „The Fetal Medicine Foundation - 11 – 13+6 weeks scan" 2005. godine, diploma i sertifikat za merenje vratne brazde. "Salzburški medicinski seminari" iz oblasti ginekologije i akušerstva, OMI (Open Medical institute), Salzburg, Austrija 2006. godine. Studijsko putovanje u Veliku Britaniju sa posetom The Fetal Medicine Foundation i King`s College u Londonu 2007. godine. Stručno usavršavanje na Odeljenju prenatalne dijagnostike Ginekološko-akušerske klinike Opšte bolnice – AKH u Beču 2010. godine. Introduction to Good Clinical Practice u Vienna School of Clinical Research u Beču, 2010.godine, položen završni ispit kursa. Stručno usavršavanje na UNIVERSITY MEDICAL CENTER–UKE u Hamburgu, 2015.godine.

ZNAČAJ MIKROBIOMA TRUDNICE I NOVOROĐENČETA

Prim. Tatjana Nikolić

Načelnik neonatalne intenzivne nege i pomoćnik direktora za neonatologiju
Klinika za ginekologiju i akušerstvo, Klinički Centar Srbije, Srbija

Sve je više dokaza da je mikrobiom jedan od najznačajnijih faktora koji određuju naše zdravstveno stanje. Mikroorganizmi, prevashodno bakterije, naseljavaju sve organe i organske sisteme čoveka i imaju brojne i veoma važne nutricione, fiziološke, metaboličke i imunološke funkcije. Stoga se dizbioza smatra faktorom rizika za razvoj širokog spektra različitih patoloških stanja uključujući alergije, autoimune, kardiovaskularne i metaboličke bolesti, digestivne poremećaje, pa čak i psihološke probleme kao što su autizam, anksioznost i depresija. Izmenjen model kolonizacije ima poseban značaj ukoliko se odvijao u kritičnom uzrastu metaboličkog i imunološkog razvoja. Imajući to u vidu, najmlađi uzrast, počevši već od koncepcije i nadalje u prve dve godine života, predstavlja značajan vremenski prozor za uspostavljanje interakcije domaćin- mikrobiom. Tokom ovog perioda, više veoma značajnih faktora određuju mikrobiotski sastav, ali se uz genetsku predispoziciju, vertikalna transmisija sa majke na dete tokom trudnoće, način završetka porođaja, gestacijska starost, tretman i ishrana u prvim danima života izdvajaju kao posebno značajni za razvoj mikrobioma.

Literatura

1. Tanaka M, Nakayama J. Development of the gut microbiota in infancy and its impact on health in later life. Allergol Int. 2017 Oct;66(4):515-522.
2. Lu J, Claud EC. Connection between gut microbiome and brain development in preterm infants. Dev Psychobiol. 2019 Jul;61(5):739-751.
3. Ihekweazu FD, Versalovic J. Development of the Pediatric Gut Microbiome: Impact on Health and Disease. Am J Med Sci. 2018 Nov;356(5):413-423.
4. Stiemsma LT, Michels KB. The Role of the Microbiome in the Developmental Origins of Health and Disease. Pediatrics. 2018 Apr;141(4):e20172437.

Tatjana Nikolić – Prim dr sc med naučni saradnik na Klinici za ginekologiju i akušerstvo Kliničkog centra Srbije. Uža naučna oblast: neonatologija.

Usavršavanja: American Austrian Founndation Salzburg- Columbia Seminar in Neonatology 2002; Ultrazvuk CNS- praktični i teoretski kursevi, Beograd 2002, Kragujevac 2003; IPOKRATES Clinical Seminar “Infectious diseases and immunology in the neonate” , Innsbruck-Austria 2003; Internship in neonatology, American Austrian foundation, Graz- Austria 2003; Internship at the Neonatal intensive care unit at rhe College of physicians and surgeons Columbia university New York, 2003; Neonatal resuscitation course, according to American Academy of Pediatrics and American Heart Association, Belgrade 2004; Residental training course in Neonatal intensive care, Genova - Italy 2005.

CARSKI REZ – GDJE SMO DANAS?

Dr Branka Semiz

Načelnik odeljenja ginekologije i akušerstva, Bolnica Srbija, Istočno Sarajevo, Republika Srpska

Dr Vladimir Radović

Bolnica Srbija, Istočno Sarajevo, Republika Srpska

Carski rez je akušerska operacija kojom se kroz rez na trbušnom zidu i donjem dijelu prednjeg zida uterusa vrši akstrakcija ploda i završava porođaj (trudnoća) abdominalnim putem.

Carski rez se spominjao još u praistorijskim vremenima. Podaci o operacijama na živim ženama se tek ponegdje pominju u Srednjem vijeku. Većina ljekara je osuđivala ovaj postupak zbog visokog mortaliteta usljed krvarenja i sepse. Tek krajem 19. Vijeka, sa razvojem aseptičnih tehnika i tehnika zašivanja reza na uterusu, mortalitet je počeo da se smanjuje.

Indo-evropska mitologija je bogata opisima abdominalnih porođaja. Dionis, grčki bog vina rođen je prije vremena dok je njegova majka bila na samrti. Porođaj Eskulapa, prvog ljekara, čiji je štap sa krilatim zmijama simbol medicine, obavio je njegov otac Apolon poslije smrti nimfe Korone.

Pisani podaci o carskim rezovima post mortem javljaju se nekoliko stotona godina prije Hrista. U „*Lex Regis de Inferendo Mortis*“ iz 175 godine p.n.e. propisano je da trudnicu koja umre treba što prije poroditi da bi se spasilo dijete. I Šekspir je u „Magbetu“ opisao rađanje carskim rezom *post mortem*.

Jedna od najvećih zabluda o porijeklu naziva „carski rez“ je da je carskim rezom rođen Julije Cezar. Međutim u to doba takva vrsta operacije je bila fatalna po majku, a poznato je da je Julija cezara majka pratila tokom njegovih osvajanja u sjevernoj Evropi 30 godina kasnije. Prvi pisani trag o carskom rezu u Srbiji potiče od dr Jovana Valente (1826-1887).

Prosječna učestalost prema zvaničnim podacima WHO u visokorazvijenim zermljama je 15-20%, u BiH 20-30%, Švajcarska i Italija preko 30%, Brazil preko 50%. Učestalost preko 10 % nije opravdana smanjenjem perinatalnog morbiditeta i mortaliteta.

Indikacije:

- Apsolutne
- Relativne
- Proširene

Apsolutne: apsolutno sužena karlica, anomalije i genitalna oboljenja koja čine prepreku rađanju, poprečni položaj ploda, centralna placenta previja, prijeteća ruptura uterusa, abrupcija posteljice težeg stepena, eklampsija-preeklampsija, genitalni herpes.

Relativne: disproporcija cephalo-pelvina, placenta previja lat., preeklampsija, I.U.G.R., akutni fetalni distres, blizanačka trudnoća s nepovoljnim plożajem ploda (plodova), dijabetes melitus (gest.), primarna inercija uterusa, distocija, stanje poslike klasične konizacije PVU

Proširene: Abrupcija posteljice manjeg stepena, karlična prezentacija, defleksioni stavovi i anomalije rotacije, prolaps pupčanika (vasa praevia, velamentozna insercija), ožiljak na materici (prethodni s.c., miomektomija, malformacije ploda, ankiloza karličnih zglobova, rekto- i vesikovaginalne

fistule, varikoziteti genitalija, veliki šiljati kondilomi, psihoze, ablacija retine, hipertireoza, starost prvorotke preko 35 godina, infertilitet, loš perinatalni ishod iz ranijih trudnoća ili porođaja.

Cilj rada je prikazivanje učestalosti carskih rezova na Ginekološko-akušersko odjeljenju JZU Bolnice“ Srbija“ Istočno Sarajevo u periodu od 2009-2018, poređenje učestalosti u dva petogodišnja perioda.

Podaci za analizu korišteni su iz Porođajnog protokola odjeljenja za ginekologiju i akušerstvo JZU Bolnice „Srbija“ Istočno Sarajevo. Određivan je procenta carskih rerzova, paritet majke, indikacije za carski rez.

Tabela 1. Paritet i starost porodilje u periodu 2009-2013. godina

GODINA	2009		2010		2011		2012		2013	
	n	%	n	%	n	%	n	%	n	%
POROĐAJ	509	100	516	100	502	100	513	100	455	100
S.C.	106	21,7	105	20,3	100	19,9	109	21,2	113	24,8
NULIPARE	61	57,5	48	45,7	64	64	62	56,9	71	62,8
MULTIPARE	45	42,5	57	54,3	36	36	47	43,1	42	37,2
DO 25	23	21,8	13	12,6	8	8	9	8,2	11	9,8
25-30	39	36,8	40	38,2	52	52	44	40,4	34	30,0
30-35	33	31,1	23	22,0	21	21	25	22,9	42	37,2
VIŠE OD 35	11	10,4	29	27,1	19	19	31	28,4	26	23,0

PROSJEK 21,6 %

Tabela 2. Indikacije u periodu 2009-2013. godina

GODINA	2009		2010		2011		2012		2013	
INDIKACIJE	n	%	n	%	n	%	n	%	n	%
PON. S.C.	30	28,3	36	34,3	24	24	28	26,0	27	23,9
ASFIKSIJA	13	12,3	12	11,5	9	9	8	7,3	11	9,8
DRUGE IND. *	10	9,4	5	4,8	6	6	3	2,7		
KARLIČNA P.	9	8,5	5	4,8	8	8	5	4,6	8	7,1
DISPROP.	7	6,7	8	7,6	10	10	13	11,9	12	10,6
INERCIJA	6	5,7	12	11,5	9	9	12	11,0	10	8,8
PIH I PREKL.	6	5,7	4	3,8	4	4	4	3,7	3	2,6
KOMOPL. PUP.	5	4,7	1	0,9	2	2	2	1,8	2	1,8
ABRUPCIJA	5	4,7	3	2,8	1	1	3	2,7	5	4,4
PROM	3	2,8	2	1,9	4	4	11	10,1	11	9,7
IUGR	3	2,8	2	1,9	4	4	2	1,9	3	2,6
PROLONG.	2	1,9	2	1,9	4	4	1	0,9	4	3,6
GEMINI	2	1,9	2	1,9	7	7	4	3,7	4	3,6
STARA PRVOR.	2	1,9	5	4,8	3	3	5	4,6	2	1,8
ANOM. UT.	1	0,9	1	0,9	1	1	3	2,7	4	3,6
OP. UT.	1	0,9	1	0,9	2	2	2	1,8	3	2,6
PL. PRAEVIA					2	2	5	4,6	2	1,8

IVF							3	2,7	2	1,8
FMU	1	0,9								

Oboljenja majke (miopija, diskus hernija, povrede kičme i karlice, trombocitopenije, dijabetes..)

Tabela 3. Paritet i starost porodilje u periodu 2014-2018. godina

GODINA	2014		2015		2016		2017		2018	
	n	%	n	%	n	%	n	%	n	%
POROĐAJ	490	100	454	100	495	100	489	100	447	100
S.C.	117	23,9	117	25,8	130	26,3	142	29	158	35,3
NULIPARE	80	64,4	56	47,9	64	49,2	87	61	85	53,9
MULTIPARE	37	31,6	61	52,1	66	50,8	55	39	73	46,1
DO 25	16	13,7	11	9,4	9	6,9	17	12	15	9,5
25-30	37	31,6	36	30,7	36	29,2	41	28,9	47	29,7
30-35	35	29,4	45	38,5	42	32,3	49	34,5	53	33,5
VIŠE OD 35	29	24,8	25	21,4	40	30,8	35	24,6	41	27,3

PROSJEK 28,6 %

Tabela 4. Indikacije u periodu 2014-2018. godina

GODINA	2014		2015		2016		2017		2018	
INDIKACIJE	n	%	n	%	n	%	n	%	n	%
PON. S.C.	22	18,1	36	30,8	41	31,5	33	23,2	55	36,2
ASFIKSIJA	12	10,2	11	9,4	13	10	17	12	17	10,7
DRUGE IND. *	4	3,4	6	5,1	8	6,2	5	3,5	3	1,8
KARLIČNA P.	15	12,8	4	3,4	10	7,7	16	11,3	8	5
DISPROP.	12	10,2	14	12,0	10	7,7	14	9,9	16	10
INERCIJA	16	13,7	15	12,8	17	13,1	18	12,7	21	13,2
PIH I PREKL.	4	3,4	7	6,0	4	3,1	7	5,0	4	2,4
KOMOPL. PUP.	2	1,7	5	4,3	5	3,8	2	1,4	3	1,8
ABRUPCIJA							2	1,4	2	1,2
PROM	11	9,4	6	5,1	4	3,1	8	5,6	7	4,3
IUGR	3	2,6	3	2,6	3	2,3	1	0,7	3	1,8
PROLONG.					3	2,3				
GEMINI	6	5,1	4	3,4	3	2,3	4	2,8	5	3,2
STARA PRVOR.	2	1,7			4	3,1	5	3,5	3	1,8
ANOM. UT.	4	3,4	1	0,8					3	1,8
OP. UT.	4	3,4	3	2,6	3	2,3	3	2,1	4	2,4
IVF	2	1,7	1	0,8	5	3,8	6	4,2	2	1,2
FMU							1	0,7	1	0,6

Ako uporedimo incidencu carskih rezova za period od 2009-2013g od 21,3% i u periodu od 2014-2018 od 28% može se zaključiti znatan porast incidence casrskih rezova. Nisu se pojavile nikakve nove indikacije,već se i dalje zadržala vodeće indikacija ponovljeni casrski rez.

Literatura

1. WHO. Appropirate technology for birth. Lancet 1985;2:436-37.
2. Robson MS. Clasification of cesaren section: a systematic review Plos ONE . 2011;6:e14566.
3. Marija Hadzi-Lega 13th World Congres of Perinatal Medicine, 2017.
4. WHO Statement on Cesarean Section Rates WHO/RHR/15.02. World Health Organization 2015.
5. Barber EL, Lundsberg LS, Belenger K, Pettker CM, Funai EF, Illuzzi JL. Indications contributing to the incrasing cesrion delivery rate. Obst Gynecol. 2011; 118(1):29-30.

Rođena u Sarajevu 1962 godine. Osnovnu školu i gimnaziju završila na Ilidži, diplomirala na Medicinskom fakultetu u Sarajevu 1986 godine. Bila zaposlena u DZ Goražde, DZ Ilidža, Zavodu za zdravstvenu zaštitu radnika Famos, UMC Sarajevo-Klinika za Ginekologiju i akušerstvo.

Početak rata 1992 je zatiče na porodiljskom odsustvu, ali se odmah zajedno sa Prim. Dr Vladimirom Mehmedbašićem, angažuje u Porodilištu DZ Srpska Ilidža (operativni zahvati obavljani u ratnoj Bolnici „Žica“ Blažuj). Od potpisivanja Dejtonskog sporazuma prelazi u Bolnicu „Kasindo“. Specijalistički ispit iz ginekologije i akušerstva polaže 1997 u KC Srbije na Klinici za Ginekologiju i akušerstvo „Narodni front“. Supspecijalistički ispit iz perinatologije polaže 2004 godine u UKC Sarajevno-Klinika za ginekologiju i akušerstvo. Prva u javnoj ustanovi u Republici Srpskoj radi amniocentezu od 2006 godine. Iz oblasti invazivnog ultrazvuka prezentira vlastita iskustva na Kongresu za ultrazvučni dijagnostiku u Beogradu i Kongersu ginekologa akušera BIH u Sarajevu.

Od 2002 do 2003 i od 2007 do 2015, te od 2019 šef odjeljenja za ginekologiju i akušerstvo. Kao vanjski ocjenivač bila angažovana u Agenciji za akreditasciju i sertifikasciju zdravsvenih ustanova Republike Srpske. Učestvuje u radu Skupštine društva doktora medicine RS-a, član Komisije za priznanja i nagrade Komore doktora medicine RS-a, učestvovala u osnivačkoj skupštini Udruženja perinatologa BIH.

Udata, majka jednog djeteta.

PERINATOLOGY

PREVREMENI PORODJAJ – „VELIKI OPSTETRIČKI SINDROM" – NASTANAK I LEČENJE

Prof. Goran Relić

Medicinski fakultet, Univerzitet u Prištini sa sedištem u Kosovskoj Mitrovici

Prevremeni porođaj predstavlja još uvek jedan od najznačajnijih problema u porodiljskoj praksi. Javlja se u 5-10% svih porođaja u većini zemalja Evrope, Severne Amerike i Australije dok je u zemljama u razvoju učestalost prevremenog porođaja veća i iznosi između 10-15 % svih porođaja. Prevremeni porođaj je odgovoran za oko 70-75 % neonatalnog mortaliteta i najveći deo neonatalnog morbiditeta, sa još uvek nepoznatom etiologijom u oko 50% slučajeva. Ovo je sigurno i razlog zašto je učestalost prevremenog porođaja u poslednjih šest decenija bez bitnijih promena, čak i u porastu, u većini industrijski razvijenih zemalja. Prematuritet predstavlja veliki problem, kako za pojedinca, tako i za porodicu i društvo u celini. Celokupno društvo izdvaja ogromna materijalna sredstva, imajući u vidu troškove lečenja velikog broja oboljenja iz grupe ranog i kasnog neonatalnog morbiditeta, kao i za negu ovakvih pacijenata.

Definisanje prevremenog porođaja kao „Velikog opstetričkog sindroma" (Romero R., 3rd International Preterm Labour Congress, Montreux, Switzerland 2006) podrazumeva multiplu etiologiju prevremenog porođaja, koji predstavlja kasnu kliničku manifestaciju hroničnog inzulta i zaštitnu manifestaciju od rizika intrauterine smrti ploda. Glavni događaj koji dovodi do prevremenog porođaja su prevremeno započete kontrakcije. Postavlja se osnovno pitanje: koji etiološki faktori dovode do narušavanja ravnoteže između elemenata koji inhibišu uterusnu aktivnost i elemenata koji na ovu aktivnost deluju stimulativno? Radi se o različitim endogenim faktorima, egzogenim faktorima i faktorima socijalne sredine. U suštini, u literaturi koja ispituje etiologiju prevremenog porođaja, postoje dve vrste studija: *kliničke (epidemiološke)* i studije koje se bave *razumevanjem* nastanka prevremenog porođaja (*različite biohemijske, patohistološke, histološke i histohemijske studije*). Ove studije objašnjavaju mehanizme uterine aktivnosti u vezi s funkcijama različitih hormona, enzima, jona i drugih agenasa, te su često u suprotnosti sa dosad utvrđenim postavkama. Danas veliki broj studija koje ispituju etiologiju prevremenih porođaja odnosi se na razumevanje biohemijskih aspekata koji do njega dovode. One su uglavnom fokusirane na prostaglandine, inhibitore aktivnosti kalcijumskih kanala i ekstarcelularni matriks. Poslednjih godina posebna pažnja se usmerava na istraživanje imunoloških činilaca. Mogući biološki putevi prevremenog porođaja:

- Kortikotropni rilizing hormoni u stresu majke i fetusa
- Citokini sa inflamacijom amniona i horiona
- Aktivnost metileterhidrofolat-reduktaze kod uteroplacentalnih vaskularnih lezija
- Mehaničko rastezanje miometrijuma usled rapidnog povećavanja veličine uterusa dovodi do aktivacije oksitocinskih receptora i sinteze prostaglandina
- Genetski poremećaji koji nastaju na račun dejstva toksina spoljašnje sredine

Prostaglandini se nalaze u suštini svih navedenih zbivanja tokom započinjanja, kako prevremenih uterinih kontrakcija, tako i normalnog započinjanja porođaja. Do sada ništa nije pronađeno što bi navelo na to da je mehanizam prevremenog porođaja i njegova patogeneza različita od normalnog mehanizma porođaja, osim različite zrelosti fetusa.

Prostaglandini igraju ključnu ulogu u inicijaciji (započinjanju) porođaja i zajedno sa oksitocinom održavaju kontinualnost porođaja. Prostaglandini iz decidualnih ćelija uterusa, posebno PGF2α i

PGE2, deluju parakrinim mehanizmom na glatke mišićne ćelije u zidu uterusa. Blizu porođajnog termina nađena je visoka koncentracija arahidonske kiseline (AA), prekursora prostaglandina, kao i samih prostagalnadina u fetalnim membranama. Prostaglandini imaju *tri* glavna efekta: *vrše snažnu stimulaciju* kontrakcija glatkih mišićnih ćelija u zidu uterusa, *potenciraju kontrakcije izazvane oksitocinom*, promocijom formiranja poroznih veza (gap junctions) između glatkih mišićnih ćelija uterusa i istovremeno dovode *do omekšavanja, dilatacije i opuštanja cerviksa* - na samom početku porođaja.

Pri kraju trudnoće u uterusu žene porastu receptori za oksitocin 100-200 puta, što se odražava u povećanoj osetljivosti na oksitocin. Pošto intravenozno unet oksitocin povećava učestalost i intenzivnost materičnih kontrakcija, prirodno je pretpostaviti da oksitocin igra važnu ulogu u inicijaciji porođaja. Prihvatanje oksitocina, kao supstancije za inicijaciju (započinjanje) porođaja ipak je teško iz dva razloga: nivo oksitocina u krvi se ne podiže pre porođaja i oslobađanje oksitocina ostaje konstantno tokom trudnoće. Iako oksitocin verovatno igra ulogu u potpori porođaja, njegova uloga u inicijaciji porođaja, bilo prevremenog ili terminskog, nije ustanovljena. Ova aktivacija porođaja dovodi se u vezu sa: infekcijom gornjeg genitalnog trakta, infekcijom decidue i intrauterinim krvarenjem. Vasik et al. (1978) podržavaju koncept da oksitocin verovatno doprinosi formiranju prostaglandina.

Oksitocin i vazopresin su usko povezani sa peptidima poznatim kao neurofizini preko kojih se i oslobađaju. Cirkulišući oksitocin vezuje se za oksitocin receptore (Gq-kuplovane) na plazma membrani glatkih mišićnih ćelija uterusa, dovode do signalne kaskadne reakcije fosfolipaze C (PLC). Stvoreni IP3 kao sekundarni glasnici otvaraju IP3- zavisne kalcijumove kanale i dovode do oslobađanja Ca2+ iz unutrašnjih depoa tj. sarkoplazminog retikuluma. Tako se povećava intracelularna koncentracija Ca2+ i aktivira kalmodulin. Ca-kalmodulin stimuliše fosforilaciju lakih lanaca miozin kinaze (MLCK), što dovodi do kontrakcije glatkih mišićnih ćelija uterusa i povećanja intrauterinog pritiska.

Danas sve veći značaj ima primarna prevencija sa ciljem redukcije faktora rizika u prekoncepcijskom periodu i ranoj trudnoći. Ona obuhvata: prekoncepcijski i intragraviditetni skrining i eradikaciju infekcije; prekoncepcijsku i intragraviditetnu endokrinu i metaboličku kontrolu; prekoncepcijsku hiruršku terapiju anatomskih poremećaja; prekoncepcijsku i intragraviditetnu terapiju imunoloških i koagulacionih poremećaja; izbegavanje faktora rizika (fizičkih i emocionalnih stresova); duži dnevni odmor u postelji u bočnom položaju.Važnu ulogu ima prenatalna nega, pravilna ishrana trudnica, sprečavanje nepovoljnih uticaja stresa, cigareta, alkohola, toksina, droga i drugih teratogena na plod, lečenje hroničnih bolesti i genitourinarnih infekcija, edukacija trudnica u cilju prepoznavanja ranih znakova prevremenog porođaja, primena serklaža, hidratacije, sedacije, antikoagulantne terapije itd. Anamnestički podaci o prethodnom prevremenom porođaju predstavlja najbolji prediktivni faktor (Mercer et al, 1999.g.). Žene koje su ranije imale sponatni prevremeni porođaj i spontano prevremeno prsnuće plodovih ovoja, imaju mnogo veći rizik, za ponovni spontani prevremeni porođaj i spontano prevremeno prsnuće plodovih ovoja u odnosu na ostale žene.

Tokoliza sigurno predstavlja jednu od najvažnijih mera u tretmanu prevremenih porođaja pored napred navedenih mera i postupaka. Tokoliza je inhibicija neželjene ili preterane uterine aktivnosti (Mosler 1975). U poslednjih 50-tak godina korišćen je veliki broj lekova za supresiju uterine aktivnosti, bilo samostalno ili u kombinaciji. Korišćenje većine tokolitičkih sredstava u terapiji prevremenih porođaja ili je bilo nedelotvorno, ili su se javljali neprihvatljivi sporedni efekti, zbog čega su se pojedini lekovi tokom vremena izbacili iz tokolitičke upotrebe. Do sada su primenjivani:

progesteron i sintetski derivati progesterona, etanol, analgetici, sedativi, hipnotici, prostaglandin sintetski inhibitori, magnezijum sulfat (MgSO4), diazoksid , nitrooksidni donori (nitric oxide donors), β-simpatomimetici, antagonisti kalcijuma (Blokatori kalcijumskih kanala), antagonisti oksitiocinskih receptora, inhibitori RhoA kinaza- studije in vitro, modulatori kalijumskih kanala

Od nabrojanih lekova, prema brojnim podacima iz literature, izgleda da su do sada najčešće korišćeni β-simpatomimetici. Faza kliničkog ispitivanja ritodrina počinje 1972. Godine, a 1979.god. u Sjedinjenim Američkim Državama (SAD) je odobren od strane Uprave za hranu i lekove, kao prvi zvanični tokolitik. Danas oni više nisu lekovi izbora u tretmanu pretećih prevremenih porođaja. Sve više se zamenjuju novim, boljim tokolitičkim sredstvima. Ovo se pre svega odnosi na primenu blokatora kalcijumskih kanala (nifedipin-a) i antagonista oksitocinskih receptora (atosiban-a).

Primena nifedipina (kao tokolitika) počela je u našoj zemlji devedesetih godina prošlog veka. Naše prvo istraživanje izvršeno je na patologiji trudnoće Ginekoloko-akušerske klinike u Novom Sadu u periodu od 01.01.1991.g. do 01.07.1992.godine. Osnovni cilj istraživanja bio je upoređivanje kliničke efikasnosti dejstva ritodrina i nifelata u sprečavanju prevremenih porođaja. Od ukupno 200 žena: 100 je tretirano ritodrinom (skraćeno RT) 8x 1/2 tbl, tbl =5 mg i 100 je tretirano nifelatom (skraćeno Nf) 3x1 tbl, tbl= 10 mg Nf).

Tabela 1. Kriterijum efikasnosti dejstva Rt (ritodrina) i Nf (nifelata)

KRITERIJUMI EFIKASNOSTI	RITODRIN	NIFELAT	STATISTIČKI ZNAČAJNA RAZLIKA
Opšti uspeh lečenja (potpun uspeh) (%)	75,2	74,2	nema
Prosečno vreme od započete terapije do završetka trudnoće (dani)	63,8	54,3	P<0,05
Gestacijska starost na kraju trudnoće (x u danima)	37,8	37,7	nema
Dostignuće 36 n.g. (%)	81,4	83,9	nema
Porođajna masa 2500 (%)	85,1	92,3	nema
Prosečna porođajna masa (g)	3230	3239	nema
Telesna dužina novorođenčadi (cm)	48,9	49,1	nema
Apgar score u 1 min.	8,6	8,8	nema
Apgar score u 5 min.	9,8	9,7	nema
Najčešći način završavanja porođaja (vag. bez intervencije) (%)	57,9	50,5	nema
Učestalost RDS-a (%)	9,5	5,5	P<0,05
Učestalost neuspešnih trudnoća (neonatalna smrt) (%)	4,1	3,2	nema

Rezultati naše tadašnje studije potvrđeni su u kasnijim mnogobrojnim velikim ispitivanjima (MEDLINE 1965-1998; Embase 1988-1998; Current Contents 1997-1998; Cochrane za 1998). U zaključku većine autora ukazuje se da je nifedipin, iako nikad nije bio izložen dobro kontrolisanoj studiji sa placebom, ipak dobio priznanje kao jedan od mogućih prvolinijskih tokolitičkih lekova.

Pokazali su se kao efikasni inhibitori oksitocin indukovanih uterusnih kontrakcija na in vitro i in vivo animalnim modelima. Najviše je ispitivan atosiban, nona- peptid analog oksitocinu, koji se kompetitivno povezuje sa oksitocin- vazopresin receptorom. Prvi rezultati primene atosibana u SAD-u nisu pokazali značajnu razliku u produženju trudnoće, tj. vremenu od početka terapije do porođaja u odnosu na placebo, ili β- simpatomimetike. Međutim, kasnije studije (Goodwin i

sar.1996; Zacharias C i sar.2001; Andersen i sar 2002 i dr.) pokazuju da je atosiban značajno efikasniji od placeba u odlaganju porođaja za 24 sata, 48 sati i 7 dana, mada ne postoji poboljšanje u perinatalnom ishodu. Klinička iskustva, posebno u našoj zemlji u vezi primene ovog leka u tokolitičke svrhe još uvek nisu dovoljna. Posebno treba imati u vidu cenu tretmana ovim lekom. Za 19 sati terapije atosibanom treba oko 240 evra, ritodrinom oko 40-80 Evra, a nifedipinom oko 17-25 evra.

Traganje za idealnim tokolitičkim sredstvima i dalje se nastavlja. Dokaz za to su i novije studije in vitro, koje govore o upotrebi inhibitora RHO kinaza u tretmanu prevremenog porođaja. Bazirane su na novim saznanjima u vezi značaja RHO kinaza u održavanju mirovanja materice. Iako precizan mehanizam dejstva nije u potpunosti objašnjen, smatra se da dva glavna RhoA proteina ROCK I (koji se još zove i p160 ROCK) i njegova izoforma ROCK II (poznat kao ROKά ili Rho kinaza) imaju ključnu ulogu u RhoA kalcijumskoj osetljivosti. Ovi glavni proteini su poznati pod imenom Rho kinaze i njihova aktivacija povećava RhoA posredovanje kacijumske osetljivosti i kontrakciju mišića. S druge strane, Kawada et al. 1999; Ishizaki et al., 2000. pokazali su, da su inhibitori Rho kinaza, relaksacioni agensi glatkog mišića.

Kalijumski kanali su najbrojnija i najheterogenija vrsta jonskih kanala. Imaju centralnu ulogu u funkcionisnju skoro svake žive ćelije. Dele se u tri klase: 1. Voltažni kalijumski kanali 2. Ulazno-ispravljački kalijumski kanali i 3. Kanali sa domenom sa dve pore. Struktura voltažnih K+ kanala slična je strukturi voltažnih klacijumskih i natrijumskih kanala (Xilian Bai et al. 2005). Postoje tri glavna tipa voltažnih kalijumskih kanala: a. Voltažno- senzitivni (kasno ispravljački), b. KCNQ kanali i c. Eag- slični K+ kanali. U ovu grupu se svrstavaju Ca+–senzitivni (ili Ca-om aktivirani) i K+ kanali, koji se otvaraju (aktiviraju) kada intracelularni nivo Ca2+ raste. Dosadašnje studije pokazuju prilično jasno da su miometralni jonski kanali nove mete za lekove koji će se koristiti u tretmanu prevremenih porođaja.

Imajući u vidu multiplu etiologiju prevremenog porođaja, u cilju uspešne predikcije i prevencije prevremenog porođaja, neophodno je identifikovati sve žene sa visokim rizikom za prevremeni porođaj.

Traganje za najboljim supstancijama u lečenju pretećih pobačaja i prevremenih porođaja još uvek nije završeno. Uvođenjem novih tokolitičkih lekova i selektivnom pristupu svakom prevremenom porođaju, uz primenu ostalih adekvatnih mera i postupaka, moglo bi u budućnosti da doprinese boljem tretmanu prevremenih porođaja. Favorizuje se akutna tokoliza u trajanju od 3 do 5 dana, primenom glikokortikoida (betametazona).

Literatura

1. Goran Relić. Savremena tokolitička terapija i prevremeni porođaj, monografija, Medicinski fakultet Kosovska Mitrovica, 2007.
2. Relić G, Bogavac M, Vlašković R, Rajović B, Cvetnić D, Zakić S, Džeković M. Da li je upotreba nifelata danas u prevenciji prevremenog porođaja zapostavljena? Novine u perinatalnoj medicini. Zbornik radova, Budva 04-07. jun 2004;126.
3. Elvira O, G van Vliet, Tobias A J Nijman, Ewoud Schuit, et al. Nifedipine versus atosiban for threatened preterm birth (APOSTEL III): a multicentre, randomised controlled trial. 2016;387(10033):2117-124.
4. Domokos D, Ducza E, Falkay G, Gaspar R. Alteration in expressions of RhoA and Rho-kinases during pregnancy in rats: their roles in uterine contractions and onset of labour. J Physiol Pharmacol. 2017;68(3):439-51.
5. Mitic R, Vukicevic D, Relic G. Modulacija kalijumskih kanala miometrijuma. Praxis medica, 2008; 36(3-4):97-101.
6. Shirish B, Soumen C, Manju G, et al. Myometrial Calcium and Potassium Channels Play a Pivotal Role in Chromium-Induced Relaxation in Rat Uterus: an In Vitro Study. Biol Trace Elem Res. 2020;198(1):198-205.
7. Sokolović D, Drakul D, Oreščanin-Dušić Z, Tatalović N, Pecelj M, Milovanović S, Blagojević D. The role of potassium channels and calcium in the relaxation mechanism of magnesium sulfate on the isolated rat uterus. Arch Biol Sci. 2019;71(1):5-11.

PREVREMENI PORODAJ – DA LI GA MOŽEMO PREVENIRATI?

Prof. Snežana Plešinac

Medicinski fakultet Univerziteta u Beogradu
Klinika za ginekologiju i akušerstvo KCS

Prevremeni porođaj je porođaj koji se dešava između 20 0/7 nedelje gestacije i 36 6/7 nedelja.

Sledeći faktori mogu dovesti do prevremenog porođaja: stres, infekcija, abrupcija posteljice, placenta previja, istorija prevremenog porođaja ili abortusa, neadekvatna prenatalna nega, pušenje, starost majke <18 ili> 40, loša ishrana, fetalna anomalija, zastoj u rastu fetusa, oligohidramnion, polihidramnion, vaginalno krvarenje, prevremena ruptura membrane (PPROM) i faktori okoline. SZO je 2005. godine ilustrovala da prevremena porođaja čine oko 9,5% porođaja širom sveta. To je gotovo 13 miliona rođenih. Tri glavne komponente doprinose prevremenom porođaju: promene na grliću materice, uporne kontrakcije materice i aktiviranje decidue i membrana. Skrining prevremenog porođaja uključuje: ultrasonografski i biohemijski skrining.

Snežana Plešinac je redovni profesor Medicinskog fakulteta Univerziteta u Beogradu. Usavršavanja: Ian Donald Inter-University School of Medical Ultrasound. Beograd 2004; Multifetalne trudnoće. Beograd. 2006; Jugoslovensku školu za patologiju cerviksa, vagine i vulve i kolposkopiju 1997. godine; Kurs za ginekološku citologiju 1997. godine; „Kako prepoznati bolesno fetalno srce“ Novi Sad. 2009; 3 D Visus. Vienna International School of 3D UltraSonography. Beograd. 2010; Zdrava trudnoća, folna kiselina ili folat-Ima li razlike? Srpsko tiroidno društvo Beograd. 2012; „FV Leiden FH G20210A i MTHFR C 677T mutacije u različitim trombotičnimmanifestacijama-učestalost i značaj u našoj populaciji. IMGTI. Beograd 2012; Advanced sonographic rechiques for the diagnosis of congenital anomalies & fetal echocardiography. ISUOG. Paris. 2012.

Predsednik Udruženja za fetalnu i neonatalnu medicinu. Šef Katedre za postdiplomsku nastavu. Načelnik odeljenja Kontrole fertiliteta, Klinika za ginekologiju i akušerstvo KCS.

PRENATALNA DIJAGNOSTIKA NEUROMIŠIĆNIH BOLESTI: PREGLED METODA I NAŠA ISKUSTVA

Prof. Ivana Novaković[1]

Predsednik sekcije Društva genetičara Srbije, Institut za humanu genetiku

Doc. Jasmina Mitrović Maksić[2], **Prof. Nataša Maksimović**[1], **Milena Janković**[3], **Dr Ana Marjanović**[1], **Dr Marija Branković**[1], **Bojana Petrović**[4], **Milica Komnenić Radovanović**[4], **Prof. Vedrana Milić Rašić**[5], **Prof. Vidosava Rakočević Stojanović**[3], **Dr Dušan Vukolić**[4], **Prof. Olivera Kontić Vučinić**[1,4]

1 Medicinski fakultet, Univerzitet u Beogradu, Srbija
2 Fakultet za specijalnu edukaciju i rehabilitaciju, Univerzitet u Beogradu, Srbija
3 Klinika za neurologiju, Klinički Centar Srbije
4 Klinika za ginikologiju i akušerstvo, Klinički Centar Srbije
5 Klinika za neurologiju i psihijatriju za decu i omladinu, Beograd

Neuromišićne bolesti čine složenu i heterogenu genetički uslovljenih oboljenja, koja se razlikuju po načinu nasleđivanja, kliničkoj slici i prognozi. Po učestalosti najčešće neuromišićne bolesti su distrofinopatije, pa se porodice u kojima postoji dijagnoza ovih bolesti često javljaju u genetičko savetovalište radi konsultacije i sprovođenja genetičkog testiranja, uključujući i prenatalnu dijagnostiku. Distrofinopatije su bolesti koje nastaju kao posledica mutacija u genu za distrofin. Dišenova mišićna distrofija (DMD) predstavlja najteži oblik iz ove grupe bolesti. Karakteriše je rani početak bolesti, progresivna mišićna slabost koja dovodi do gubitka pokretljivosti bolesnika, i kardio-pulmonalne slabosti zbog zahvatanja srčanog i interkostalnih mišića. Bekerova mišićna distrofija (BMD) se javlja kasnije, ima blaži tok bolesti, ali sa velikom varijabilnošću u kliničkoj slici. Nasleđuju se X-vezano recesivno, oboljevaju muškarci dok su žene uglavnom zdravi prenosioci bolesti. Procenjeno je da su 2/3 majki koje imaju obolele sinove nosioci, 5-10% ima gonadni mozaicizam, dok 25-30% nema mutaciju. Gen za distrofin (DMD gen) je najveći opisani gen u humanom genomu i često je podložan promenama. Najčešće su prisutne intragenske delecije (65%-70%) i duplikacije (5-15%) jednog ili više egzona, a tačkaste mutacije su prisutne u 20% slučajeva. 1/3 bolesnika ima de novo mutaciju (1). Za sada nema uspešne terapije distrofinopatija, pa je jedini način prevencije bolesti prenatalna dijagnostika kao i utvrđivanje statusa nosioca kod ženskih članova u familiji.

Genska analiza omogućuje direktno ili indirektno otkrivanje mutacija u genu za distrofin. Dijagnostičko genetičko testiranje se izvodi kod simptomatskih bolesnika, kod žena u cilju određivanja statusa prenosioca i kao prenatalna dijagnoza u indikovanim slučajevima. U zavisnosti od toga, DNK za analizu može biti izolovana iz periferne krvi bolesnika ili nosioca (najčešće limfociti), zatim uzorci horiona, amnionske tečnosti ili krvi iz pupčanika ploda – kada je u pitanju prenatalna dijagnostika. Metode za uspostavljanje genske dijagnoze su:

- Za velike delecije/duplikacije – multipli PCR, MLPA, a danas ređe i Q-PCR, MAPH, SCAIP, Southern blot
- Za tačkaste mutacije; male delecije/duplikacije – Nova Generacija Sekvenciranja (Next-generation sequencing, NGS), sekvencioniranje po Sangeru, Resekvencioniranje, Linkage analiza mikrosatelitnim markerima

Grupisanje delecija u predilekcionim regionima DMD gena olakšava njihovo otkrivanje. Metoda multiple lančane reakcije polimerizacije (engl. – Polymerase chain reaction, multipli PCR), koju su opisali Chamberalain (2,3) i Beggs (4) korišćena je za detekciju parcijalnih delecija u genu za distrofin i analizom samo 19 egzona omogućila je otkrivanje oko 95% svih delecija DMD gena. Ukoliko se analizom obuhvati veći broj egzona moguće je preciznije odrediti veličinu i lokalizaciju mutacije.

Kod bolesnika sa delecijom u DMD genu, egzoni koji su u deletiranim regionima se neće umnožiti prilikom PCR reakcije, a njihovo odsustvo će se potvrditi gel elektroforezom. Zbog hemizigotnosti, delecije kod muškaraca se mogu lako otkriti ovom metodom. Međutim, kod žena nosioca, delecije u genu za distrofin bivaju maskirane amplifikacijom normalnog X hromozoma, pa ova metoda nije od koristi. Takođe, PCR metoda ne otkriva delecije koje su van predilekcionih regiona u DMD genu, kao ni duplikacije, kod probanada i ženskih nosioca. U ovu svrhu korišćene su metode Southern blotting, qPCR (engl. quantitative Polymerase chain reaction) i MAPH (engl. Multiplex amplification and probe hybridization), ali su se pokazale komplikovane za izvođenje u svakodnevnoj praksi (5). Svakako, prednost PCR metode je brzina njenog izvođenja.

Noviji pristup u otkrivanju mutacija u genu za distrofin je metoda višestrukog umnožavanja vezanih proba (engl. Multiplex ligation-dependent probe amplification, MLPA). Ova metoda je prvi put opisana 2002. godine, sa svrhom kvantitativne analize (6). MLPA metoda omogućuje analizu svih 79 egzona DMD gena (7), i otkriva delecije koje su van "vrućih mesta" u genu, kao i duplikacije, kod probanada i ženskih nosioca. MLPA metoda se temelji na PCR reakciji, kombinujući hibridizaciju specifičnih proba i amplifikaciju ciljnih sekvenci putem umnožavanja proba sa kojima hibridizuju. Za odvijanje procesa amplifikacije dovoljna su dva PCR prajmera. MLPA metodom je moguće istovremeno analizirati do 96 različitih uzoraka, a rezultati se dobijaju za 24 sata.

Ograničenja MLPA metode ogledaju se u nemogućnosti otkrivanja tačkastih mutacija, kao i promena koje leže izvan sekvence detektovane MLPA sondom. Lažno negativni ili lažno pozitivni rezultati mogu biti posledica kontaminacije uzorka, korišćenja nekvalitetnih preparata, nedovoljne količina DNK, upotrebe neadekvatnih uzoraka, i dr.

Ukoliko se standardnim metodama ne otkriju delecije i duplikacije u DMD genu, traga se za tačkastim mutacijama. Metoda izbora je sekvenciranje DNK kojom se određuje tačan redosled nukleotida u molekulu DNK, tj. njegova primarna struktura. Međutim, zbog izuzetne veličine DMD gena i slučajnog rasporeda tačkastih mutacija, doskora je sekvenciranje primenom klasične metode po Sangeru rađeno prilično retko. Pojavom najsavremenijih metoda poznatih pod nazivom Nova Generacija Sekvenciranja (NGS), analiza tačkastim mutacija u DMD genu postal je mnogo dostupnija. Ipak, kod sumnje na ovaj tip promena još uvek je aktuelna indirektna molekularno genetička dijagnostika. Analiza vezanosti (engl. linkage analysis) je indirektna dijagnostička metoda koja podrazumeva praćenje nasleđivanja određenih polimorfnih DNK markera koji se nalaze u okviru DMD gena, ili u njegovoj blizini (8). Genetički polimorfizam podrazumeva alelske varijante koje se javljaju stabilno u populaciji u učestalosti koja je dovoljno velika da se ne smatra samo proizvodom mutacionog procesa i generalno je veća od 1% (9). To su varijabilni regioni koji se nalaze i u genomu zdravih ljudi, a javljaju se u dve ili više različitih formi (i do 70). Polimorfni DNK markeri koji su međusobno blisko postavljeni na istom hromozomu, nasleđivaće se zajedno (engl. genetic linkage). Ranije su kao DNK markeri korišćene varijabilne forme koje utiču na promenu restrikcionog mesta (ukida postojeće ili kreira novo restrikciono mesto), što rezultuje restrikcionim fragmenatima različite dužine (engl. restriction fragments lenght polymorphism, RFLPs). Otkrivanje ovih polimorfizama zasniva se na Southern analizi. Međutim, danas su u

upotrebi mnogo informativniji i pouzdaniji genetički markeri, tzv. mikrosateliti. Mikrosatelitnu DNK čine kratki tandemski ponovci koji su rasprostranjeni širom humanog genoma. Građeni su od uzastopno ponavljajućih sekvenci dužine 2-4 parova nukleotida (engl. short tandem repeats, STR) i pokazuju visok stepen polimorfizma dužine, što je moguće ispitati primenom PCR tehnike. Minisateliti su ponavljajuće sekvence dužine od 5 do nekoliko desteina baznih parova (engl. variable number of tandem repeats, VNTRs). Savremeni tip DNK markera su i polimorfizmi u jednom nukleotidu (engl. single nucleotide polymorphism, SNP), do kojih se došlo na osnovu saznanja de je u genomu čoveka svaki hiljaditi nukleotid polimorfan, tj. da se razlikuje između dva lokusa na homologim hromozomima, kod različitih osoba, ali i kod jedne iste osobe.

U okviru DMD gena, kao i u njegovoj blizini, otkriveno je više dinukleotidnih mikrosatelitnih polimorfnih regiona, uglavnom CA ponovaka (engl. VNTR CA-repeats), koji se mogu analizirati PCR metodom (10,11). Npr. DXS1238 sa lokalizacijom u intronu 44 DMD gena, DXS1237 lokalizovan u intronu 45, i drugi (Leiden muscular Dystrophy pages, dostupno na www.dmd.nl) (12). Zbog čestih rekombinacija unutar DMD gena potrebno je kombinovanje više markera, kako bi se povećala pouzdanost zaključivanja. Prilikom indirektne analize, najpre se utvrdi koju formu markera ima obolela osoba, a zatim se praćenjem tog markera u porodici indirektno zaključuje da li je član porodice nasledio mutaciju u DMD genu ili nije. Indirektna analiza se koristi i u prenatalnoj dijagnozi, utvrđivanju očinstva, i prilikom isključivanja mogućnosti kontaminacije horiona majčinim tkivom. Prednost analize vezanosti je što ne zahteva poznavanje tipa mutacije, već je dovoljno znati odgovorni lokus. Ipak, ova analiza ima ograničenja zbog mogućih rekombinacija kojim dolazi do razdvajanja markera i gena sa kojim je blisko vezan, ili rekombinacije unutar analiziranog regiona, ograničene informativnosti markera, a i zahteva veći broj članova porodice (8). Konačno, u cilju definisanja preciznog mesta i prirode mutacije, potrebno je izvršiti sekvenciranje regiona od interesa.

Davanje genetičkog saveta bazira se na postavljenoj genskoj dijagnozi i/ili tumačenju porodične istorije (rodoslov) ili medicinske dokumentacije, kako bi se procenio rizik ponovnog javljanja bolesti u porodici. Kod X vezanih recesivnih bolesti, kao što su DMD/BMD, značajna je primena molekularno-genetičkih testova u otkrivanju žena koje su fenotipski zdravi prenosioci mutacije. Osim informacija o načinu nasleđivanja bolesti i mogućim rizicima, genetički savet podrazumeva i davanje instrukcija u daljem testiranju i mogućnostima prevencije, kao što je prenatalna dijagnoza. Ovaj proces podrazumeva i psihološku podršku pojedincu ili porodicama u razumevanju i prihvatanju bolesti, mogućim izborima, kao i davanje smernica u daljem odlučivanju.

Pre nego što je omogućena DNK analiza, prenatalna dijagnoza kod Dišenove mišićne distrofije bazirala se isključivo na utvrđivanju pola kod ploda. Indirektna analiza praćenjem polimorfnih markera omogućila je preciznije predviđanje rizika u prenošenju mutiranog gena i davanje genetičkog saveta. Međutim, čak i kada se utvrdi da fetalna DNK poseduje isti haplotip kao proband, fetus ne mora biti pogođen ukoliko je mutacija kod probanda bila sporadična. Stoga je neophodno da se prisustvo mutacije prethodno ispita kod majke. Ako se kod majke ne utvrdi mutaciija u somatskim ćelijama, rizik oboljevanja ploda je mali, ali i dalje ostaje mogućnost da majka ima gonadni mozaicizam (13). U tom slučaju, procenjen je rizik od 20% da majka ima gonadni mozaicizam, i rizik od 5% da će plod biti zahvaćen (14). Ipak, majka koja nema mutaciju, a ima više od jednog zahvaćenog deteta, ima i veći rizik za gonadni mozaicizam. U tom slučaju, u svakoj narednoj trudnoći treba predlagati prenatalnu dijagnozu, s obzirom da je rizik kod gonadnog mozaicizma nepredvidiv i zavisi od veličine mutiranog klona. Svakako, najpouzdanija dijagnostička metoda je direktna genska analiza kod ploda. U prenatalnoj dijagnozi, prvi korak je utvrđivanje pola deteta (citogenetička analiza, FISH ili PCR-om) i ako je plod muški, sprovodi se direktna ili

indirektna detekcija mutacije. Kod ženskog ploda direktna ili indirektna genska analiza može se vršiti u ciju utvrđivanja statusa nosioca.

Naše istraživanje je sprovedeno sa ciljem da se utvrde i analiziraju delecije i duplikacije u genu za distrofin kod probanada, i da se u slučajevima potvrđenih delecija i duplikacija kod probanada utvdi status prenosioca kod njihovih ženskih srodnka. Takođe, da se u slučajevima bez dokazanih delecija i duplikacija kod probanada, ispita mogućnost indirektne genetičke analize za određivanje statusa ženskih prenosioca, kao i da se u indikovanim slučajevima izvrši prenatalna molekularno genetička analiza DMD gena, primenom adekvatne metode za datu porodicu.

Uzorak su činila 72 DMD/BMD probanda, 69 ženskih članova iz 44 porodice probanada i 12 trudnica (16 trudnoća). Trudnice kod kojih je rađena prenatalna dijagnostika bile su pacijenti Odseka za perinatalnu i reproduktivnu genetiku i endokrinologiju Klinike za ginekologiju i akušerstvo KCS u Beogradu. Za detetekciju delecija i duplikacija u DMD genu kod probanda primenjene su metode multipli PCR i MLPA; za detekciju ženskih nosioca primenjena je MLPA metoda i analiza vezanosti; za prenatalnu dijagnozu primenjena je PCR metoda, analiza vezanosti i MLPA metoda. U jednoj porodici, uključujući i prenatalnu dijagnostiku, rađena je metoda sekvenciranja DMD gena (NGS i sekvenciranje po Sangeru). Genomska DNK za analizu je izolovana iz limfocita periferne krvi ispitanika metodom isoljavanja prema standardnoj proceduri, a za prenatalnu dijagnozu, DNK je izolovana iz uzorka horionskih resica, plodove vode ili krvi pupčanika ploda.

Primenom PCR i/ili MLPA metode kod 29 DMD i 43 BMD probanada je otkriveno 68,1%, velikih mutacija, tj. 87,7% delecija i 12,3% duplikacija. Delecije i duplikacije su zahvatile veći broj egzona u 79,6% slučajeva, a najčešća lokalizacija je bila u štapićastom domenu gena, u 85,7%. Kod ispitanih ženskih srodnika probanada, velike mutacije su bile nađene u 39,6% slučajeva. Od 37 ispitanih majki probanada, potvrđenih nosioca je bilo 45,9%. Kod izolovanih DMD slučajeva je nađeno 50% majki nosioca, odnosno 37,5% kod BMD. Među DMD/BMD slučajevima sa delecijom, majke su bile potvrđene kao nosioci u 56% slučajava, a u DMD/BMD slučajevima sa duplikacijom majke su bile nosioci u 75% slučajeva. Od preostalih 16 ženskih srodnika, kod 25% su bile nađene delecije koje ima i proband sa kojim su u srodstvu. U analizi vezanosti najinformativniji je bio marker DXS1237 (intron 45) u 77,8% slučajeva. Samo analiza vezanosti je urađena kod 8 porodica, i utvrđena je učestalost ženskih hetrozigota od 82,3%. Kod 6 porodica analiza vezanosti je bila dopunjena MLPA analizom, a predviđanje statusa nosioca na osnovu analize vezanosti je bilo potvrđeno kod 57,1% ispitanih. Kod 3 trudnice primenjena je indirektna molekularno genetička metoda. Za dva muška ploda očekivani ishod je da će biti zdravi. Kod trećeg ploda predviđeni ishod, da će biti bolestan, nije bio potvrđen MLPA analizom. Kod 8 trudnica (12 trudnoća) primenjena je direktna molekularno genetička metoda. Kod jedne majke dva od tri ploda (jedan muški, jedan ženski) su imala deleciju; kod druge majke oba muška ploda su imala deleciju u DMD genu. U jednoj porodici je metodom NGS detektovanom tačkasta mutacija kod probanda i kod ćerke – prenosioca, koja je potom ostvarila trudnoću. Prenatalna dijagnostika u ovoj trudnoći je pokazala da je reč o muškom plodu bez mutacije u DMD genu.

U porodicama sa dokazanim delecijama ili duplikacijama u DMD genu, direktna molekularno genetička analiza omogućuje precizno otkrivanje žena prenosioca ovog tipa mutacije i utvrđivanje stope de novo i nasleđenih mutacija. U slučajevima bez dokazanih delecija ili duplikacija u DMD genu kod obolelog, indirektnom molekularno genetičkom analizom tj. analizom vezanosti, može se pratiti nasleđivanje rizičnog hromozoma kod svih članova u porodici. Metoda NGS učinila je dostupnom detekciju tačkastih mutaija u DMD genu, što je do nedavno bilo vrlo teško. Na

osnovu dobijenih podataka realizuje se prenatalna dijgnostika u planiranim trudnoćama po odgovarajućem algoritmu.

Literatura

1. Maksić J, Dobričić V, Rasulić L, Maksimović N, Branković M, Milić Rašić V, et al. Analysis of duplications versus deletions in the dystrophin gene in Serbian cohort with dystrophinopathies. Vojnosanitetski pregled. 2018; 89.
2. Chamberlain JS, Gibbs RA, Rainer JE, Nguyen PN, Caskey CT. Deletion screening of the Duchenne muscular dystrophy locus via multiplex DNA amplification. Nucleic Acids Res. 1988;16(23):11141-56.
3. Chamberlain JS, Gibbs RA, Rainer JE, Caskey CT. Multiplex PCR for the diagnosis of Duchenne muscular dystrophy. Innis MA, Gelfand DH, Sninsky JJ, White TJ, eds. PCR Protocols: A Guide to Methods and Applications. Academic Press New York. 1990;272-81.
4. Beggs AH, Koenig M, Boyce FM, Kunkel LM. Detection of 98 % of DMD/BMD gene deletions by polymerase chain reaction. Hum Genet. 1990;86(1):45-8.
5. White S, Kalf M, Liu Q, Villerius M, Engelsma D, Kriek M, et al. Comprehensive Detection of Genomic Duplications and Deletions in the DMD Gene, by Use of Multiplex Amplifiable Probe Hybridization. Am J Hum Genet. 2002;71(2):365-74.
6. Schouten JP, McElgunn CJ, Waaijer R, Zwijnenburg D, Diepvens F, Pals G. Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. Nucleic Acids Res. 2002;30(12):e57.
7. Lalić T, Vossen R HAM, Cofa J, Schouten JP, Guc-Scekic M, Radivojević D, Đurišić M, Breuning MH, White SJ, den Dunnen J. Deletion and duplication screening in the DMD gene using MLPA. Eur J Hum Genet. 2005; 13:1231-4.
8. Darras BT, Harper JF, Francke U. Prenatal diagnosis and detection of carriers with DNA probes in Duchenne's muscular dystrophy. N Engl J Med. 1987;316(16):985-92.
9. Frazer KA, Murray SS, Schork NJ, Topol EJ. Human genetic variation and its contribution to complex traits. Nat Rev Genet. 2009;10(4):241-51.
10. Oudet C, Heilig R, Hanauer A, Mandel JL. Nonradioactive assay for new microsatellite polymorphisms at the 5' end of the dystrophin gene, and estimation of intragenic recombination. Am J Hum Genet. 1991;49(2):311-9.
11. King SC, Stapleton PM, Walker AP, and Love DR. Polymorphisms at the DMD locus. Human Molecular Genetics. 1994;3(3):523.
12. Leiden muscular Dystrophy pages; Markers in and around the dystrophin gene (last modified January 6, 2006). http://www.dmd.nl; poslednja poseta 26. Februara 2018.
13. Van Essen AJ, Abbs S, Baiget M, Bakker E, Boileau C, van Broeckhoven C, et al. Parental origin and germline mosaicism of deletions and duplications of the dystrophin gene: a European study. Hum Genet. 1992; 88(3):249-57.
14. Bakker E, Veenema H, den Dunnen JT, van Broeckhoven C, Grootscholten PM, Bonten EJ, et al. Germinal mosaicism increases the recurrence risk for 'new' Duchenne muscular dystrophy mutations. J Med Genet. 1989;26(9):553-9.

ULTRAZVUČNI PREGLED U PRVOM TRIMESTRU I RANA DETEKCIJA ANOMALIJA

Doc. Srboljub Milićević

Head of ultrasound department
Clinic for Gynecology and Obstetrics, Clinical Center of Serbia
Faculty of Medicine, University of Belgrade, Serbia

Ultrazvučni ciljevi za bilo koju ranu trudnoću treba da budu konstatovanje viabiliteta i starost ploda ili fetusa, detekcija broja beba kao i ako se radi o višeplodnom graviditetu određivanje horioniciteta i amnioniciteta kao i otkrivanje velikih abnormalnosti. U 10. nedelji embrion je manji od polovine dužine odraslog palca, ali poseduje već nekoliko hiljada identifikovanih struktura i praktično svaka od njih može imati razvojna odstupanja. Većina urođenih anomalija se i pojavi u tom periodu te je njihova rana detekcija ultrazvukom naš cilj.

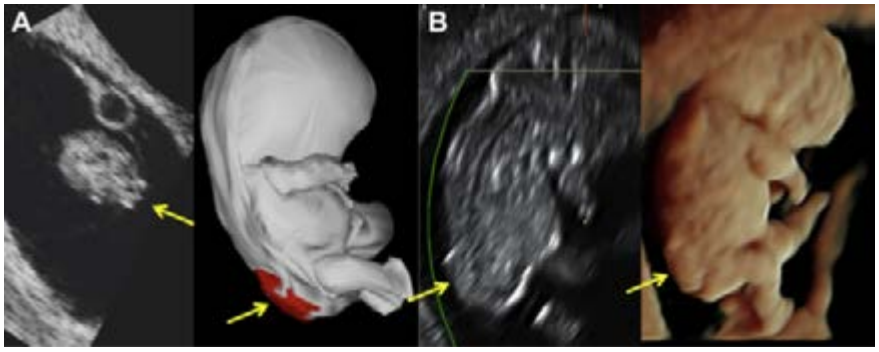
Tačna definicija prelaza između trimestara nije moguća jer nema konkretnih razvojnih faza koje bi ukazivala takve granice4. Uvođenje 11-13+6 nedelje fetusa je uspostaviljeno kao praktični period opservacije kao i 13+6 do 14 nedelja završetkom prvog tromesečja. Treba napraviti razliku između skrininga tokom 11-13+6 nedelje i onog pre ovog perioda tokom embrionalnog perioda5-7. Transvaginalni pristup je poželjan za sve preglede pre 11-12 nedelje trudnoće.

Centralni nervni sistem

Prvi rad o dijagnostikovanju anomalija CNS-a u prvom trimestru je bio prikaz ananencefalije 25 godina nakon prvog opisa anomalija CNS-a u trećem trimestru8. Od anomalija CNS a mogu se uočiti akranije kao i encefalocela u 8-9 nedelji trudnoće9,10. Encefalocela je takođe poznat deo Mekel-Gruber sindroma. U dva slučaja Meckel-Gruber sindroma u 8 nedelji, encefalocela nije viđena, ali šupljina u rhombencephalona je bila proširena11, a poznat je slučaj sa polidaktilijom11. Holoprozenkefalija je anomalija centralnog nervnog sistema koja proističe iz primarnog defekta rostralnog dela nervne cevi (bazalni deo prednjeg mozga). Ovaj nedostatak dovodi do različitog stepena nepotpunog odvajanja moždane hemisfere i anomalija lica. Holoprozenkefalija se ocenjuje prema težini anomalije mozga kao alobarna, semilobarna, lobara i srednje interhemispherična varijanta12,13. Razvoj telencefalona u moždane hemisfere postaje vidljiv tokom 7. nedelje, tako da se dijagnoza alobarne holoprosencefalije može očekivati u 8. nedelji trudnoće.

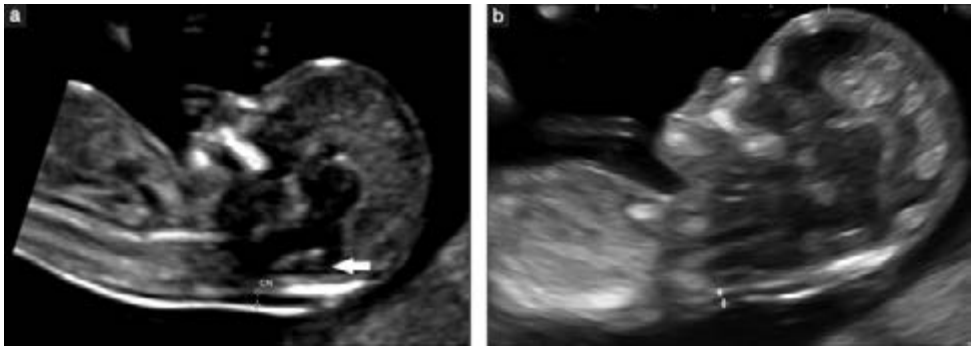
Spina bifida se može detektovati u 9. nedelji embrionalnog perioda14. Detekcija ove embrionalne ili fetalne malformacije obično se vrši dvodimenzionalnim ultrazvukom, ali i primena trodimenzionalnog ultrazvuka može povećati stepen detekcije (Sl 1.)

Slika 1



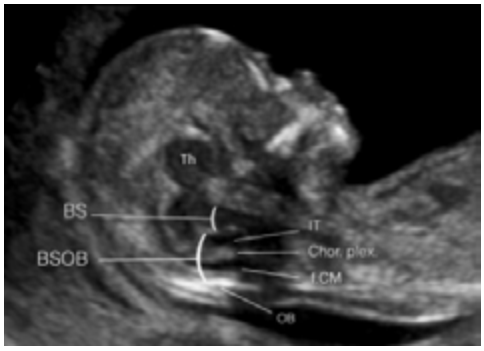
Dakle broj strukturnih CNS malformacija koje se vide u prvom tromesečju uključuju15: akraniju, anencefaliju, holoprozenkefaliju, cerebelarni defekti, hidrocefalus, encefalokelu i spinu bifidu. Proširenje intrakranijalne translucencije i proširenje moždanog stabla do potiljačne kosti su potencijalni markeri za abnormalnosti zadnje lobanjske jame i u prvom tromesečju16. Ultrasonografi treba da budu obučeni da vrše merenja Intrakranialne translucencija (IT) od 11 do 13 nedelje trudnoće, što bi dovelo do veće stope detekcije 17. U otkrivanju spine bifide u prvom trimestru, nevizuelizacija zadnje lobanjske jame (cisterna magna) ili cistena magna i četvrta moždana komora (IT) se smatra najboljom metodom skrininga18. (slika 2,3)

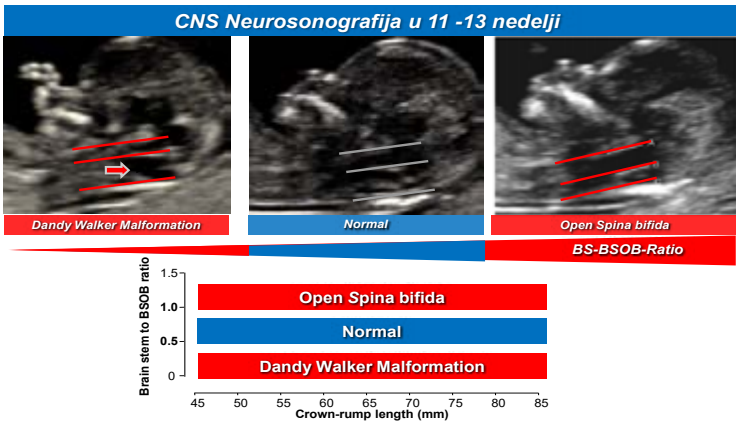
Slika 2,3

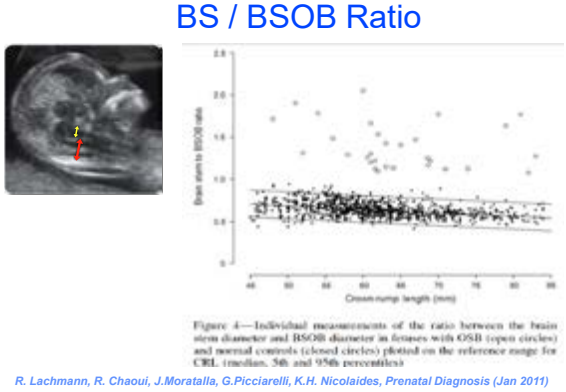


Slike2 i 3. fetusa u srednje sagitalnoj ravni u 11-13 nedelji u i fetusa sa otvorenom spinom bifidom. Slika (a) pokazuje potpunu usaglašenost u pogledu kvaliteta slike za oba debljine: nuhalne translucencije (NT) i intrakranijalne translucencije (IT). Cisterna magna je odsutna a četvrta moždana komora je normalna (strelica). Slika (b) pokazuje umereno manju NT. Cisterna magna i četvrta komora su odsutne

Slika 4,5







R. Lachmann, R. Chaoui, J.Moratalla, G.Picciarelli, K.H. Nicolaides, Prenatal Diagnosis (Jan 2011)

Srednja sagitalna ravan je najbolja za dijagnostikovanje intrakranijalne translucencije (IT) i zadnjeg dela mozga u 13 oj nedelji gestacije mada neki eksperti kao prof Chaoiu podjednako dobro koriste aksijalni presek mozga za detekciju otvorene spine bifide.. Talamus (Th) i moždano stablo (BS) imaju hipoehogen izgled. Četvrta komora, takođe nazvana IT, pojavljuje kao anehogen region sa dve horizontalne hiperehogene granice, omogućavajući pouzdanu identifikaciju: prednja granica IT je zadna granica BS, a zadnja granica IT je horoidni pleksus u četvrtom ventrikulu. Horoidni pleksus je dobro uočljiva struktura koja pluta u tečnosti IT i buduće cisterne magne (f.CM), koje su i dalje povezane jedna sa drugom. Rastojanje moždano stablo-okcipitalna kost (BSOB) izgleda veće nego sam prečnik stabla. OB označava potiljačnu kost. (slika 4,5,6,)

Tim profesora Nicolaidesa je izasao sa jasnim rezultatima 2011. g. da je kod otvorene spine bifide širina moždanog stabla (BS) veća nego rastojanje moždano stablo-okcipitalna kost (BSOB) za razliku od normalnih fetusa što se vidi na slici 119. Detekcija otvorene spine bifide u prvom trimestru je 14 %. 20 do 25% 21. Takođe isti tim je 2012. konstatovao da se frontomaxilarni ugao lica smanjuje za 9,9^0 kod fetusa sa otvorenom spinom bifidom u odnosu na normalan fetus iste starosti trudnoće u prvom trimestru.

U tom istraživanju su akranija, alobarna holoprozenkefalija, i exomphalos bile detektovane u svim slučajevima, dok nijednom nisu uočene agenezija korpus kalozuma I cerebelarna hipoplazija20.

Broj strukturnih malformacija CNS koje se vide u prvom tromesečju uključuju 22: Akraniju - anencefaliju, holoprozenkefaliju, cerebelarni defekti, hidrocefalus, encefalokelu i spinu bifidu. Uvećanje intrakranijalne translucencije i uvećanje rastojanja od moždanog stabla do potiljačne kosti su potencijalni markeri za detekciju abnormalnosti zadnje lobanjske jame i u prvom tromesečju. 23 Ultrasonografi treba da budu obučeni da vrše merenja Intrakranialne transluce (IT) od 11 do 13 nedelje trudnoće, što bi dovelo do veće stope detekcije otvorene spine bifide. 24 U otkrivanju spine bifide u prvom trimestru, nevizuelizacija zadnje lobanjske jame (cisterna magna) se smatra najboljom metodom skrininga 25.

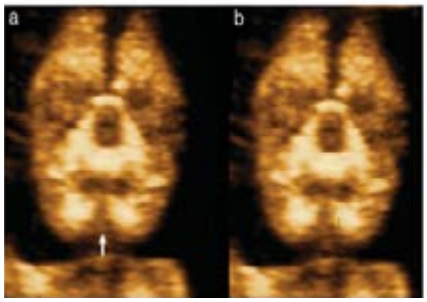
Vredi napomenuti skorašnje, iz 2013 godine, indirektno otkrivanje agenezije korpusa kalozuma usled promene odnosa duzine dijametra srednjeg mozga u odnosu dužine dijametra falxa cerebri sa senhzitivnošću od 87 %.26

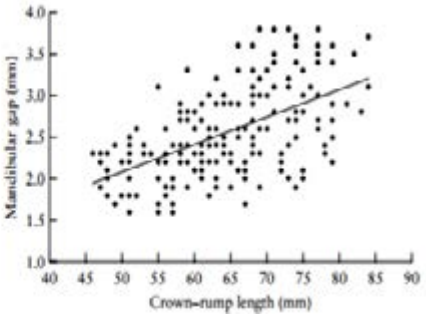
Anomalije lica i vrata

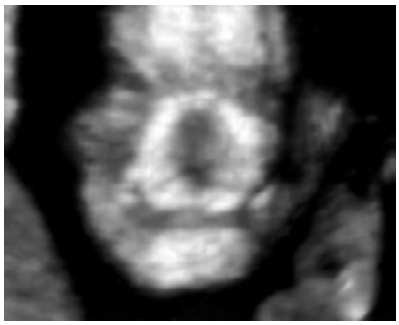
Na kraju embrionalnog perioda identifikuju se oči, maksile i mandibula. Tipični anomalije lica udružene sa alobarnom holoprozenkefalijom su proboscis i ekstremni hipotelorisam ili kiklopija i mogu se konstatovati ultrazvukom u embrionalnom periodu,27. Multislajs presecima u 3D skenu može se stopa detekcije hipotelorisma povećati. Bilateralni rascep usne i nepca je najranije opisan kod 10 nedelja i 3 dana starog fetusa sa derVoude sindromom 28. Sapulveda sa saradnicima je 2010. uključio procenu retronasalnog trougla kao ultrazvučnog parametra u rutinskoj proceni postojanja rascepa nepca u trudnoći od 11 do 13, 6 nedelje 29. Pošto fetusi sa rascepom nepca imaju abnormalnu konfiguraciju retronasalnog trougla, fokusiranje na skeniranje sredine lica, u vreme merenja nuchalne translucencije, može olakšati rano otkrivanje rascepa nepca u prvom trimestru. Primena ove veštine omogućiće da se ova anomalija, koja je do sada imala stopu detekcije oko 5%19 u prvom trimestru, lakše i sa sigurnošću detektuje.

Takođe isti autor sa svojim timom je dve godine kasnije, 2012 g uočio da se odsustvom mandibularnog razmaka može konstatovati postojanje mikrognatije.

Slika 7,8







Ultrazvučne slike fetusa sa mikrognatijom pokazuju odsustvo mandibularnog razmaka. Mandibularni razmak je zamenjen hiperehogenom, koštanom strukturom koja predstavlja uvučenu bradu 30.

Cistični higrom vrata se može se skoro uvek uočiti u prvom trimestru.

NT i loš ishod trudnoće

Pored snažne povezanoti sa detekcijom aneuploidija fetusa , uvećanje NT je povezano sa rizikom od neželjenog perinatalnog ishoda uključujući fetalne malformacije, displazije, deformitete, i genetske sindrome. Ovi rizici nemaju značaj sve dok NT nije ≥ 3,5 mm (> 99 procenata) 41. Stopa mortaliteta fetusa zavisi od stepena abnormalnosti NT (od 3,5-4,4 mm smrtnosti = 2,7%, preko> 6,5 mm smrtnosti = 19%) 42 Nasuprot tome, ako fetus preživi do sredinjeg trimestra i na ultrazvučnom pregledu se neuoče abnormalnosti, rizik od nepovoljnog ishoda se neće značajno povećati. 43

Treba istaći da je potrebna specijalizovana obuka i sertifikacija za sonografe koji mere NT.

Ishod trudnoće

Prekid trudnoće je opcija za sve žene koje nose fetus sa teškim strukturnim anomalijama CNS-a (Akranija-eksncephalija, alobarna holoprozenkefalija i Encefalocela i u jasno definisaniom cistichnog higroma21 .

Preporuke

Prvi trimestar je podeljen na embrionalni, rani fetalni period 10-11 nedelje i kasniji period od 11-13+6 nedelja.

Transvaginalni ultrazvuk je poželjan u embrionalnom periodu, dok se transabdominalna sonografija obično primenjuje kasnije.

Preduslov za bilo kakvu anatomsku evaluaciju i dijagnostiku strukturnih abnormalnosti u I trimestru je znanje normalnog embrionalnog razvoja.

U kasnom periodu I trimestra od 11-13+6 nedelja, upotreba soft markeraza aneuploidije pomaže da se identifikuju fetusi sa rizikom za strukturne anomalijama. U tim slučajevima, osim odgovarajuće daljeg ispitivanja kao što je kariotipizacija, treba sprovesti temeljan ultrazvučni pregled na anomalije uz prednost korišćenja trasvaginalne sonde i uz pomoć trodimenzionalnog ultrazvuka.

I na kraju treba istaći da lekar mora biti vrlo dobar u skeniranju II trimestra, biti brz u prilagođavanju novom položaju fetusa ,razumeti fetalni razvoj

Izvući najbolje od UZ aparata i kombinovati abdominalni i transvaginalni UZ kao i 2D, 3D i Color Doppler kao i da ultrazvučno ispitivanje bude sistematično.

Reference

1. Robinson HP, Fleming JEE. A critical evaluation of sonar crown-rump length measurements. Br JObstet Gynaecol 1975;82 CRL
2. Bottomley C, Bourne T. Dating and growth in the first trimester. Best Pract Res Clin Obstet Gynaecol 2009
3. Loughna P, Chitty L, Evans T, Chudleigh T. Fetal size and dating: charts recommended for clinical obstetric practice. Ultrasound 2009
4. O'Rahilly R, Müller F. Human embryology and teratology. New York: Wiley-Liss; 1994.
5. Blaas H-G, Eik-Nes SH, Kiserud T, et al. Early development of the forebrain and midbrain: a longitudinal ultrasound study from 7 to 12 weeks of gestation. Ultrasound Obstet Gynecol 1994;4:183–92.
6. Blaas H-G, Eik-Nes SH, Kiserud T, et al. Early development of the hindbrain: a longitudinal ultrasound study from 7 to 12 weeks of gestation. Ultrasound Obstet Gynecol 1995;5:151–60.
7. Blaas H-G, Eik-Nes SH, Kiserud T, et al. Early development of the abdominal wall, stomach and heart from 7 to 12 weeks of gestation: a longitudinal ultrasound study. Ultrasound Obstet Gynecol 1995;6:240–9.
8. Sundén B. On the diagnostic value of ultrasound in obstetrics and gynecology. Thesis Acta Obstet Gynecol Scand 1964; 43(Suppl.):1–121.
9. Blaas H-G, Eik-Nes SH. Ultrasound assessment of early brain development. In: Jurkovic D, Jauniaux E, editors. Ultrasound and early pregnancy. New York–London: The Parthenon Publishing Group; 1996. 3–18.
10. Blaas H-G, Eik-Nes SH. Das Zentralnervensystem. Die normale Entwicklung und die Entwicklung von Anomalien – Ultraschalldiagnostik in der Frühschwangerschaft. Gynäkologe 1999;32:181–91.
11. Zalen-Sprock RMv, Vugt JMGv, Geijn HPv. First-trimester sonographic detection of neurodevelopmental abnormalities in some single-gene disorders. Prenat Diagn 1996;16:199–202.
12. DeMyer W. Holoprosencephaly (cyclopia-arhinencephaly). In: Vinken P, Bruyn G, editors. Handbook of clinical neurology. Amsterdam: North-Holland Publishing Co; 1977. pp. 431–78.
13. Blaas H- GK. Holoprosencephaly, chapter 39. In: Copel J, D'Alton M, Gratacós E, et al., editors. Obstetric imaging. Philadelphia: Elsevier Saunders; 2012.
14. Blaas H-GK, Eik-Nes SH, Isaksen CV. The detection of spina bifida before 10 gestational weeks using 2D- and 3D ultrasound. Ultrasound Obstet Gynecol 2000;16:25–9.
15. Goetzl L. Adverse pregnancy outcomes after abnormal first-trimester screening for aneuploidy. Clin Lab Med. 2010 Sep;30(3):613-28.
16. Bornstein E1, Goncalves Rodríguez JL, Álvarez Pavón EC, Quiroga H, Or D, Divon MY. First-trimester sonographic findings associated with a Dandy-Walker malformation and inferior vermian hypoplasia. J Ultrasound Med. 2013 Oct;32(10):1863-8.
17. Fong KW1, Dengler J2, Toi A2, Menezes RJ2, Karimzad Y2, Okun N2. Prospective study of intracranial translucency and the posterior brain in normal fetuses at the 11- to 13-week scan. J Ultrasound Med. 2014 Aug;33(8):1373-9.
18. Mangione R1, Dhombres F, Lelong N, Amat S, Atoub F, Friszer S, Khoshnood B, Jouannic JM. Screening for fetal spina bifida at the 11-13-week scan using three anatomical features of the posterior brain. Ultrasound Obstet Gynecol. 2013 Oct;42(4):416-20.
19. Robert Lachmann1,2, Rabih Chaoui3, Jose Moratalla1, Gemma Picciarelli1 and Kypros H. Nicolaides1,2* Posterior brain in fetuses with open spina bifida a 11 to 13 weeks Prenat Diagn 2011; 31: 103–106.
20. Syngelaki A1, Chelemen T, Dagklis T, Allan L, Nicolaides KH. Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11-13 weeks. Prenat Diagn. 2011 Jan;31(1):90-102.
21. Grande M1, Arigita M, Borobio V, Jimenez JM, Fernandez S, Borrell A. First-trimester detection of structural abnormalities and the role of aneuploidy markers Ultrasound Obstet Gynecol. 2012 Feb;39(2):157-63
22. Goetzl L. Adverse pregnancy outcomes after abnormal first-trimester screening for aneuploidy. Clin Lab Med. 2010 Sep;30(3):613-28.
23. Bornstein E, Goncalves Rodríguez J, Álvarez Pavón E, Quiroga H, Or D, Divon MY. First-trimester sonographic findings associated with a Dandy-Walker malformation and inferior vermian hypoplasia. J Ultrasound Med. 2013 Oct;32(10):1863-8.
24. Fong KW1, Dengler J2, Toi A2, Menezes RJ2, Karimzad Y2, Okun N2. Prospective study of intracranial translucency and the posterior brain in normal fetuses at the 11- to 13-week scan. J Ultrasound Med. 2014 Aug;33(8):1373-9.
25. Mangione R1, Dhombres F, Lelong N, Amat S, Atoub F, Friszer S, Khoshnood B, Jouannic JM. Screening for fetal spina bifida at the 11-13-week scan using three anatomical features of the posterior brain. Ultrasound Obstet Gynecol. 2013 Oct;42(4):416-20.
26. Robert Lachmann, Danielle Sodre,Michail Barmpas ,Ranjit Akolekar, Kypros H. Nicolaides .Midbrain and Falx in Fetuses with Absent Corpus Callosum at 11–13 Weeks Fetal diagn Ther 2013;33:41-46
27. Blaas H-GK, Eriksson AG, Salvesen KÅ, et al. Brains and faces in holoprosencephaly: Pre- and postnatal description of 30 cases. Ultrasound Obstet Gynecol 2002;19:24–38.
28. Blaas H-G, Eik-Nes SH. First-trimester diagnosis of fetal malformations, Ch. 49. In: Rodeck C, Whittle M, editors. Fetal medicine:basic science and clinical practice. London: Harcourt Brace; 1999.pp.581–97.

29. Sepulveda W1, Wong AE, Martinez-Ten P, Perez-Pedregosa J Retronasal triangle: a sonographic landmark for the screening of cleft palate in the first trimester Ultrasound Obstet Gynecol. 2010 Jan;35(1):7-13.
30. Sepulveda W, Wong AE, Viñals F, Andreeva E, Adzehova N, Martinez-Ten P Absent mandibular gap in the retronasal triangle view: a clue to the diagnosis of micrognathia in the first trimester.Ultrasound Obstet Gynecol. 2012 Feb;39(2):152-6.
31. Duhamel B. Embryology of exomphalos and allied malformations. Arch Dis Child 1963;38:142–7.
32. Blaas H-G, Eik-Nes SH. First-trimester diagnosis of fetal malformations, Chapter 49. In: Rodeck C, Whittle M, editors. Fetal medicine: basic science and clinical practice. London: Harcourt Brace; 1999. pp. 581–97.
33. Becker R, Runkel S, Entezami M. Prenatal diagnosis of body stalk anomaly at 9 weeks of gestation. Fetal Diagn Ther 2000; 15:301–3.
34. Bonilla-Musoles FM, Raga F, Ballester MJ, et al. Early detection of embryonic malformations by transvaginal and color Doppler sonography. J Ultrasound Med 1994;13:347–55.
35. McAuliffe, Fong,Toi A, Chitayat D, Johnson JA. Ultrasound detection of fetal anomalies in conjunction with first-trimester nuchal translucency screening: a feasibility study. Am JObstet Gynecol. 2005Sep;193(3Pt2):1260-5.
36. Ashhurst DE. Assessing skeletal development. Ultrasound Obstet Gynecol 1997;9:373.
37. Fisk N, Vaughan J, Smidt M, et al. Transvaginal ultrasound recognition of nuchal edema in the first-trimester diagnosis of achondrogenesis. J Clin Ultrasound 1991;19:586–90.
38. Chen C-P, Hsu C-Y, Su J-W, et al. Conjoined twins detected in the first trimester: a review. Taiwan J Obstet Gynecol 2011; 50:424–31.
39. Papaioannou GK, Syngelaki A, Maiz N, et al. Sonographic markers of aneuploidies at 6–10 weeks of gestation. Early Hum Dev 2011;87:453–6.
40. Borrell A, Robinson JN, Santolaya-Forgas J. Clinical value of the 11- to 13 þ 6-week sonogram for detection of congenital malformations: a review. Am JPerinatol 2011;28:
41. Souka AP1, Von Kaisenberg CS, Hyett JA, Sonek JD, Nicolaides KH. Increased nuchal translucency with normal karyotype. Am J Obstet Gynecol. 2005 Apr;192(4):1005-21.
42. Salman Guraya S. The associations of nuchal translucency and fetal abnormalities; significance and implications. J Clin Diagn Res. 2013 May;7(5):936-41.
43. Souka AP1, Von Kaisenberg CS, Hyett JA, Sonek JD, Nicolaides KH. Increased nuchal translucency with normal karyotype. Am J Obstet Gynecol. 2005 Apr;192(4):1005-21.
44. Bahado-Singh RO1, Wapner R, Thom E, Zachary J, Platt L, Mahoney MJ, Johnson A, Silver RK, Pergament E, Filkins K, Hogge WA, Wilson RD, Jackson LG; First Trimester Maternal Serum Biochemistry and Fetal Nuchal Translucency Screening Study Group. Elevated first-trimester nuchal translucency increases the risk of congenital heart defects. Am J Obstet Gynecol. 2005 May;192(5):1357-61.
45. Mogra R1, Alabbad N, Hyett J. Increased nuchal translucency and congenital heart disease. Early Hum Dev. 2012 May;88(5):261-7.
46. Borrell A1, Grande M, Bennasar M, Borobio V, Jimenez JM, Stergiotou I, Martinez JM, Cuckle H. First-trimester detection of major cardiac defects with the use of ductus venosus blood flow. Ultrasound Obstet Gynecol. 2013 Jul;42(1):51-7.
47. Wiechec M, Nocun A, Wiercinska E, Beithon J, Knafel A. First trimester tricuspid regurgitation and fetal abnormalities. J Perinat Med. 2014 May 3.
48. Khalil A1, Nicolaides KH. Fetal heart defects: potential and pitfalls of first-trimester detection. Semin Fetal Neonatal Med. 2013 Oct;18(5):251-60.
49. Blaas H-GK. Detection of structural abnormalities in the first trimester using ultrasound Best Practice & Research Clinical Obstetrics and Gynaecology 28 (2014) 341–353.

TROMBOFILIJE I TRUDNOĆA: ZNAČAJ I TERAPIJA

Dr. Vesna Perković Maksimović

Clinic for Gynecology and Obstetrics, Clinical Center of Republic of Srpska, University of Banja Luka, Republic of Srpska

Trombofilija je stanje urođenog ili stečenog poremećaja zgrušavanja krvi, koji za posledicu ima povećanu sklonost ka trombozama. Trombofilije mogu biti:

Urođene visokog rizika: Leidenova mutacija faktor V - homozigot, mutacija Protrombin II gena G20210A - homozigot, deficit Antitrombina III, leidenova mutacija faktor V - heterozigot + Mutacija Protrombin II - heterozigot.

Urođene srednjeg rizika: Leidenova mutacija faktor V - heterozigot, Mutacija Protrombin II gena G20210A - heterozigot, deficit Proteina C, deficit Proteina S, MTHFR polimorfizam + PAI1(4G/4G).

Urođene niskog rizika: MTHFR heterozigot, PAI1 (4G/5G).

Stečene: Antifosfolipidni sindrom (APS).

Trudnoća je fiziološko hiperkoagulabilno stanje. Faktori hiperkoagulabilnosti:

povećana koncentracija supstanci koje utiču na povećano zgrušavanje krvi (*fibrinogen, faktor II, VII, VIII, X i XII*), smanjena koncentracija supstanci inhibitora koagulacije krvi (javlja se otpornost na aktivirani potein C, opada aktivost proteina S), u trudnoći se usporava cirkulacija krvi u velikim venama donjih ekstremiteta.

Značaj hiperkoagulabilnosti: sprečava se iskrvarenje posle porođaja ili tokom krvarenja u trudnoći. Negativna posledica - češće tromboze i embolije u trudnoći i puerperiumu (6x češće nego izvan trudnoće; 0.7-1.0 VTE na 1000 trudnoća!)

Trombofilija može, ali i ne mora da ima uticaj na trudnoću i da izazove ozbiljne probleme. Mehanizam ispoljavanja trombofilije se zasniva na tome da li je došlo do tromboze na nivou krvnih sudova. Ako nema tromboza na nivou krvnih sudova, nema simptoma - 20% trudnoća sa trombofilijom ima asimptomatski oblik. Ako dođe do tromboza na nivou krvnih sudova razvijaju se kliničke slike različitog intenziteta (od blagih, srednje teških do veoma teških). Tromboza na nivou fetoplacentarne cirkulacije uzrokuje poremećaje na nivou fetoplacentarne cirkulacije, te nastanak patoloških stanja u postojećoj trudnoći, sa različitim kliničkim manifestacijama: spontani abortusi u ranim trudnoćama (do grav hbd 10) i kasnim (do grav hbd 20), IUZR ploda, smrt ploda, preeklampsija, abrupcije posteljice, druga patološka stanja.

Nastanak tromboza na većim krvnim sudovima ima dramatičan tok i teške kliničke manifestacije: tromboembolija pluća, tromboembolija srca, tromboembolija mozga, duboke venske tromboze. Najčešće se javljaju tromboembolije pluća i duboke venske tromboze.

Svjesni težine perinatalnog ishoda u trudnoćama udruženim sa raznim oblicima trombofilije, pred ginekologom je veliki zadatak. Postoje brojna ispitivanja koja imaju za cilj – šta činiti da ne dolazi do takvih stanja. Uloga ginekologa i hematologa su od neprocjenjivog značaja! Veliki značaj ima rano otkrivanje i profilaksa i terapija

Rano otkrivanje počinje od prenatalnih pregleda i prvog pregleda po izostanku menstruacije. Prenatalni pregledi su pregledi prije planiranja trudnoće. I kod jednih i kod drugih, veoma je važna detaljna anamneza. Ona ima ključnu ulogu!

U okviru detaljne anamneze saznajemo, u ličnoj anamnezi da li je pacijentkinja imala ranije neka od stanja VTE, da li ima neka od drugih patoloških stanja (poremećaj rada štitaste žlijezde, poremećaj glikoregulacije, gojaznost, pušenje, ranije operacije...). U okviru porodične anamneze: da li su postojala stanja VTE kod najbližih članova porodice, naročito prije 45. godine. Da li je imala porođaja i kakav je perinatalni ishod? Da li je imala spontanih pobačaja?

Ukoliko se pri detaljnoj anamnezi dobiju pozitivni podaci indikuje se uraditi testove na trombofiliju. Ako su testovi na trombofiliju pozitivni pacijentkinja se upućuje hematologu. Hematolog analizira testove na trombofiliju, uzima detaljnu anamnezu (ranije navedenu) i obavlja klinički pregled. U okviru analize testova na trombofiliju, hematolog zaključuje o kojoj vrsti trombofilije je riječ, kao i da li postoji udruženost 2 ili više trombofilija. Posle detaljnog pregleda hematologa, hematolog procjenjuje rizik za nastanak tromboza i donosi odluku o potrebi uvođenja profilaktične terapije.

Terapija je individualna. U osnovi stoji preporuka hematologa. Kod blažih oblika trombofilije, bez ranijih VTE u ličnoj i porodičnoj anamnezi, liječenje nije potrebno. Preporučuje se - Folan tbl + higijensko-dijetetski režim te nastaviti redovne kontrole ginekologa. Kod srednje teških oblika trombofilije, bez VTE u ličnoj i porodičnoj anamnezi, terapija podrazumijeva primjenu Aspirin tbl 50-100 mg jednom dnevno, Folan tbl, higijensko dijetetski režim. Potrebno je praćenje D-dimera na 2 do 4 nedelje i korekcija terapije u slučaju njegovog porasta (duplo od referentne vrijednosti). Nastaviti dalje redovne kontrole kod ginekologa. Kod teških oblika trombofilije, sa VTE u ličnoj i porodičnoj anamnezi, uz dodatne faktore (gojaznost, starija životna dob, ranije operacije) potrebno je uvesti NMH od početka trudnoće do kraja i 6 nedjelja posle porođaja, Folan tbl, higijensko dijetetski režim. Potrebno je praćenje D-dimera na 2 do 4 nedelje i korekcija terapije u slučaju njegovog porasta (duplo od referentne vrijednosti). Kod daljeg rasta D-dimera, kontroliše se AntiXa.

Kod praćenja trudnica sa trombofilijom, rade se redovne kontrole ginekologa i kontrole sledećih nalaza: KKS i feritin (jednom mjesečno), Homocistein (kod postojanja MTHFR), D-dimer se kontroliše na početku trudnoće, potom po savjetu hematologa. Kod porasta D-dimera duplo od referentne vrijednosti koriguje se terapija (uvodi NMH). Kod daljeg porasta, kontroliše se AntiXa. Takođe se kontroliše INR, aPTT po procjeni hematologa. Terapija i praćenje se čine do porođaja.

Porođaj kod trudnica sa trombofilijama završavamo vaginalnim putem i carskim rezom. Carskim rez se radi ako postoje akušerske indikacije!

Terapijski postupak kod *vaginalnog* porođaja:

- Primjena NMH se obustavlja sa dobijanjem prvih kontrakcija
- Terapija NMH se nastavlja 8-10 sati nakon porođaja, a po preporuci hematologa i ranije (6 sati posle porođaja)
- Dužina terapije NMH posle porođaja - po procjeni hematologa (3-6 nedelja po porođaju, zavisno od vrste trombofilije i drugih faktora)

Terapijski postupak kod porođaja *carskim rezom*:

- Kod planiranog carskog reza primjena NMH se obustavlja 12h prije operativnog zahvata (a kod težih oblika trombofilije i ranije, po preporuci hematologa!)
- Nastavak NMH terapije 8-10 sati posle carskog reza (a kod težih oblika trombofilije i ranije, po preporuci hematologa!)

- NMH se nastavlja 6 nedelja posle porođaja, a kod lakših oblika i do 3 nedelje posle porođaja (preporuka hematologa)
- Ako se planira epiduralna anestezija, potrebno je ukinuti NMH najmanje 12-24 sata prije anestezije, i nastaviti 12-24 sata nakon anestezije, u zavisnosti od vrste porođaja.

Trudnoća je fiziološko hiperkoagulabilno stanje. Trudnoća komplikovana trombofilijom, kod 20% trudnica ima asimptomatski oblik, dok kod ostalih trudnoća je komplikovana raznim patološkim stanjima koja imaju različite kliničke manifestacije u zavisnosti od vrste trombofilije, udruženosti 2 i više trombofilija, postojanja pozitivne lične, porodične i akušerske anamneze uz dodatne faktore (gojaznost, pušenje...).

Odluka o testiranju na trombofilije i profilaktičnoj primjeni antikoagulantne terapije donosi se na osnovu individualne procjene rizika i koristi, što je odluka hematologa i ginekologa. Za sada nema konsenzusa za indikacije za odabir trudnica za testove na trombofiliju. Ne preporučuje se rutinski raditi testove na trombofiliju, iz razloga što nije racionalno i nije ekonomski opravdano.

Literatura

1. Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J (June 2008). "Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)". Chest. 133 Suppl 6: 844S–886S.
2. Dalen JE (June 2008). "Should patients with venous thromboembolism be screened for thrombophilia?". Am. J. Med. 121(6):458-63.
3. Heit JA (2007). "Thrombophilia: common questions on laboratory assessment and management". Hematology Am. Soc. Hematol. Educ. Program. 2007 (1): 127-35.
4. Kupferminc MJ, Rimon E, Ascher-Landsberg J, Lessing JB, Many A. Perinatal outcome in women with severe pregnancy complications and multiple trombophilias. J Perinat Med. 2004;32(3):225-7.
5. Trombofilija i njezin utjecaj na ishod trudnoće. Portal Hrvatskog društva za ginekologiju i opstetriciju. https://www.hdgo.hr/Default.aspx?sifraStranica=607

THE TREATMENT OF PREMALIGNANT AND MALIGNANT LESIONS OF THE UTERINE CERVIX IN PREGNANCY

Prof. Zoran Protrka

Clinic for Gynecology and Obstetrics, Clinical Center of Kragujevac
Faculty of medical sciences, University of Kragujevac, Serbia

Algorithms in treatment premalignant and malignant lesions of the uterine cervix in non-pregnant patients are well known. Treatment of these lesions during pregnancy is a great dilemma for many gynecologists.

The indications for cervical cytology screening in pregnancy: Views of certain gynecologists that due to changes in squamous and cylindrical epithelium during pregnancy, it's unnecessary to perform the cervical cytology screening, due to a large number of false positive results, are unfounded. The indications are the same as in non-pregnant women. In many countries it is a mandatory part of prenatal diagnosis.

The indications for colposcopy in pregnancy: Macroscopically suspicious uterine cervix, abnormal cytological screening, cervical bleeding in the first and second trimesters, the presence of koilocytes in the cervical smear (may be a sign of HPV infection).

The indications for cervical punch biopsy in pregnancy: Abnormal cytological screening, colposcopic diagnosis clear cervical lesion and in the case of a normal cytological screening, colposcopic diagnosis suspected lesion to a greater degree than intraepithelial. Cervical punch biopsy is taken from a colposcopic suspicious site (1, 2).

A tissue sample taken by cervical punch biopsy for histological examination must be: taken from a representative place, have preserved epithelium, a sufficient amount of stroma (3, 4)

Difficulties in performing a cervical punch biopsy in pregnancy:

- *Objective*: bleeding, that can be of varying intensity due to high blood flow of the uterine cervix.
- *Subjective*: fear of gynecologists (this is the reason for postponing the intervention after childbirth) (5, 6).

Management of bleeding during cervical punch biopsy in pregnancy: Tamponade with a hard gauze stiletto, application of *Monsel* solution (aqueous ferric sulphate solution, with addition nitric and sulfuric acid), suturing, Lapis application (poor results) (7, 8).

Pap cytology: IIIa Bethesda nomenclature: ASC-US (atypical squamous cells of undetermined significance): colposcopic diagnosis without major changes: cervical punch biopsy should not be done, 6– 8 weeks after delivery repeat colposcopy and cervical cytology. Colposcopic diagnosis with major changes: cervical punch biopsy is needed and further procedure according to the histological findings (9-12).

Pap cytology: IIIa Bethesda nomenclature: ASC-H (atypical squamous cells cannot rule out high grade SIL): colposcopic diagnosis without major changes: cervical punch biopsy should not be done, 6 – 8 weeks after delivery repeat colposcopy and cervical cytology. Colposcopic diagnosis with major changes: cervical punch biopsy is needed and further procedure according to the pathological findings. Endocervical curettage should not be done (9-12).

Pap cytology: IIIa Bethesda nomenclature: AGC (atypical glandular cells): Colposcopic diagnosis without major changes: cervical punch biopsy should not be done, 6 – 8 weeks after delivery repeat colposcopy and cervical cytology. Colposcopic diagnosis with major changes: cervical punch biopsy is needed and further procedure according to the pathological findings. (9-12).

Pap cytology: IIIb and more: colposcopic targeted biopsy is mandatory. Further procedure according to the pathological findings (1-15).

Treatment of L – SIL in pregnancy: there is a large percentage of regressions. Colposcopy and cervical cytology needs to be repeated at 6-8 weeks. In case of progression colposcopic diagnosis or cervical citology, the cervical punch biopsy needs to be repeated. It is not an indication for a Cesarean Section (birth trauma is considered destructive for neoplastic epithelium, due to the loss of its connection with the stroma and favorably affects regression of SIL) (13-15).

Treatment of H – SIL in pregnancy: a longer period of time until progression (less than 4% had progression in less than a year). Colposcopy and cervical cytology needs to be repeated at 6-8 weeks – look for signs of invasion: abnormal, significantly dilated, blood vessels. In case of progression, the cervical punch biopsy needs to be repeated. It is not an indication for a Cesarean Section. Conization is recommended 6-8 weeks after delivery, with mandatory prior cervical punch biopsy, as a check (13-15).

Treatment of Ca in situ in pregnancy: pathological diagnosis obtained from cervical punch biopsy requires conisation (loop electrosurgical excision procedure-LEEP or cold knife conization-CKC). Conization can be done until the 30th W.G. (usually with a previous cerclage), the recommendatation is from the 14th to the 20th W.G. It is not an indication for a Cesarean Section. Detailed postpartum examination (16, 17).

Necessary pathological parameters for the detection of carcinoma micro invasive: depth of invasion, the lateral extent of the lesion, tumor differentiation, lympho-vascular space involvement (LVI), eesection margin status.

Treatment of FIGO stage IA1 in pregnancy without LVI:

- The pathological diagnosis is made solely by conization (loop electrosurgical excision procedure-LEEP or cold knife conization-CKC).
- Conization can be done until the 30th W.G. The recommendatation is until the 20th W.G. (whenever a biopsy diagnosis microinvasive cancer).
- It is not an indication for a Cesarean Section (18-20).
- Detailed postpartum examination, due to the high percentage of residual disease.
- In the absence of a desire to reproduce, extrafascial hysterectomy is considered.

Treatment of FIGO stage IA2 in pregnancy:

- Conization is a sufficient treatment.
- It is an indication for an elective Cesarean Section.
- Detailed postpartum examination.
- If there is a peritumor lympho-vascular space involvement, radical abdominal trachelectomy is considered.
- If the patient has no desire to fertility preservation, 6 – 8 weeks after delivery (due to the risk of bleeding and genitourinary injuries) modified radical hysterectomy is indicated.
- During this period, none of the patients had disease progression (21-24).

Diagnosis of FIGO stage IA carcinoma of the uterine cervix: should be based on conization by applying a technique that leaves no cauterized margins.

Complications of conization in pregnancy: bleeding, spontaneous abortion, premature birth, cervical stenosis, chorioamnionitis, preterm premature rupture of the membranes, higher incidence of residual disease (due to an unsatisfactory cone) (17, 18).

FIGO staging of invasive carcinoma of the uterine cervix in pregnancy: the pathological diagnosis is made solely by cervical punch biopsy or conization (loop electrosurgical excision procedure-LEEP or cold knife conization-CKC), gynecological examination with the speculum, bimanual gynecological examination is difficult, magnetic resonance imaging is used to assess parametrial infiltration and lymphadenopathy, ultrasonography is used to diagnose hydronephrosis, an radiography of the chest is done with a shelter of the abdomen (25,26).

Treatment of operable stages invasive cervical carcinoma in the first trimester of pregnancy:

- Surgical menagement: radical hysterectomy with pelvic lymphadenectomy along with pregnancy. Termination of pregnancy is not indicated. Radical abdominal trachelectomy is considered.
- Adjuvant therapy: is determined as in nonpregnant women, according to the postoperative pathological findings (27-30).

Treatment of inoperable stages invasive cervical carcinoma in the first trimester of pregnancy:

- External beam radiotherapy with concurrent platinum-based chemotherapy. If a spontaneous abortion does not occur within 2 to 5 weeks, the pregnancy is terminated surgically.
- After termination of pregnancy, brachytherapy is continued in the standard way (27-30).

Treatment of operable stages invasive cervical carcinoma in the early second trimester of pregnancy (< 20 W.G.):

- Surgical management: as with operable stages in the first trimester.
- Adjuvant therapy: as with operable stages in the first trimester.

Conditions that should be met for the radical trachelectomy in pregnancy:

- Histological type of cervical cancer (squamous, adeno, adenosquamous).
- FIGO stage IA to IB1, tumor size less than 2 cm.
- Desire to fertility preservation.
- Satisfactory colposcopic finding (R0, margina > 5mm).
- Negative lymph nodes.
- The remaining length of the uterine cervix is greater than 1 cm.
- Age less than 35 (39) years? (28, 29).

Treatment of operable stages invasive cervical carcinoma in the late second trimester of pregnancy (< 20 W.G.):

- FIGO stage Ib1: therapy may be delayed for up to 10 weeks, and then surgical management as with operable stages in the third trimester.
- FIGO stage Ib2 to IIa: surgical management as with operable stages in the first trimester.
- Adjuvant therapy: is determined as in nonpregnant women, according to the postoperative pathological findings (31-34).

Treatment of inoperable stages invasive cervical carcinoma in the second trimester of pregnancy:

- External beam radiotherapy with concurrent platinum-based chemotherapy. If a spontaneous abortion does not occur within 2 to 5 weeks, the pregnancy is terminated surgically.
- After termination of pregnancy, brachytherapy is continued in the standard way. (31,32,33,34)

Treatment of operable stages invasive cervical carcinoma in the third trimester of pregnancy:

- After establishing the maturity of the fetus in cooperation with a pediatrician, a medial laparotomy and corporal Cesarean Section is performed and in the same act radical hysterectomy with pelvic lymphadenectomy. Not later than 34 weeks of pregnancy.
- Adjuvant therapy: is determined as in nonpregnant women, according to the postoperative pathological findings. (31-34).

Treatment of inoperable stages invasive cervical carcinoma in the third trimester of pregnancy:

- Stages IB2 and IIA2 may be included in this category in certain cases (tumor diameter greater than 4 cm).
- After establishing the maturity of the fetus in cooperation with a pediatrician, a medial laparotomy and corporal Cesarean Section is performed. Not later than 34 weeks of pregnancy.
- Two weeks after the operation, external beam radiotherapy with concurrent platinum-based chemotherapy is performed.
- Brachytherapy is continued in the standard way (31-34).

Neoadjuvant platinum-based chemotherapy during the second and third trimesters has been described as a feasible treatment option to achieve disease control until birth. Although there is accumulating evidence in the literature regarding the administration of platinum during pregnancy, its safety remains uncertain (35-39).

Neoadjuvant chemotherapu during the pregnancy can cause: spontaneous abortion, F.M.U., intrauterine growth retardation, preterm birth, major malformation- teratogenesis, mutagenesis, mental retardation, carcinogenesis of other organs, organic dysfunction, and low birth weight (40-43).

References

1. Kesić V. Kolposkopija i bolesti donjeg genitalnog sistema žene. Beograd: Zavod za udžbenike i nastavna sredstva; 2000.
2. Van Calsteren K, Vergote I, Amant F. Cervical neoplasia during pregnancy: diagnosis, management and prognosis. Best Pract Res Clin Obstet Gynaeco. 2005;19:611-30.
3. Selleret L, Mathevet P. Precancerous cervical lesions during pregnancy: diagnostic and treatment. J Gynecol Obstet Biol Reprod. 2008;37:S131-8.
4. Boardman LA, Goldman DL, Cooper AS, Heber WW, Weitzen S. CIN in pregnancy: antepartum and postpartum cytology and histology. J Reprod Med. 2005;50:13-8.
5. Douvier S, Filipuzzi L, Sagot P. Management of cervical intra-epithelial neoplasm during pregnancy. Gynecol Obstet Fertil. 2003; 31:851-5.
6. Conolly TP, Evans AC. Atypical Papanicolau smear in pregnancy. Clin Med Res. 2005; 1:13-8.
7. Vincens C, Dupaigne D, de Tayrac R, Mares P. Management of pregnant women with advanced cervical cancer. Gynecol Obstet Fertil. 2008; 36:365-72.
8. Frega A, Scirpa P, Corosu R, Verrico M, Scarciglia ML, Primieri MR, et al. Clinical management and follow-up of squamous intraepithelial cervical lesions during pregnancy and postpartum. Anticancer Res. 2007;27:2743-6.
9. Song F, Wang Y, Wang T. Natural evolution and clinical management of cervical intraepithelial neoplasia during pregnancy and postpartum. Int J Gynecol Obstet. 2009; 107(Suppl 2):S345.
10. Fader AN, Alward EK, Niederhauser A, Chirico C, Lesnock JL, Zwiesler DJ, et al. Cervical dysplasia in pregnancy: a multiinstitutional evaluation. Am J Obstet Gynecol. 2010; 203:113-6.
11. Coppolillo EF, De Ruda Vega HM, Brizuela J, Eliseth MC, Barata A, Perazzi BE. High-grade cervical neoplasia during pregnancy: diagnosis, management and postpartum findings. Acta Obstet Gynecol Scand. 2013; 92:293-7.
12. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis.

Lancet. 2006; 367:489-98.

13. Jakobsson M, Gissler M, Sainio S, Paavonen J, Tapper AM. Preterm delivery after surgical treatment for cervical intaepithelial neoplasia. Obstet Gynecol. 2007; 109:309-13.
14. Bruinsma F, Lumley J, Tan J. Precancerous changes in the cervix and risk of subsequent preterm birth. Int J Obstet Gynecol. 2006; 101:70-80.
15. Muller CY, Smith HO. Cervical neoplasia complicating pregnancy. Obstet Gynecol Clin North Am. 2005; 32:533-46.
16. Sadler L, Saftlas A. Cervical surgery and preterm birth. J Perinat Med. 2007; 35:5-9.
17. Andía D, Mozo de Rosales F, Villasante A, Rivero B, Díez J, Pérez C. Pregnancy outcome in patients treated with cervical conization for cervical intraepithelial neoplasia. Int J Gynecol Obstet. 2011; 112:225-8.
18. Pavlidis NA. Coexistence of pregnancy and malignancy. Oncologist. 2002;7(4):573–287.
19. Köhler C, Oppelt P, Favero G, et al. How much platinum passes the placental barrier? Analysis of platinum applications in 21 patients with cervical cancer during pregnancy. Am J Obstet Gynecol. 2015;213(2):206.
20. Cibula D, Pötter R, Planchamp F, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/ European Society of Pathology Guidelines for the Management of Patients with Cervical Cancer. Virchows Arch. 2018;472(6):919-36.
21. Latimer J. Gynaecological malignancies in pregnancy. Curr Opin Obstet Gynecol. 2007;19(2):140-4.
22. Lee JM, Lee KB, Kim YT, et al. Cervical cancer associated with pregnancy: results of a multicenter retrospective Korean study (KGOG-1006). Am J Obstet Gynecol. 2008;198(1):92.e1–6.
23. Amant F, Halaska MJ, Fumagalli M, et al; ESGO task force 'Cancer in Pregnancy'. Gynecologic cancers in pregnancy: guidelines of a second international consensus meeting. Int J Gynecol Cancer. 2014;24(3): 394-403.
24. de Vincenzo R, Amadio G, Ricci C, et al. Treatment of cervical cancer in Italy: strategies and their impact on the women. Vaccine. 2009; 27(Suppl 1):A39–A45.
25. Ferrandina G, Ercoli A, Fagotti A, et al. Completion surgery after concomitant chemoradiation in locally advanced cervical cancer: a comprehensive analysis of pattern of postoperative complications. Ann Surg Oncol. 2014;21(5):1692–9.
26. Pentheroudakis G, Pavlidis N. Cancer and pregnancy: poena magna, not anymore. Eur J Cancer. 2006;42(2):126-40.
27. Benhaim Y, Haie-Meder C, Lhommé C, et al. Chemoradiation therapy in pregnant patients treated for advanced-stage cervical carcinoma during the first trimester of pregnancy: report of two cases. Int J Gynecol Cancer. 2007;17(1):270-4.
28. Ostrom K, Ben-Arie A, Edwards C, Gregg A, Chiu JK, Kaplan AL. Uterine evacuation with misoprostol during radiotherapy for cervical cancer in pregnancy. Int J Gynecol Cancer. 2003;13(3):340-3.
29. Morice P, Uzan C, Leary A. Are the outcomes of neoadjuvant chemotherapy for stage IB2 cervical cancer similar in pregnant and nonpregnant patient? Gynecol Oncol. 2012;127(1):257-8.
30. Morice P, Uzan C, Gouy S, Verschraegen C, Haie-Meder C. Gynaecological cancers in pregnancy. Lancet. 2012;379(9815):558-69.
31. Ilancheran A. Neoadjuvant chemotherapy in cervical cancer in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2016;33:102–107. 316. Zagouri F, Sergentanis TN, Chrysikos D, Bartsch R. Platinum derivatives during pregnancy in cervical cancer: a systematic review and meta-analysis. Obstet Gynecol. 2013;121(2 Pt 1):337-43.
32. Yousefi Z, Hoshyar AH, Kadkhodayan S, Hasanzade M, Kalantari MR, Mottaghi M. Neoadjuvant chemotherapy and radical surgery in locally advanced cervical cancer during pregnancy: case report and review of literature. Oman Med J. 2013;28(1):60-2.
33. Dawood R, Instone M, Kehoe S. Neo-adjuvant chemotherapy for cervical cancer in pregnancy: a case report and literature review. Eur J Obstet Gynecol Reprod Biol. 2013;171(2):205-8.
34. Ayhan A, Dursun P, Karakaya BK, Ozen O, Tarhan C. Neoadjuvant chemotherapy followed by cesarean radical hysterectomy in a triplet pregnancy complicated by clear cell carcinoma of the cervix: a case presentation and literature review. Int J Gynecol Cancer. 2012;22(7): 1198-202.
35. Fruscio R, Villa A, Chiari S, et al. Delivery delay with neoadjuvant chemotherapy for cervical cancer patients during pregnancy: a series of nine cases and literature review. Gynecol Oncol. 2012;126(2): 192-7.
36. Lanowska M, Köhler C, Oppelt P, et al. Addressing concerns about cisplatin application during pregnancy. J Perinat Med. 2011;39(3):279-85.
37. Gambino A, Gorio A, Carrara L, et al. Cancer in pregnancy: maternal and fetal implications on decision-making. Eur J Gynaecol Oncol. 2011; 32(1):40-5.
38. Chun KC, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. Neoadjuvant chemotherapy with paclitaxel plus platinum followed by radical surgery in early cervical cancer during pregnancy: three case reports. Jpn J Clin Oncol. 2010;40(7):694-8.
39. Rabaiotti E, Sigismondi C, Montoli S, Mangili G, Candiani M, Viganò R. Management of locally advanced cervical cancer in pregnancy: a case report. Tumori. 2010;96(4):623-6.
40. Boyd A, Cowie V, Gourley C. The use of cisplatin to treat advancedstage cervical cancer during pregnancy allows fetal development and prevents cancer progression: report of a case and review of the literature. Int J Gynecol Cancer. 2009;19(2):273-6.
41. Seamon LG, Downey GO, Harrison CR, Doss B, Carlson JW. Neoadjuvant chemotherapy followed by post-partum chemoradiotherapy and chemoconsolidation for stage IIIB glassy cell cervical carcinoma during pregnancy. Gynecol

Oncol. 2009;114(3):540-1.
42. Favero G, Lanowska M, Schneider A, Marnitz S, Köhler C. Laparoscopic pelvic lymphadenectomy in a patient with cervical cancer stage Ib1 complicated by a twin pregnancy. J Minim Invasive Gynecol. 2010;17(1):118-20.
43. Marnitz S, Köhler C, Oppelt P, et al. Cisplatin application in pregnancy: first in vivo analysis of 7 patients. Oncology. 2010;79(1–2):72-7.

Dr. Zoran Milan Protrka was born on April 25th, 1964 in Kragujevac. He finished primary school and secondary Medical school in Kragujevac. He graduated at the Department of Medical Faculty in Belgrade, located in Kragujevac on January the 9th, 1991. Specialization in Gynecology and Obstetrics he completed on September the 24th, 1996 at the Gynaecology and Obstetrics Clinic "Narodni Front" at Belgrade Medical Faculty. At the Gynecology and Obstetrics Clinics of the Clinical Center Kragujevac, he is employed since 1997. and is currently working as the head of the Department for Fertility Control. Since 1998. he has been employed as an assistant of Gynecology and Obstetrics subject at the Medical Faculty in Kragujevac until 2007., then as an assistant professor since 2007., and since 2012. as an associate professor, and since 2018. as an professor. Since 2000, he is the Secretary of the Department of specialized studies of Gynecology and Obstetrics. He speaks English.

Master's Thesis entitled "Immune response of a mother to alloantigens of a father in couples with habitual abortions of unknown etiology", he defended on July the 14th, 1995. at the Faculty of Medicine in Kragujevac.

The doctoral thesis entitled "The significance of the expression of proto-oncogenes in cervical carcinogenesis", he defended on December the 13th, 2006. at the Faculty of Medicine in Kragujevac.

INFERTILITY, PREGNANCY AND THROMBOPHILIA: EVIDENCE-BASED APPROACH

Prof. Predrag Miljić

Clinic of Hematology, Clinical Center of Serbia
Faculty of Medicine, University of Belgrade, Serbia

Inherited thrombophilia is a genetic disorder (mutation) associated with a significantly increased risk of thrombosis. Therefore, thrombophilia means a predisposition for thrombosis, and its clinical manifestation usually occurs only when additional, most commonly acquired prothrombogenic factors such as hormonal contraceptives, pregnancy, puerperium, major surgery or immobilization are superimposed on this condition. Thrombophilic conditions differ in their characteristics. Congenital deficiency of antithrombin, protein C or protein S as well as prothrombin Belgrade mutation are very rare but strong thrombophilias with a high degree of clinical expression in carriers of these mutations. On the other hand, the overall prevalence of the FV Leiden or FII 20210A mutation in the European population is between 5-10%, but the clinical expression is low, which means that almost 90% of heterozygous carriers of these mutations never experience a thrombotic complication reflecting mild thrombophilic nature of these conditions. Several other polymorphisms in the genes for coagulation factors, such as polymorphism 4G/5G in the PAI-1 gene, have been reported in the past as congenital thrombophilias. However, because these polymorphisms are associated with slightly increased risk of thrombosis or not increased risk, compared to individuals without these mutations, they should not be considered as thrombophilic conditions.

In addition to participating in the pathogenesis of venous thromboembolism, it is assumed that blood hypercoagulability caused by the presence of thrombophilic mutations may play an important role in pregnancy failure or some placenta-mediated complications. Uteroplacental circulation resembles systemic venous circulation in many respects, primarily in low resistance and slow blood flow, so it can be assumed that thrombophilia could compromise placental circulation in a similar way as it creates ptorhrombotic condition in systemic veins. Thrombosis of the placental vessels could result in placental infarction and placental insufficiency producing clinical manifestations in the form of early or late fetal loss, fetal growth restriction, preeclampsia or placental abruption. Similarly, microthrombosis due to blood hypercoagulability could interfere with the invasion of syncytiotrophoblasts at the site of embryo implantation and interfere with this process, resulting in infertility.

However, despite the abundant literature in this field, the presumed association between congenital thrombophilic conditions and human reproduction failure is still quite controversial mainly due to the contradictory results of previous studies. Interpretation of the results of the studies investigating influence of congenital thrombophilia on infertility or pregnancy failure is complicated by the fact that the frequency of different thrombophilic conditions is not the same in different parts of the world and ethnic groups and that previous studies had a very heterogeneous designs. Previous studies also frequently investigated influence of gene polymorphisms that do not generally represent thrombophilic conditions. In general, in small, observational or case-control studies, thrombophilia has been found to play more important role in etiology of pregnancy failure than it is found in in large, prospective and randomized trials. Most important, both hematological and gynecological professional associations recommend against routine

testing for congenital thrombophilic conditions in women with infertility or pregnancy failure. Such position is the result of analysis of large studies that have shown that the use of heparin did not significantly increase the success of pregnancy in women with thrombophilia who had early or late fetal loss. However, since the benefit of heparin and aspirin administration in women with antiphospholipid syndrome and previous pregnancy failure has been demonstrated, testing for the presence of antiphospholipid antibodies is recommended in women who meet the clinical criteria for the existence of this syndrome.

Inherited thrombophilic conditions represent a very heterogeneous group of genetic diseases that differ in frequency, degree of clinical expression and mechanisms by which they lead to blood hypercoagulabilit and induction of the thrombophilic phenotype. Bearing in mind the complexity of thrombophilic conditions, it can be assumed that their relationship with failure of human reproduction can be much more complex than it seems at first glance. Therefore, it is considered that the relationship between these two areas is still not fully clarified and the results of a large, well-designed randomized and controlled, ongoing study that is investigating effects of LMW heparin on pregnancy outcome in women with thrombophilia and previous pregnancy loss (ALIFE 2 study that started in 2013) that should shed more light on this issue, are eagerly awaited.

Although leading professional societies, after considering results of randomized and controlled studies, recommend against routine testing for congenital thrombophilic conditions in women with pregnancy failure or placenta-mediated complications, results of several observational studies indicated improved pregnancy outcome in thrombophilic women with previous pregnancy failure who were receiving LMW heparin in the next pregnancy. Therefore, expert recommendations related to thrombophilia testing should not be ignored, because they are based on the best current evidence from the professional literature, but these recommendations cannot be considered definitive, giving that pregnancy and thrombophilia relation is a dynamic area that is still intensively researched. In addition, the recommendations of leading professional associations and societies are not completely aligned, so for example RCOG in the publication from 2011 recommends testing for the presence of the FV Leiden mutation, the FII 20210A mutation, and protein S deficiency in women with late fetal loss what is not in agreement with guidelines proposed by ACOG (American College of Obstetricians and Gynecologists) or ESHRE (European Society of Human Reproduction and Embryology). In every day clinical practice, when deciding to test for thrombophilia in a woman with infertility or pregnancy failure, relying on guidelines and recommendations issued by leading professional societies, but also taking into account individual characteristics such as the presence of thrombosis in the vasculature of the placenta, previous venous thrombosis or a positive family history of thrombosis, could be a rational approach.

References

1. Ashraf N, Visweshwar N, Jaglal M, Sopkol L, Laber D. Evolving paradigm in thrombophilia screenimng. Blood Coagul Fibrinolysis. 2019,30:249-52.
2. Skeith L, Blondon M, Ni Ainle F. Understanding and preventing placenta-mediated complications. Haemostaseologie 2020,40:356-63.
3. Skeith L, Carrier M, Kaaja R, et al. A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. Blood. 2016 31;127(13):1650-5.
4. Royal College of Obstetrician and Gynaecologist. The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. Green-top guideline No 17. April 2011.
5. ESHRE Early Pregnancy Guideline Development Group. Recurrent pregnancy loss. Version 2.November 2017.

Dr Predrag Miljic graduated from Faculty of Medicine, Belgrade University, in 1991. Since then, he has been employed in Clinic of Haematology, Clinical Center of Serbia in Belgrade. Dr Miljic is Board Certified in Haematology and Internal Medicine. In 2007 he completed postgraduate training in Hemophilia Center, Royal Infirmary of Edinburg, UK, under supervision of Professor C.A. Luddlam. Currently he is Head of Haemophilia Comprehensive Care Center in Clinic of Haematology and Professor of internal medicine at Faculty of Medicine University in Belgrade. His main professional and scientific interests are disorders of haemostasis and improvement of haemophilia care, especially management of adult patients with chronic haemophilic arthropathy. He published several papers in national and international journals and presented many papers on international congresses and meetings.

SCREENING PERFORMANCE OF CONGENITAL HEART DEFECTS IN FIRST TRIMESTER USING SIMPLE CARDIAC SCAN

Assist. Prof. Nataša Karadžov Orlić

Clinic for Gynecology and Obstetrics Narodni Front
School of Medicine, University of Belgrade, Serbia

Congenital heart defects (CHD) represent the one third of all major congenital anomalies with a prevalence of 4-9 per 1000 live births (1). First trimester screening recently started to play a pivotal role in the management of pregnancies. By the combination of maternal age, serum biochemistry, ultrasound anomaly scan, and additional ultrasonographic markers, this screening can identify most fetal aneuploidies and structural abnormalities in the fetus (1,2). In addition, most CHD can be detected in the first trimester using increased nuchal translucency (NT) and by color Doppler assessment, absent/ reverse a-wave following atrial contraction in ductus venosus (DV) and tricuspid regurgitation (TCR) (2-7). Use of combination of these parameters increased a detection rate of CHD in the first trimester to 60-80% (8,9). Currently, detailed echocardiographic examination in the first trimester is recommended to be an integral part of the pregnancy management (10,11). Major CHD that can be recognized from this type of screening might be adequately treated or pregnancy termination may be considered by the mother. Of note, there is no evidence that extensive fetal echocardiography with longer fetal exposure and pulsed Doppler in the first trimester is safe for fetus. Therefore, simple cardiac scan, which is in accordance with ALARA principle (as low as reasonably achievable), giving a certain diagnostic accuracy in revealing CHD in first trimester, might become a part of routine clinical strategy (12).

The objective of this study was to analyze if the addition of simple cardiac scan in cases with increased nuchal translucency (NT) and/or abnormal ductus venosus (DV) blood flow, and/ or tricuspid regurgitation (TCR) can improve detection of congenital heart defects (CHD) in chromosomally normal fetuses without non-cardiac defects at 11-13 + 6 gestational weeks in a population of singleton pregnancies.

During the 10 years period, all singleton pregnancies at 11-13 + 6 weeks were routinely scanned for NT, DV blood flow and TCR assessment and, if a single of these parameters was abnormal, simple cardiac scan with 2D gray scale and color and/or directional power Doppler in 4-chamber (4-CV) and 3 vessel and trachea views (3VTV) was performed.

Results: The sensitivity and specificity of NT ≥ 95th + DV R/A a-wave + TCR in detecting CHD were 77% and 97%, respectively, and of simple cardiac scan, 67% and 98%, respectively. Area under the curve of receiver operating characteristic curve of NT ≥ 95th + DV R/A a-wave + TCR was 0.838, and of NT ≥ 95th + DV R/A a-wave + TCR + simple cardiac scan was 0.915.

In chromosomally normal fetuses without non-cardiac anomalies, addition of simple cardiac scan to the combined first trimester screening parameters improves detection of major CHD during first trimester.

References

1. van der Linde D, Konings EEM, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systemic review and meta- analysis. Am J Cardiol.2011;58:2241-7.
2. Ghi T, Huggon IC, Zosmer N, Nicolaides KH. Incidence of major structural cardiac defects associated with increased nuchal translucency but normal karyotype. Ultrasound Obstet Gynecol. 2001;18:610-4.
3. Sotiriadis A, Papatheodorou S, Elefteriades M, Makrydimas G. Nuchal translucency and major congenital heart

defects in fetuses with normal karyotype: a meta-analysis. Ultrasound Obstet. Gynecol. 2013;42:383-9.

4. Makrydimas G, Sotiriadis A, Huggon IC, et al. Nuchal translucency and fetal cardiac defects: a pooled analysis of major fetal echocardiography centers. Am J Obstet Gynecol. 2005;192:89-5.
5. Matias A, Gomes C, Flack N, Montenegro N, Nicolaides KH. Screening for chromosomal abnormalities at 10-14 weeks: the role of ductus venosus blood flow. Ultrasound Obstet Gyneco.1998;12:380-4.
6. Matias A, Huggon I, Areias JC, Montenegro N, Nicolaides KH. Cardiac defects in chromosomally normal fetuses with abnormal ductus venosus blood flow at 10-14 weeks. Ultrasound Obstet Gynecol. 1999;14:307-10.
7. Borrell A. The ductus venosus in early pregnancy and congenital anomalies. Prenat Diagn. 2004;24:688-92.
8. Smrcek JM, Berg C, Geipel A, et al. Detection rate of early fetal echocardiography and in utero development of congenital heart defects. J Ultrasound Med. 2006;25:187-96.
9. Becker R, Wagner RD. Detailed screening for fetal anomalies and cardiac defects at the 11-13 week scan. Ultrasound Obstet Gynecol. 2006;27:613-8.
10. Practice I. Guidelines (updated): sonographic screening examination of the fetal heart. Ultrasound Obstet Gynecol.2013;41:348-59.
11. Carvalho JS. Fetal heart scanning in the first trimester. Prenat Diagn. 2004;24:1060-7.
12. Selvesen K, Abramowicz C, Brezinka C, ter Haar G, Maršál K. Opinion. Safe use of Doppler ultrasound during the 11 to 13 + 6 week scan: is it possible? Ultrasound Obstet Gynecol. 2011;37:625-8.

Nataša Karadžov Orlić – Docent lekar specijalista ginekologije i akušerstva. Predavač po pozivu „YUGO“ škole, Jugoslovenskog udruženja za ultrazvuk u ginekologiji i akušerstvu. Završila kurs „Prevencija vertikalne transmisije HIV-a sa roditelja/majke na dete”. Pohađala prekongresni kurs „Color Doppler u obstetriciji“ kao i kurseve iz fetalne ehokardiografije „Fetalna ehokardiografija I i II treimestra“ i „Recent advances in perinatal cardiology“. Poseduje sertifikat Competence of „Ultrasound examination at 11-13+6 weeks“ od The fetal Medicine Fondation, London, uključujući i „first trimester examinatiom of the fetal nasal bone and fetal tricuspid flow“.

Studijski boravak na Universitetskoj Klinici Eppendorf-Hamburg, Centar sa perinatalnu medicinu, pod rukovodstvom Prof Dr K.Hehera, 2017 godine.

PREDICTION OF PRETERM DELIVERY AT SYMPTOMATIC AND ASYMPTOMATIC WOMAN

Prof. Marija Hadži Lega

Department of Fetal medicine, Clinic for Obstetrics and Gynecology, Ss. Cyril and Methodius University in Skopje, North Macedonia

Preterm delivery is the leading cause of neonatal mortality and morbidity in the world. Its worldwide incidence ranges from around 5%-15%, depending on the population. The worldwide rates of preterm birth have increased in the past couple of decades in spite of the efforts to alleviate the problems associated with preterm delivery and the medical advances made. Preterm deliveries and associated complications account for over 75% of the neonatal mortality rates and for around half of the neurological sequalle in newborn children.

Consequently, women presenting with threatened preterm labor are often treated with hospitalization and the administration of tocolytics to avoid preterm delivery. Randomized studies on the use of tocolytics in threatened preterm labor have demonstrated a significant prolongation of pregnancy by about 7 days but no significant reduction in the incidence of preterm delivery, perinatal morbidity or mortality

Preterm delivery exerts numerous negative effects on the neonate: a substantially higher risk of neurological complications, chronic lung disease, respiratory distress syndrome, necrotizing enterocolitis and increases the social burden of these children. This is especially true for extremely preterm neonates, i.e. neonates delivered before 28 gestational weeks.

According to Romero and coleagues, preterm labor (PRL) can be considered a syndrome that is initiated by a myriad of mechanisms, such as inflammation, uterine over-distension, utero-placental hemorrhage and ischemia and other immunologic and non-immunologic processes. The author also published that all these different initiation mechanisms converge into a single terminal inflammatory pathway that results in increased uterine contractility, cervical ripening and decidua activation.

Timely prediction and prevention at asymptomatic patient is important for reducing preterm delivery. Transvaginal ultrasonographic cervical length measurement is a commonly used and powerfull method for prediction of preterm delivery and its combination with vaginal progesteron, significantly contributes to the prevention of premature delivery.

In 2013, Romero published a meta-analysis of individual data from randomized clinical trials who shows that vaginal progesterone reduces the rate of preterm birth in singleton gestation <33 weeks by 44%, reduction of the NICU hospitalization rate by 25%, respiratory distress syndrome by 52%, mechanical ventilation by 34%, neonatal morbidity / mortality by 43%, and delivery of newborns <1500 grams by 45%.

According to the new meta-analysis of individual patient data of randomized controlled trials of Romero from 2017, administration of vaginal progesterone in asymptomatic women with a twin gestation and a sonographic CL≤25mm in the mid-trimester lead to significantly decrease in the risk of preterm delivery from 31 % in pregnancy <33 gestation weeks, respiratory distress syndrome for 33%, birth weight<1500 g for 47%, use of mechanical ventilation for 46 % and morbidity and mortality for 47%.

Treatment with progesterone is only one of the solutions to prevent preterm delivery, we can expect the intervention to be successful only if specific pathways leading to premature delivery are discontinue, and this should be considered in all further clinical trials.

Research aimed to reduce the incidence and consequences of PTD has been focused either on early detection and prediction through the identification of risk factors or on the treatment of symptomatic and clinically manifest patients by mitigating PTD via tocolytic agents. The latter approach, however, has a limited effectiveness and only prolongs PTD by 48 hours, which provides clinicians with adequate time to administer corticosteroids to accelerate fetal lung maturation and transfer the patient to a tertiary health care center equipped with a neonatal intensive care unit, which in turn improves the outcome of prematurely delivered neonates.

However, only a small portion, 8-38% of patients admitted because of clinical symptoms of PTL will go on to deliver prematurely. The ability to distinguish between these two groups of patients (high-risk and low-risk patients) is of paramount importance for the reduction of unnecessary hospitalization and treatment of low-risk patients. Recently, biomedical research has been rapidly developing newer tools such as genomics and proteomics, with promising results

In order to contribute to the efforts for prediction of preterm delivery, we conducted a prospective cohort study at the Clinic for Gynecology and Obstetrics, Skopje.

Patients were eligible to join this prospective cohort study if they attended the University Clinic for Gynecology and Obstetrics, Skopje and were admitted to Department of High Risk Pregnancy Unit with symptoms of preterm labor (symptoms of uterine activity, three regular uterine contractions in 10 minutes).

The aim of this study was to determine the relationship between sonographic cervical length, fetal fibronectin(fFN), phIGFBP-1 (Actim partus test), cytokines (IL-6,IL-2R and TNF-alpha) and spontaneous preterm birth(SPTB) up to 14 days from sampling.

In this stydy was include symptomatic and asymptomatic patient at 24.0 to 36.6 gestation weeks. The studied biochemical markers in our study were only moderately successful in the prediction of preterm delivery. The best predictor model in our study was the combination of the fFN test, Actim partus test, concentration of IL-6 in the cervical fluid, the cervical length <21.5 mm, concentration of CRP and IL-6 in the serum.

Our study is only the begining of this type of research in our population. Further research is required in terms of the evaluation of cost-benefit of using such test to prevent subsequent uncecessary interventions in the low-risk group, as well as achieve the benefits from such intervention in the high-risk groups of patietns.

References

1. Ville Y, Rozenberg P. Predictors of preterm birth. Best Pract Res Clin Obstet Gynaecol. 2018;52:23-32.
2. Suff N, Story L, Shennan A. The prediction of preterm delivery: What is new? Semin Fetal Neonatal Med. 2019; 24(1):27-32.
3. Bittar RE, da Fonseca EB, de Carvalho MH, Martinelli S, Zugaib M. Predicting preterm delivery in asymptomatic patients with prior preterm delivery by measurement of cervical length and phosphorylated insulin-like growth factor-binding protein-1. Ultrasound Obstet Gynecol. 2007;29(5):562-7.
4. Melchor JC, Khalil A, Wing D, Schleussner E, Surbek D. Prediction of preterm delivery in symptomatic women using PAMG-1, fetal fibronectin and phIGFBP-1 tests: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;52(4):442-51.
5. Oskovi Kaplan ZA, Ozgu-Erdinc AS. Prediction of Preterm Birth: Maternal Characteristics, Ultrasound Markers, and Biomarkers: An Updated Overview. J Pregnancy. 201;2018:8367571.

Prof.Dr. Marija Hadji Lega

MD,PhD,Specialist, Obstetrics & Gynecology – Fetal Medicine

EDUCATION

Prof.Dr. Marija Hadji Lega earned her Medical Degree from St. Cyril & Methodius University, Medical Faculty, FYRO Macedonia, 1997. She completed her Specialization in Obstetrics & Gynecology from the same university, 2005 and also Subspecialisation in Perinatal Medicine (Maternal-Fetal Medicine) in 2014 also from the same university. She earned her PhD degree in Clinical Medicine (Prediction of preterm deliveries) from Medical Faculty, University of Nish, Serbia. She had a lot of fellowships and education abroad mainly in field of Fetal Medicine:

Certificate for III level for First and second trimester screening, Medical Faculty, University of Triests, Italy, University Hospital „Burlo Garofolo Hospital“, Trieste, Italy (fellowship by European School for maternal health); Observership and education at Harris Birthright Research Center, King ‘s College Hospital, Fetal Medicine Foundation, London (especially first and second trimester screening, fetal cardiology); Education in the field of prenatal diagnostics and fetal interventions (especially in monochorionic twin pregnancies) Eppendorf Clinic, Hamburg, Germany; Education in AKH Vienna Medical University, Department of Fetal Medicine, Austria; Education and Certificate for Hospital Management, Fukuoka, JICA, Japan; Certificate for prenatal screening of heart defects from ISUOG, Royal Brompton Hospital, London.

She is invited lecturer at many World, European and local congresses(Fetus as a Patient, Congresses of WAPM-World Association of Perinatal Medicine, Congresses of European Society of Perinatal Medicine-ECPM, Congresses of South East European Society of Perinatal Medicine, Ian Donald School for Ultrasound in Gynecology and Obstetrics ,MEDUOG (Mediteranean Society for Ultrasound in Gynecology and Obstetrics) etc.

She is a member of the Executive Board of South – Eastern Europe Society of Perinatal Medicine, Member of board of MEDUOG (Mediteranean Society for Ultrasound in Gynecology and Obstetrics) and also member of Editorial board of Oficial Journal of South East European Society of Perinatal Medicine Gynaecology Obstetrics & Reproductive Medicine. She has published many papers in Journals on SCI list and PubMed.

PRIJEVREMENI POROD

Dr Bojana Popović

Klinika za ginekologiju i akušerstvo, Univerzitetski Klinički Centar Republike Srpske, Banja Luka, Republika Srpska

Prijevremeni (preterminski) porod je jedan od najaktuelnijih problema perinatalne medicine danas. Svaki porođaj , nezavisno o porođajnoj masi ploda, koji je prije navršene 37 nedjelje gestacije jeste prijevremeni. Nedonesenost je najvažniji pojedinačni uzrok neonatalnog morbiditeta, mortaliteta i kasnih posljedica na preživjelima.

Osnovni cilj rada je analiza prijevremenog poroda, gestacijska dob u kojoj je najučestaliji, način i završetak prijevremenog poroda, kao i najučestaliji etiološki faktori prijevremenog poroda na KGA BL UKCRS u 2019. godini.

Na KGA BL UKC RS u 2019. godini sprovedena je retrospektivna studija o prijevremenom porodu, koja je obuhvatila 230 trudnica, kod kojih je trudnoća završena prijevremenim porodom. Podaci su prikupljeni iz Porođajnog protokola za 2019. godinu.

U 2019. godini na KGA BL bilo je ukupno 3148 porođaja, od toga je 230 (7,3%) prijevremenih poroda. Analiza je vršena prema etiološkom uzroku prijevremenog poroda, načinu završetka kao i gestacijskoj dobi trudnoće. Od etioloških faktora za prijevremeni porod najčešći je PPROM i to kod 111 (46,63%) trudnica. Operativnim putem, carski rez, prijevremeni porod je završen kod 132 (57,39%) trudnice, a vaginalnim putem kod 98 (42,61%) trudnica. Prijevremeni porod je najučestaliji u gestacijskoj dobi od 34 do 36+6 ng 144 (62,60%) trudnice, potom od 28 do 33+6 ng kod 64 (27,82%), te ispod 27+6 ng (9,58%) trudnica.

Naša studija je utvrdila da i pored napretka dijagnostike i tretmana prijevremenog poroda u modernoj opstetriciji prijevremeni porod i dalje ostaje najveći problem savremene opstetricije i neonatologije.

Literatura

1. Frey HA, Klebanoff MA. The epidemiology, etiology, and costs of preterm birth. Semin Fetal Neonatal Med. 2016 Apr;21(2):68-73.
2. Harrison MS, Goldenberg RL. Global burden of prematurity. Semin Fetal Neonatal Med. 2016 Apr;21(2):74-9.
3. Fuchs F, Senat MV. Multiple gestations and preterm birth. Semin Fetal Neonatal Med. 2016 Apr;21(2):113-20.
4. Sen C. Preterm labor and preterm birth. J Perinat Med. 2017 Nov 27;45(8):911-3.

GYNECOLOGIC ONCOLOGY

NEOADJUVANT CHEMOTHERAPY IN CERVICAL CANCER FOLLOWED SURGERY. OPTION OR FAILURE?

Prof. Aljoša Mandić

President of Society for Gynecological Oncology of Serbia (UGOS)
Institute for oncology of Vojvodina
Medical Faculty, University of Novi Sad, Serbia

The role of neoadjuvant chemotherapy in the treatment of the advanced stage cervical cancer is still debatable and the focus of further research. The reason to think about this approach could be:

- reduction of the primary tumor size, allowing operability
- eradication of micro metastatic disease and
- potential increase in tumor vascularisation and reduction of the number of hypoxic cells.

Most of the studies conducted over these years to seek for the efficacy of NACT followed by surgery or radiotherapy and its possible benefit over standard treatment alone. Our focus will be NACT + surgery. The meta-analysis compared neoadjuvant chemotherapy followed by surgery demonstrates better survival of patients treated with NACT + surgery than with radiotherapy alone (HR 0,65, the absolute gain of 14% in 5-year survival). The role of neoadjuvant chemotherapy plus surgery versus surgery alone for early and locally advanced cervical cancer was assessed in Cochrane review and showed better PFS, less recurrence, less lymph node metastasis and parametrial invasion and better resection rate in NACT group, but without benefit on OS. Also, neoadjuvant chemotherapy followed by surgery significantly reduces the need for adjuvant radiotherapy compared to surgery alone in early stage bulky cervical cancer by decreasing tumor size, decreasing the ratio of lymphovascular invasion, deep stromal invasion, lymph node and distant metastasis. Also meta-analysis comparing NACT followed by surgery versus surgery alone confirmed that patients treated with NACT had higher local control. Exploratory analysis of pathological response showed a significant decrease in adverse pathological findings with NACT for lymph node status; for parametrial infiltration). The main regimen of neoadjuvant chemotherapy (NAC) used includes cisplatin, but several protocols are used in study and the most effect regiments were Cisplatil/Paclitaxel weekly or standard three-week interval. What we can conclude based on currently available data? Recently preliminary results are not promising; as EORTC 55994, confirmed the short term severe adverse events (≥G3) occurred more frequently in arm1 (NACT Group) than in arm2 (35% vs 21%, $p<0.001$). The 5 year OS was 72% in arm1 and 76% in arm2 (not statistically significant, difference =4.0% (95%CI: -4%–12%); HR 0.87, 95%CI: 0.65–0.15, $p=0.332$). The authors concluded that these preliminary results revealed no difference in 5-year OS between NACTS and CCRT, indicating that quality of life and long-term toxicity across prognostic factors are important to decide on optimal treatment. NCT00193739 study by Gupta et al. also concluded cisplatin-based concomitant chemo radiation resulted in superior DFS compared with neoadjuvant chemotherapy followed by radical surgery in locally advanced cervical cancer. Still preliminary data are encouraging, results of Phase III INTERLACE trial are still awaited that using weekly Paclitaxel/Carboplatin protocol for 6 weeks.

In recent guidelines published by ESGO/ ESTRO/ ESMO NACT followed by surgery (B-C1 based on treatment response) is another alternative treatment option for patients but, still contraversional alternative and not observed as standard treatment modality, yet.

References

1. Neoadjuvant Chemotherapy for Cervical Cancer Meta-Analysis Collaboration (NACCCMA) Collaboration. Neoadjuvant chemotherapy for locally advanced cervix cancer. Cochrane Database Syst Rev. 2004;(2):CD001774.
2. Rydzewska L, Tierney J, Vale CL, Symonds PR. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. Cochrane Database Syst Rev. 2012;12:CD007406.
3. Li R, Lu S, Si J, Liu B, Wang H, Mei Y, et al. Prognostic value of responsiveness of neoadjuvant chemotherapy before surgery for patients with stage IB(2)/IIA(2) cervical cancer. Gynecol Oncol. United States. 2013 Mar;128(3):524–9.
4. Kim HS, Sardi JE, Katsumata N, Ryu HS, Nam JH, Chung HH, et al. Efficacy of neoadjuvant chemotherapy in patients with FIGO stage IB1 to IIA cervical cancer: an international collaborative meta-analysis. England: Eur J Surg Oncol; 2013.
5. Greggi S, Kenter G, Vergote I, Katsaros D, Kobierski J, Massuger LFAG, et al. Results from neoadjuvant chemotherapy followed by surgery compared to chemoradiation for Stage IB2-IIB cervical cancer. IJGC. 2019;29(Suppl 4).
6. Gupta S, Maheshwari A, Parab P, Mahantshetty U, Hawaldar R, Sastri S, et al. Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial. Clin Oncol. 2018;36:1548-55.
7. Baillie K, Crearie C, Laskey J, Bennie M, Harrand R, Sadozye A, et al. What are the real-world outcomes of locally advanced cervical cancer patients who receive neo-adjuvant chemotherapy? IJGC. 2019;29,(Suppl 4).
8. Cibula D, Potter R, Planchamp F, Avall-Lundqvist E, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients With Cervical Cancer International Journal of Gynecological Cancer. 2018;28(4).
9. Marth C, Landoni F, Mahner S, McCormack M. A. Gonzalez-Martin5 & N. Colombo, on behalf of the ESMO Guidelines Committee Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Ann Oncol. 2017;28(Suppl 4):iv72–83.

Aljoša Mandić je zaposlen u Institutu za onkologiju Vojvodine, Sremska Kamenica. Uža naučna oblast: Ginekološka onkologija. Član sam od novembra 2006. Redakcionog Odbora Journal of Balkan Union of Oncology. Ujedno sam i recenzent u navedenim časopisima.

Autor zdravstveno-edukativnih publikacija: 1. »Seksualno prenosive bolesti, promene na grliću materice i Papanikolau test«. Institut za onkologiju Vojvodine Sremska Kamenica, Štamparija Zamurović, 2006 i 2007; 2. Monografije: »Vakcina kao novi vid prevencije HPV infekcije, prekanceroznih i kanceroznih lezija donjeg genitalnog trakta žena« Institut za onkologiju Vojvodine; Sremska Kamenica, Štamparija Zamurović, 2007.

Kao predavač učestvovao je u radu Simpozijuma u organizaciji UGOS-a i ESGO-a od 18-19.05.2006 u Beogradu sa nazivom:» Karcinom grlića materice-od dijagnostike do terapije». Stalni predavač Nacionalne škole za patologiju cerviksa, vagine, vulve i kolposkopiju od 2007. godine. 2008. kao predavač učestvovao na edukativnom seminaru: Karcinom cerviksa. Epidemiološke karakteristike i mogućnosti prevencije. U okviru Kontinuirane medicinske edukacije na Medicinskom Fakultetu u Novom Sadu. 2009. u organizaciji UGOS i GAS-SLD održan je u Novom Sadu jednodnevni simpozijum:“ Intraepitelijalne neoplazije i karcinom vulve “ na kojem je održao predavanje:“ Sentinealni limfni čvorovi kod karcinoma vulve“.

Takođe je kao kordinator edukacionog tima organizovao 4 Simpozijuma u sklopu Kontinuirane medicinske edukacije 2013.-2016 u Institutu za onkologiju Vojvodine Učestvovao u izradi Nacionalnog Vodiča za karcinom grlića materice 2012. I karcinoma jajnika 2013. U januaru 2013. i 2017. održao pozivno predavanje u Zagrebu na 2. i 4-tom Hrvatskom Simpozijumu sa međunarodnom učešćem o prevenciji i lečenju raka grlića materice. Urednik i autor monografije „Grlić materice“ u izdanju Medicinskog fakulteta Novi Sad, 2016. Predsednik Udruženja Ginekologa onkologa Srbije

REKONSTRUKCIJE GENITOPERINEALNE REGIJE NAKON ONKOLOŠKIH RESEKCIJA

Doc. Jelena Jeremić

Klinika za opekotine, plastičnu i rekonstruktivnu hirurgiju, Klinički Centar Srbije
Medicinski fakultet, Univerzitet u Beogradu, Srbija

Hirurgija predstavlja zlatan standard u lečenju malignih tumora vulve, koji su zastupljeni u 3-5% svih ginekoloških maligniteta. (Judson et al., 2006; Carramaschi et al., 1999) U oko 90% slučaja u pitanju su planocelularni karcinomi. (Del Pino et al., 2013; Lazzaro et al., 2010) Prema statističkim podacima iz literature karcinom vulve je dijagnostikovan u 39% slučaja u stadijumu III ili IV bolesti. (Di Donati et al., 2017) Kod većih tumora, lokalni recidivi su učestaliji od udaljenih metastaza i mogu se uspešno lečiti hirurgijom i zračnom terapijom. Nakon radikalnih ekcizija zapuštenih tumora zaostaju ekstenzivni mekotkivni defekti, čija rekonstrukcija doprinosi boljem kvalitetu života pacijentkinja. Lokalni recidivi su češći od pojave metastaza kod pacijentkinja sa većim tumorima. (Carramaschi et al, 1999) Brojne hirurgije recidiva, zračne terapije i široke ekcizije tumora dovode do nastanka ekstenzivnih mekotkivnih defekata, koji odlažu zarastanje rana i povećavaju postoperativni morbiditet, što sve negativno utiče na kvalitet života pacijentkinja. Rekonstrukcije postresekcionih defekata mekih tkiva vulvo perinealne regije doprinose smanjenju morbiditeta i poboljšanju kvaliteta života. (Chen et al., 1995). Karcinomi vulve se najčešće tretiraju en block vulvektomijom, zbog visokog procenta recidiva. Defekti mekih tkiva vulvo perinealne regije se mogu rekonstrujisati širokom paletom rekonstruktivnih opcije, od slobodnih kožnih transplantata, preko lokalnih i regionalnih faciokutanih i miokutanih režnjeva, kao i udaljenim režnjevima. (Carramaschi et al., 1999, Lin et al., 1992) Poslednjih godina, učestala je primena mišićnih i mišićno kožnih režnjeva kod pacijentktkinja sa ginekološkim malignitetima. (Confalonieri at al., 2017; Conri et al, 2016). Primena mišićnih i slobodnih režnjeva produžava vreme operacije, i povećava mogućnost nastanka komplikacija poput parcijalne ili totalne nekroze režnja. (Carramaschi et al., 1999; McCraw et al., 1976; Chen et al., 1995).

Moguće i česte postoperativne komplikacije kod direktne aproksimacije nategnutih ivica defekta su pre primene režnjeva bile dehiscencije i usporeno zarastanje rane. (Carramaschi et al., 1999). Postoperative dehiscencije, limfociste i limfedema su zastupljeni u 64- 85% slučaja. Primenom režnjeva, tj. rekonstrukcijom defekta tkivom koje se mobiliše iz obliznje regije, gde ga ima u višku, omogućilo je primarno zatvaranje defekta u istom hirurškom aktu kada i uklanjanje tumora, bez bojazni od dehiscencije. Pored kozmetskog izgleda, koji je primenom režnjeva poboljšan, očuvana je i funkcija mikcije i defekacije.

U ovom radu su prikazani klinički slučajevi pacijentkinja kod kojih su nakon radikalnih ekscizija ekstenzivnih planocelularnih karcinoma i dermatofibrosarkoma vulvo-perinealne regije uz bilateralnu ingvinalnu disekciju, defekti pokriveni V-Y lokalnim klizajućim režnjevima, lokalnim fasciokutanim režnjevima i vertikalnim miokutanim režnjem m. rectus abdominus-a.

VY klizajuci režanj je lokalni fasciokutani režanj kojim se mobilise fascija i koža oko defekta kako bi se rekonstruisao primarni defect nastao nakon radikalne ekcizije tumora. Pocetni rez na koži je u obliku slova V, a nakon rekonstrukcije dobija oblik slova Y uz direktno zatvaranje sekundarnog defekta. Ovaj režanj se može upotrebiti kada postoji dovoljno mobilne kože u obližnjoj glutealnoj regiji. (Carramaschi et al., 1999; Tateo et al., 1996; Benedetti Panici et al., 2014; Lee et al., 2006). Rekonstrukcija defekta se izvodi u primarnom aktu, kada i uklanjanje tumora. U predstojećem

postoperativnom periodu režanj će nedeljama biti edematozan i eritematozan, sto se vremenom gubi, kako se uspostavlja limfna drenaža i ožiljak sazreva. Prednosti VY klizajuceg režnja su jednostavnost izvodjenja, sigurni su u smislu vaskularizacije i preživljavanja i dobre su teksture kože. Rezanj se ishranjuje putem perforatora a. pudende interne i muskulokutanim perforatorima mišića koji leže ispod režnja. Senzitivna inervacija potiče od pudendalnog i zadnjeg kožnog nerva butine.

Prikazan je slucaj 56 godisnje pacijentkinje sa dijagnozom invazivnog planocelularnog karcinoma vulvarne regije stadijuma Ib, koja je primljna na Kliniku za ginekologiju i akušerstvo Kliničkog Centra Srbije. Nakon radikalne vulvekomije sa disekcijom ingvinalnih limfnih čvorova, bilateralni defekt mekih tkiva je rekonstrujisan VY klizajućim režnjem. Postoperativni tok je protekao uredno, režnjevi su vitalni, bez znakova dehiscencije i nekroze.

Vertikalni režanj m. rectus abdominisa je pored miokutanog režnja m. gracilisa, najprimenljiviji režanj u pokrivanju ekstenzivnih defekta genitoperinealne regije. To je aksijalni peteljkast režanj čija se vaskularizacija bazira na a. epigastrici inferior i komitantnim venama. Režanj je kompozitan, jer se sastoji od m. rectus femorisa i kože iznad njega. Rotacijom oko vaskularne peteljke za 180 stepeni može pokriti trodimenzionalne defekte vulvo perinealne regije. Davajuća regija na trbuhu se direktno ušiva, tako da je morbiditet davajuće regije minimalan.

Prikazan je slucaj 41-godišnje pacijentkinje koja je primljena na Kliniku za ginekologiju i akušerstvo Kliničkog Centra Srbije, zbog zapuštene bezbolne, karfiolaste i nekrotične tumorske mase, koja je zahvatala čitavu vulvo-perineo-glutealnu regiju. Na prijemu je pacijentkinja lošeg opšteg stanja anemična hemoglobin 25, MCV 61,4, leukociti 25,9, trombociti 505. Prema anamnastickim podacima tumor je narastao poslednjih 6 meseci. Patohistoloski nalaz je ukazao na planocelularni karcinim stadijum FIGO II, klinički IVa, zbog maligne infiltracije distalnog dela vagine i glutealne regije. Pacijentkinja je operisana, učinjena je radikalna vulvektomija i bilateralna ingvinofemoralna disekcija sa parcijalnom vaginektomijom. Mekotkivni defekt dimenzija 25 x 12 cm je rekonstrujisan sa distalno baziranim reznjem m. rectus abdominisa VRAM. Davajuća regija trbuha je direktno zatvorena. Postoperativni period je protkao uredno, bez komplikacija. Režanj je vitalan, bez znakova nekroze. Nakon tri nedelje u drugom aktu je rekonstrujisana rektoanalna veza, kreiran novi ulaz za vaginu. Pacijentkinja je dalje prosledjena na zračnu terapiju.

Dermatofibrosarkom protuberans vulve je redak, sporoprogredirajući fibrozni tumor kože, niskog do srednjeg stepena maligniteta. Karakteriše ga lokalna kožna i potkožna invazija, ali i destruktivan rast i infiltracija okolnog tkiva poput mišića, fascija i kostiju. Standardna terapija je kompletna hirurška ekcizija.

Prikazana je 55-godišnja pacijentkinja sa ekstenzivnim tumorom dimenzija 18x10x8 cm u prepubicnoj regiji, koji je progredirao unazad 19 godina. Biopsija je potvrdila dijagnozu dermatofibrosarcoma protuberans, a MSCT je ukazao da nema invazije kostiju. Pacijentkinja je operisana, ucinjena je radikalna ekcizija 3 cm u zdravo tkivo. Ekstenzivni mekotkivni defekt je pokriven sa dva fasciokutana režnja transponirana iz susedne regije. Postoperativni tok je protekao uredno, režnjevi su vitalni.

U prikazanim slučajevima pacijentkinja nije bilo većih komplikacije poput nekroza i parcijalnih nekroza režnjeva. Pacijentkinje su kontrolisane prvih mesec dana od strane plastičnog hirurga, a zatim naredne dve godine na svaka tri meseca od strane ginekologa onkologa. U okviru prve godine od operacije nije bilo znakova recidiva bolesti.

Kod pacijentkinja u odmaklim stadijumima FIGO III i IVa i koje zahtevaju radikalnu vulvektomiju sa bilateralnom ingvinalnom disekcijom, pokrivanje resekcionih defekta predstavlja hirurški izazov. Pokrivanje ekstenzivnih defekata vulvo-perinealne regije, nakon radikalnih ekscizija tumora, primenom lokalnih, regionalnih i miokutanih režnjeva, doprinosi smanjenju postoperativnih komplikacija i poboljšanju funkcionalnog i kozmetskog izgleda, čime se značajno poboljšava kvalitet života pacijenta.

Literatura

1. Carramaschi F., Ramos M.L.C., Nisida A.C.T., Ferreira M.C., Pinotti J.A. V-Y flap for perineal reconstruction following modified approach to vulvectomy in vulvar cancer. Int. J. Gynecol. Obstet. 1999;65(2):157-63.
2. Judson P.L., Habermann E.B., Baxter N.N., Durham S.B., Virnig B.A. Trends in the incidence of invasive and in situ vulvar carcinoma. Obstet. Gynecol. 2006;107(5):1018-22.
3. Del Pino M., Rodriguez-Carunchio L., Ordi J. Pathways of vulvar intraepithelial neoplasia and squamous cell carcinoma. Histopathology. 2013;62:161-75.
4. Lazzaro L., Guarneri G.F., Rampino Cordaro E., Bassini D., Revesz S., Borgna G. Vulvar reconstruction using a “v-Y” fascio-cutaneous gluteal flap: a valid reconstructive alternative in post-oncological loss of substance. Arch. Gynecol. Obstet. 2010;282(5):521-27.
5. Di Donato V., Bracchi C., Cigna E., Domenici L., Musella A., Giannini A. Vulvo-vaginal reconstruction after radical excision for treatment of vulvar cancer: Evaluation of feasibility and morbidity of different surgical techniques. Surg. Oncol. 2017;26:511-21.
6. Chen S.H.T., Hentz V.R., Wei F.C., Chen Y.R. Short gracilis myocutaneous flaps for vulvoperineal and inguinal reconstruction. Plast. Reconstr. Surg. 1995;95(2):372-7.
7. Lee JH, Shin JW, Kim SW, Oh DY, Park JS, Hur SY, Rhie JW, Ahn ST. Modified gluteal fold V-Y advancement flap for vulvovaginal reconstruction. Ann Plast Surg. 2013 Nov;71(5):571-4.
8. 8.C onfalonieri P.L., Gilardi R., Rovati L.C., Ceccherelli A., Lee J.H., Magni S. Comparison of V-Y Advancement Flap Versus Lotus Petal Flap for Plastic Reconstruction after Surgery in Case of Vulvar Malignancies: a Retrospective Single Center experience. Ann. Plast. Surg. 2017;79(2):186-91.
9. Conri V., Casoli V., Coret M., Houssin C., Trouette R., Brun J.L. Modified gluteal fold V-Y advancement flap for reconstruction after radical vulvectomy. Int. J. Gynecol. Cancer. 2016;26(7):1300-6.
10. McCraw J.B., Massey F.M., Shanklin K.D., Horton C.E. Vaginal reconstruction with gracilis myocutaneous flaps. Plast. Reconstr. Surg. 1976;58(2):176-83.
11. Tateo A., Tateo S., Bernasconi C., Zara C. Use of V-Y flap for vulvar reconstruction. Gynecol. Oncol. 1996;62(2):203-7.
12. Benedetti Panici P., Di Donato V., Bracchi C., Marchetti C., Tomao F., Palaia I. Modified gluteal fold advancement V-Y flap for vulvar reconstruction after surgery for vulvar malignancies. Gynecol. Oncol. 2014;132(1):125-9.

Jelena Jeremić je specijalista plastične i rekonstruktivne hirurgije zaposlena na Klinici za opekotine, plastičnu i rekonstruktivnu hirurgiju Kliničkog Centra Srbije. Rodjena je u Beogradu, gde je završila osnovnu i srednju školu sa Vukovom diplomom. Medicinski fakultet u Beogradu je upisala 1993 godine, a 1999 godine diplomirala sa prosečnom ocenom studiranja 9,91.

U Kliničkom Centru Srbije je 2000 godine je stupila u radni odnos, odlukom Ministarstva zdravlja, u grupi najboljih postdiplomaca sa prosečnom ocenom preko 9. Specijalizaciju iz plastične i rekonstruktivne hirurgije je upisala 2001 godine, a 2006 godine je položila specijalistički ispit sa odličnom ocenom i stekla zvanje specijaliste plastične i rekonstruktivne hirurgije.

Magistarsku tezu pod nazivom “Uspeh hirurškog lečenja fleksornih tetiva šake u zavisnosti od vremena započete rehabilitacije i dužine imobilizacije” uspešno je odbranila 2004 godine, a doktorsku disertaciju pod nazivom “ Procena uspeha rekonstrukcije defekata glave i vrata primenom slobodnih mikrovaskularnih režnjeva” 2009 godine, i stekla naziv doktora nauka.

2011 godine je izabrana za kliničkog asistenta na Katedri hirurgije sa anesteziologijom, a 2018 godine u zvanje docenta Medicinskog Fakulteta u Beogradu.

Dr Jelena Jeremić kao docent za užu naučnu oblast Hirurgija sa anesteziologijom (plastična i rekonstruktivna hirurgija), obavlja praktičnu nastavu u svim vidovima u skladu sa studijskim programom Medicinskog fakulteta Univerziteta u Beogradu. Redovno je učestvovala u izvođenju praktične nastave u punom fondu časova prema zadatom planu i programu u okviru sledećih predmeta: Hirurgija sa anesteziologijom, Prva pomoć, Osnovi kliničke prakse I i II.

Sposobnost prezentiranja stručnog znanja dr Jeremić izražena je kroz brojne naučno istraživačke radove i nastupe na stučnim skupovima, kroz studentske vežbe, kliničke časove i predavanja. Imala je značajna izlaganja rezultata stručnog rada na skupovima i simpozijumima reprezentujući Medicinski fakultet i Kliniku za opekotine, plastičnu i rekonstruktivnu hirurgiju KCS u Beogradu.

Stručni doprinos Dr Jelene Jeremić u oblasti specijalnosti plastične i rekonstruktivne hirurgije je značajan. Izvodi široki spektar hirurških operacija iz oblasti plastične i rekonstruktivne hirurgije. Kao načelnik odeljenja plastika 1, svakodnevno se bavi onkološkom hirurgijom karcinoma kože i mekih tkiva i rekonstruktivnom hirurgijom postresekcionih defekata tkiva.

U okviru svakodnevnog hirurškog rada zauzima značajno mesto u timu Klinike za opekotine, plastičnu i rekonstruktivnu hirurgiju, kroz izvođenje visokospecijalizovanih hirurških intervencija.

PROPHYLACTIC HPV VACCINE IN PREVENTION OF CERVICAL CANCER -ADDITIONAL EVIDENCE

Dr. Vladimir Petrović

Director of Institute for Public Health of Vojvodina, Serbia

There are around 140 different HPV types. Around 40 HPV types cause sexually transmitted infections. Most of the infections are asymptomatic and transitory. HPV types are divided on LOW-Risk (LR) and HIGH-Risk (HR) types. Nearly All HPV-Related Cancers and Diseases are Caused by 9 HPV types. Screening and HPV immunization are key measures of prevention.

This review paper has an aim to analyze and describe scientific evidence in favor of HPV immunization introduction as a measure of prevention of cervical cancer.

Descriptive epidemiological method was used. Results of latest clinical and prospective studies were analyzed from countries that introduced HPV immunization more than 10 years ago into their NIP (Australia, Denmark, USA, Finland and Sweden).

We included studies investigating HPV vaccination on incidence and prevalence of HPV infections, genital warts, precancerous lesions and those that investigated impact of vaccination on invasive cervical cancer in total population and vaccinated vs nonvaccinated. Results from studies in Denmark (1,2) show reduction of prevalence of genital warts in vaccinated cohorts, four years after vaccine introduction, as well as reduction of presence of precancerous lesions among vaccinated. Similar results regarding genital warts and HPV infections caused by HPV were registered in Australia (3). In USA, lower estimated number of cervical lesions was estimated in 2016 compared to 2008 among vaccinated females younger than 24 in comparison with older females, and those 40-64 years of age who suffered from cervical lesions in even higher numbers. Number of females with cervical lesions caused by HPV types included in the vaccine declined significantly. (4). First evidence of impact of HPV immunization on reduction of number of cases of invasive cervical cancer was reported from Finland in 2018 (5). A significant decrease in the incidence of cervical cancer among young females after the introduction of human papillomavirus vaccine in USA may indicate early effects of human papillomavirus vaccination (6). Among Swedish girls and women 10 to 30 years old, quadrivalent HPV vaccination was associated with a substantially reduced risk of invasive cervical cancer at the population level (7).

Results indicate clear evidence of HPV immunization reducing all consequences of the infection in countries that started immunization early. Free of charge HPV immunization should be introduced in Serbia and high coverage should be achieved.

References

1. Baandrup L, et al. Significant decrease in the incidence of genital warts in young Danish women after implementation of a national human papillomavirus vaccination program. Sex Transm Dis. 2013;40:130-5.
2. Baldur-Felskov, et al. Early impact of human papillomavirus vaccination on cervical neoplasia--nationwide follow-up of young Danish women. J Natl Cancer Inst. 2014.
3. Tabrizi SN, et al. Fall in human papillomavirus prevalence following a national vaccination program. J Infect Dis. 2012;206:1645–165.
4. McClung, et al. Estimated Number of Cases of High-Grade Cervical Lesions Diagnosed Among Women — United States, 2008 and 2016. MMWR.2019.
5. Luostarinen et al. Vaccination protects against invasive HPV-associated cancers. Int J Cancer. 2018;142: 2186-87.
6. Fangjian G, et al. Cervical Cancer Incidence in Young U.S. Females After Human Papillomavirus Vaccine Introduction. Am J Prev Med. 2018;55(2):197–204.
7. Jiayao L, et al. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med. 2020;383:1340-8.

Vladimir Petrović je epidemiolog. Rođen je 1973. godine u Karlovcu Hrvatska). Diplomirao je na Medicinskom fakultetu Univerziteta u Novom Sadu 1997. godine. Trenutno je direktor Instituta za javno zdravlje Vojvodine u Novom Sadu na kojem je zaposlen od 1999. godine. Redovni je profesor na Medicinskom fakultetu u Novom Sadu pri Katedri za epidemiologiju. Specijalizaciju iz epidemiologije je završio 2003. godine, 2004. godine odbranio magistarsku tezu, a 2008. godine i doktorsku tezu. Autor je i koautor u više od 90 naučnih i stručnih radova i publikacija. Jedan je od autora poglavlja „Aktivna imunizacija“ u udžbeniku Epidemiologija koji se primenjuje na nekoliko Medicinskih fakulteta u zemlji u prvom i u drugom izdanju. Bio je član brojnih radnih grupa/komisija Ministarstva zdravlja Republike Srbije, Pokrajinskog sekretarijata za zdravstvo AP Vojvodine. Aktivan je u domaćim i međunarodnim organizacijama i udruženjima, a učestvovao je u brojnim domaćim i međunarodnim naučnim i stručnim projektima. Zvanični je ekspert SZO za Međunarodni zdravstveni pravilnik 2013. godine u oblasti masovnih skupova i drugih događaja koji mogu biti praćeni težim društvenim posledicama.

Vladimir Petrović is an epidemiologist. He was born in 1973 in Karlovac, Republic of Croatia. He graduated at University of Novi Sad, Medical Faculty in 1997. Since 1999 he is employed in the Institute of Public Health of Vojvodina and currently he is a director of the institute. His academic career started in 2000 when he became an teaching assitant at the Chair of Epidemiology, and now he is the Full time Profeso and Head of the Chair. He finished his specialization in Epidemiology in 2003, defended his magsiters thesis in 2004 and Ph.D in 2008. He authored and co-authored more than 90 scientific original research and expert articles and publications. He is one of two authors of the chapter Active immunization in the national textbook of Epidemiology, which is apllied in majority of Medical faculties in Serbia. He was a member of various expert working groups and commitees of Ministry of Health of Serbia and Provincial Secretariate of Health of Autonomus Province of Vojvodina for immunization and communicable diseases. He is active in domestic and international expert associations and has participates in numerous domestic and international scientific projects. Since 2013 he is an official member of Roster of experts for International Health Regulations nominated bt the World Health Organization for the area of mass Gatherings and other High Visibility/High Consequence Events.

PREGNANCY FOLLOWING CHORIOCARCINOMA TREATMENT

Prof. Saša Kadija

Deputy General Manager and chief of department of general gynecology of the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia
School of Medicine, University of Belgrade, Serbia

Gestational trophoblastic disease (GTD) represents a group of tumors derived from placental trophoblastic tissue. At the end of the disease spectrum are malignant forms collectively known as gestational trophoblastic neoplasia (GTN). Choriocarcinoma can arise after any type of pregnancy. Human chorionic gonadotropin (hCG) is an excellent biomarker of disease progression, response to therapy, and post-treatment follow-up. Before the era of chemotherapy these tumors were highly lethal. Today, the treatment of choice for GTN is chemotherapy, based on FIGO stage and WHO risk score of the disease. The multi-drug chemotherapy regimen of choice for the treatment of high-risk GTN is EMA/CO protocol. With excellent cure rates and good prognosis, given the fact that majority of patients are reproductive age women, fertility preservation and the outcome of future pregnancies represents one of the major post-treatment issues.

We have successfully treated two patients for choriocarcinoma (CC) with multi-agent chemotherapy, who subsequently became pregnant, had an uneventful pregnancy course and deliver healthy infants. In described cases, CC was preceded by term pregnancies, both patients had prolonged postpartum vaginal bleeding and elevated hCG levels. In both patients, the diagnosis was confirmed histologically after the uterine curettage. The side effects of HT in young women include possible infertility, risk for early menopause, teratogenic and mutagenic effects on subsequent pregnancies. A number of studies has addressed this questions, but many of the publications are based on small sample sizes and frequently on different, sometimes outdated treatment protocols, which hampers adequate conclusion draw and makes patient counseling difficult. The major problem is lack of the distinction between the outcomes after single- and multi-drug protocols in the reported studies. Transient amenorrhea, is occasionally seen in patients with GTN and happened twice more often in group of patients treated with multi-agent protocol. The overall conception rate in patients treated for GTD varies between 69% and 69%. Latest reports claim that miscarriages rate among patients received chemotherapy for GTN are similar to that of the general population and that increased miscarriage rate was mainly associated with conception within the first year after the completion of treatment.

Regarding the reproductive outcomes following the treatment of GTN, the first important aspect is the timing of pregnancy. As the disease recurrence monitoring is based on the hCG surveillance, an increase of this hormone level associated with pregnancy may compromise adequate follow-up. About 90% of the disease recurrence occurs during the first year. It is a standard practice to advise patients to avoid pregnancy up to 1 year following treatment in order to monitor for a potential relapse as well as gonadotoxic effects to the ova, but also because of greater risk for a molar pregnancy or miscarriages.

An increased incidence of the de novo primary malignant tumors after chemotherapy treatment of the GTN is another important question.

Conclusion: Multi-agent chemotherapy can be safely administered to the patients with desire of future childbearing. The reproductive outcomes following the GTN treatment are generally favorable and similar to that of the general population. The pregnancy should be postponed for

at least 1 year after the treatment completion, in order to assure adequate disease monitoring and reduce the possible teratogenic effects of the therapy. Thus, proper patient counselling is of paramount importance along with the meticulous follow-up during the first year, so the GTN survivors can be reassured about the future reproductive potential and pregnancy outcomes.

References

1. Seckl MJ, Sebire NJ, Fisher RA, Golfier F, Massuger L, Sessa C; ESMO Guidelines Working Group. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:39-50.
2. Ngan HY, Kohorn EI, Cole LA, Kurman RJ, Kim SJ, Lurain JR, Seckl MJ, Sasaki S, Soper JT. Trophoblastic disease. Int J Gynaecol Obstet. 2012;119 Suppl 2:S130-6.
3. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. Lancet. 2010.
4. Santaballa A et al. SEOM clinical guidelines in gestational trophoblastic disease (2017). Clin Transl Oncol. 2018;20(1):38-46.
5. Cioffi R. Reproductive Outcomes After Gestational Trophoblastic Neoplasia. A Comparison Between Single-Agent and Multiagent Chemotherapy: Retrospective Analysis From the MITO-9 Group. Int J Gynecol Cancer. 2018;28(2):332-7.
6. Lok CA, van der Houwen C, Kate-Booij MJ, van Eijkeren MA, Ansink AC. Pregnancy after EMA/CO for gestational trophoblastic disease: a report from The Netherlands. BJOG. 2003;110(6):560-6.

Positions: Full professor of gynecology and obstetrics, Department of gynecology and obstetrics, School of Medicine, University of Belgrade (since 2018); Head of the General Gynecology Department, Clinics for gynecology and obstetrics, Clinical Center of Serbia;

Education: PhD in Human reproduction (1998), School of Medicine, University of Belgrade; Master's Degree (1994), School of Medicine, University of Belgrade; specialization in gynecology and obstetrics (1994), School of Medicine, University of Belgrade;

Field of expertize: gynecologic oncology; cancer surgery; gestational trophoblastic diseases; critical care Ob&Gyn patient; Long experience in running Ob&Gyn ICU and performing wide variety of radical oncologic operations on female reproductive system.

CONTEMPORARY SURGICAL APPROACH TO ADVANCED OVARIAN CANCER

Prof. Herman Haller

Director of the Clinic for Gynecology and Obstetrics, Medical Center of Rijeka, University of Rijeka, Croatia

Dr. Marko Klarić[1], Dr. Danilo Vejnović[1], Dr. Lana Glavan[1], Dr. Senija Eminović[2], Dr. Danijela Vrdoljak-Mozetič[2], Dr. Ana Mihaljević Ferari[3], Dr. Jasna Marušić[3]

1 Department of Obstetrics and Gynecology, Clinical Hospital Centre Rijeka, Croatia
2 Department of pathology and cytology, Clinical Hospital Centre Rijeka, Croatia
3 Department of radiotherapy & Oncology, Clinical Hospital Centre Rijeka, Croatia

Complete cytoreduction on upfront surgery in advanced ovarian cancer patient is considered standard of care. It is of clear benefit residual disease (R0) which carries significantly better prognosis measured by five years overall survival and diseases free survival. In order to achieve complete elimination of disease more extensive upper abdominal surgical resections is needed, as stripping and/or resection of diaphragm, splenectomy, partial liver resection, distal pancreatectomy and more intestinal resection. Named surgical procedures necessitated active involvement of abdominal surgeon. Chorus study (1-2) compared neoadjuvant chemotherapy (NACT) with upfront surgery in 87 hospital and found that in women with stage III or IV ovarian cancer, survival with primary chemotherapy is non-inferior to primary surgery. The study demonstrated that there was no significant diference in survival between patients having primary surgery or NACT, but that there was less morbidity and mortality in the group having neoadjuvant chemotherapy. In adition the study defined that survival was better if there was no residual disease at the end of the interval surgery. The comparable survival and reduced morbidity make the therapeutic option attractive in everyday practice.

Various methods for detection of disease involvement are defined, as CT or PET-CT with different success rate in predicting residual tumor. Introduction of minimal invasive method (3) and development of laparoscopic score system offer better insight in the intraperitoneal disease status prior to initiation of treatment.

The patients should be treated by multidisciplinary team in centralized i.e. tertiary referral centre with a large volume of patients. Interval debulking surgery (4) has less bowel resection and less extensive surgical radicality, less intra i postoperative complication, shorter surgical time, better preparation for surgery, same patient's outcome if reached optimal debulking.

In conclusion upfront debulking surgery and interval debulking surgery are cornerstone of advanced ovarian cancer treatment. There is no competition between primary and interval debulking surgery. Use of laparoscopy in the triage for primary cytoreductive surgery (to define extent of disease, histology) is recommended. When is not feasible to obtain complete cytoreduction (R=0) on first surgery because of extent of disease, or organizational problem, or absence of anesthesiologic support in intensive care unit, or unattainable abdominal surgeons, or .... – Interval debulking surgery (IDS) is an option and is performed after 3 or 4 course of chemotherapy with or without Bevacizumab. The goal in both surgical procedures, upfront surgery and interval debulking surgery is to achieve intraperitoneal complete cytoreduction.

References

1. Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet. 2015; 386 (9990):249-57.
2. Vergote I, et al. Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. Lancet Oncol. 2018;19(12):1680-7.
3. Fagotti A, Ferrandina G, Ludovisi M, et al. A laparoscopy-based score to predict surgical outcome in patients with advanced ovarian carcinoma: a pilot study. Ann Surg Oncol. 2006;13:1156–61.
4. Fagotti A, et al. Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850). Int J Gynaecol Cancer. 2020;30:1657-64.

Prof. Herman Haller, M.D., Ph.D. – Department of Obstetrics & Gynaecology, Clinical Hospital Center Rijeka, Croatia, Medical faculty University of Rijeka, Croatia.

Date of birth: 2. September 1958. Graduated at Medical faculty University of Rijeka in 1982, specialization in obstetrics and gynecology in 1995, subspecialization in gynecology oncology in 2005. Since 2000, Full professor at Medical faculty University of Rijeka, Croatia. Since 2013, full professor at Medical faculty University of Mostar, Bosnia & Herzegovina. Since 2001 head of Dept. of Obstetrics and Gynaecology, Clinical Hospital Center Rijeka, Croatia. From 2006 lead reference center of Croatian Ministry of Health for malignant diseases of endometrium, fallopian tube and ovary. Currently, I am actively involved in Croatian national task force for cervical cancer screening.

RADICAL VAGINAL TRACHELECTOMY AFTER TEN YEARS; ONCOLOGIC AND REPRODUCTIVE RESULTS

Prof. Borut Kobal

Head of the Division of Gynecology and Obstetrics, University Medical Centre Ljubljana, Slovenia

Dr. Leon Meglič, Dr. Matija Barbič, Dr. Branko Cvjetičanin

University Medical Centre Ljubljana, Division of Gynecology

Deputy General Manager and chief of department of general gynecology of the Clinic for Gynecology and Obstetrics, Clinical Center of Serbia
School of Medicine, University of Belgrade, Serbia

Trachelectomy with pelvic lymphadenectomy is considered a viable surgical procedure for fertility preservation in patients with early stage cervical carcinoma. The purpose of this study was to analyse postprocedural follow-up of oncological and fertility outcomes at a single centre.

We conducted a retrospective analysis of women with early stage cervical carcinoma, treated at the University Medical Centre Ljubljana, between 2007 and 2017. The study group was compiled of 26 women, age 22 to 40 years old (mean 32,8 years old).

Out of 26 women with early stage cervical cancer, 25 women were treated with vaginal radical trachelectomy (VRT) and laparoscopic pelvic lymphadenectomy (LPL) and one with only VRT. Mean age and BMI were 32,8 years and 21,54 kg/m2; respectively. One patient was IA1, two IA2, twenty-two IB1 and one IB2. Histology subtypes included squamous cell carcinoma (n=16), adenocarcinoma (n=8), endometrioid adenocarcinoma (n=1) and clear cell carcinoma (n=1). No perioperative complications were documented, postoperative complications included urinary retention and anaemia. All were treated with conservative measures. Within the follow-up period (12 – 60 months) 3 women (12%) developed disease recurrence, all were treated with local excision and adjuvant chemoradiotherapy. One patient died 15 months after primary treatment, following progression of the disease. Two remaining patients are in remission. Of the 24 women who had neither additional surgical procedures, nor adjuvant therapy, we documented 14 attempted pregnancies. All women with successful pregnancies had a separate procedure; laparoscopic cerclage. Out of 14 pregnancies five ended in miscarriage, one pregnancy resulted in second trimester delivery (24/25. week) and eight resulted in third trimester delivery (34.-38. week). All births were performed with a Caesarean section.

Cervical carcinoma effects women in reproductive age, limiting their chance for a successful pregnancy. Radical trachelectomy with SNL or pelvic lymphadenectomy should be an option for women that wish to preserve fertility.

Good preoperative staging is essential in the process. Our data suggest that surgical approach is associated with low perioperative morbidity. Our recorded pregnancy rate is similar to that described in the literature.

References

1. Costales A, Michener C, Escobar-Rodriguez PF. Radical Trachelectomy for Early Stage Cervical Cancer. Curr Treat Options Oncol. 2018;19(12):75.
2. Salvo G, Ramirez PT, Leitao M, Cibula D, Fotopoulou C, Kucukmetin A, et al. International radical trachelectomy assessment: IRTA study. Int J Gynecol Cancer. 2019;29(3):635-638

3. Van Kol KGG, Vergeldt TFM, Bekkers RLM. Abdominal radical trachelectomy versus chemotherapy followed by vaginal radical trachelectomy in stage 1B2 (FIGO 2018) cervical cancer. A systematic review on fertility and recurrence rates. Gynecol Oncol. 2019;155(3):515-21.
4. Neves F, Aldinhas P, Sousa R, Sá L. Letter to the Editor: Radical Vaginal Trachelectomy - 9-Year Experience of the IPO Coimbra. Acta Med Port. 2018;31(5):291-2.

Borut Kobal

Date and place of birth: 2. 8. 1958, Ljubljana, Slovenia

Education: april 1993 became specialist in ob/gyn, november 1992 become PhD for the ob/gyn, march 1989 become MA for the ob/gyn, november 1985 research fellow for human reproduction and start of specialisation in gynecology, march 1985 state examination of general medicine, december 1982 Medical faculty – general medicine – University of Ljubljana.

POSTGRADUATE EDUCATION: Basic and Advanced Course on Gynecological Endoscopic Surgery, Clermont-Ferrand (France), February, 1994; The third International Conference on the Macrolides, Azalides And Streptogramines, Lisbona, 24.-26. Januar, 1996; 2emes Journees Parisiennes d'Echographie Gyneco-Obstetricale, Paris, June,1996; Hysterectomy; laparoscopy contra laparotomy, Clermont-Ferrand (France), November 1996; Prise en charge des Kystes de l'ovaire, Clermont-Ferrand (France), September 1996; European School of Oncology, Postgraduate course on Gynecological Oncology 1996, Amsterdam, December 1996; European Diploma of Hysteroscopy, Clamart (France), December 1996; Advanced Echography of the breast, Zagreb (Croatia) November 1998; European post-graduate course on gynaecological imagery during consultation, Paris, December 1998; 8th International Ultracision Symposium, Hamburg-Norderstedt, Germany, 21-22 september 2000; L' atto chirurgico in oncologia ginecologica: filosofia ed evoluzione tecnica, alternative e controllo di qualita. Santa Margherita Ligure, November 2000; Corso interattivo di ginecologia oncologica; Tumori maligni dell' utero: dall'Evidence based Medicine ai percorsi clinici. Santa Margherita Ligure, November 2002; Update symposium on minimal invasive surgery in Gynaecologic oncology. ISGE, Toulouse October 2003

POSITION: Head of Dpt of Gynecology at University Medical Centre Ljubljana from 2008 to 2020. Medical Director University Medical Centre, Division of Gynaecology and Obstetrics from 2020.

ACADEMIC CAREER: Head of Chair for Obsterics and Gynecology; Medical faculty of Ljubljana from 2006 - 2010; In 2016 promoted to associate professor for Ob/Gyn at Ljubljana7s Medical faculty; In 2000 and again in 2005 and 2010 promoted to assistant professor for Ob/gyn at Ljubljana's Medical Faculty; Mentor for trainees in Ob/gyn from 2005; In 1990, and again1995 promoted to assistant for Ob/gyn at Ljubljana's Medicine Faculty; Lectures for medical students from 2000 on.

MEMBERSHIPS: Slovenian society for Gynecologic oncology, ESGO, ESGE.

Publications in scientific monographs: 7. Scientific publications in Domestic and International journals: n =46 (PUBMED=26). Abstract and communications: n > 300.

ADVANCES IN THE SURGICAL TREATMENT OF OVARIAN CANCER

Monika Sobočan, Darja Arko, Iztok Takač

Divison of Gynecology and Perinatology, University Medical Centre Maribor, Ljubljanska ul 5, 2000 Maribor, Slovenia
Department of Obstetrics and Gynecology, Faculty of Medicine, University of Maribor, Taborska ul 5, 2000 Maribor, Slovenia

Ovarian cancer represents an important subtype of gynecological cancers, that is usually diagnosed in an advanced stage due to the lack of evident disease symptoms and primary screening programs. The disease has an incidence of 12 per 100 000 women and 90 % of the cases are epithelial ovarian cancers. Primary diagnostic assessment includes the evaluation of the suspected mass using transabdominal and transvaginal ultrasound as well as more focused imaging with CT scans and MRI. Based on the persumed disease stage a treatment plan may consist of surgical excision or neoadjuvant systemic therapy with possible further surgical treatment. The gold standard in primary surgical treatment of ovarian cancer is an open surgical procedure that allows the exploration of the abdomino-pelvic peritoneal cavity, the performance of a staging surgery including also a bilateral pelvic and para-aortic lymph node dissection. After primary treatment including usually also including systemic therapy, there has been much contraversy on how to approach ovarian cancer recurrence treatment. New data based on the Descriptive Evaluation of Preoperative Selection Criteria for Operability in Recurrent Ovarian Cancer (DESKTOP) trials and other support resesearch on this topic have shown, that in certain patient subgroups an improved outcome following secondary surgery can be achieved. Metanalysis of ongoing trials show, that secondary cytoreductive surgery allows for improved progression free survival (PFS), but did not show an impact on overall survival (OS).

RADIOGUIDED DETECTION OF SENTINEL LYMPH NODE IN VULVAR CANCER: ACHIEVEMENTS AND LIMITATIONS

Assist. Prof. Joško Zekan

Clinic for Gynecology and Obstetrics, Clinical center of Zagreb, Croatia
Faculty of Medicine, University of Zagreb, Croatia

Vulvar cancer accounts for 6% of all female genital malignant neoplasms. Although vulvar cancer was previously almost exclusively seen in women between 65 and 75 years of age, recent studies have shown that 20% of these cancers now occur in women younger than 50 years. Standard treatment for an early stage vulvar cancer is a partial or total vulvectomy with inguinofemoral lymph node dissection (ILND). However, a significant treatment-related morbidity has been observed concomitantly. Early and late complications after ILND were reported in more than 50% of patients. Main complications are wound breakdown and/or infection of the groin, lymphocyst formation and chronic leg lymphedema. An increasing incidence of a tumor precursor (vulvar intraepithelial neoplasia) and invasive vulvar cancer has been noted over the last few decades, what is explained by the extending life span of the female population and the increasing prevalence of oncogenic types of human papillomavirus infections.

Surgical management of vulvar cancer involves local teratment (partial or total vulvectomy), bilateral or ipsilateral ILND, sentinel lymoph node (SLN) biopsy and reconstructive surgery. The dissemination pattern of squamous cell carcinoma of the vulva is predominantly lymphogenic, while spread by a direct extension may occur, although less frequent. Hematogenous spread is extremely rare, especially in the absence of lymph node metastases. Inguinofemoral lymphadenectomy is the standard of care because unrecognised disease in the inguinofemoral lymph nodes is usually fatal. In early clinical stages of vulvar cancer the probability of inguinofemoral lymph node involvement is only 15–25%. This data suggests that more than 70% of patients are overtreated when undergoing elective ILND associatedw ith a high morbidity rate and a remarkably decreased quality of life. A validation study of SLN biopsy should establish standard guidelines for deciding on the extent of lymphadenectomy in vulvar cancer but still allow staging of a tumor. Protocol of radioguided detection of SLN includes the peritumoral intradermal injection of 15–20 MBq Technetium-99m-nanocolloid at least 3 h before surgery and transport of patient from the nuclear medicine unit into the operating suite. The local colloid application is almost always painful procedure for patients. These shortcomings and limitations hasten the introduction of new tracers and procedures. Foremost, the hand-held gamma detecting probe was used before making the skin incision in order to identify the area of the greatest activity to confirm the location of SLN. A small incision was made over the hot spot and surgical extirpation of SLN was performed. The SLN was excised together with a rim of the surrounding tissue and sent as a separate specimen for histological examination. The removed SLN were measured ex vivo in order to ensure that the correct nodes were removed. If no metastases were found in hematoxylin-eosin slides, immunohistochemical staining was performed for the definitive pathohistological diagnosis. Sentinel lymph node biopsy using technetium-99m and ultrastaging with immunohistochemistry is highly accurate when restricted to carefully selected patients, within a rigorous protocol, with close follow-up and where sufficient numbers for learning curve optimisation exist. Its efficacy as a tool in reducing the need for radical surgery and associated patient morbidity without reducing survival.

References

1. Merisio C, Berretta R, Gualdi M, Pultrone DC, Anfuso S, et al. Radioguided sentinel lymph node detection in vulvar cancer. Int J Gynecol Cancer. 2005;15(3):493-7.
2. Zekan J, Mutvar A, Huic D, Petrovic D, Karelovic D, Mitrovic L. Reliability of sentinel node assay in vulvar cancer: the first Croatian validation trial. Gynecol Oncol. 2012;126(1):99-102.
3. Radziszewski J, Kowalewska M, Jedrzejczak T, Kozlowicz-Gudzinska I, Nasierowska-Guttmejer A, Bidzinski M,et al. The accuracy of the sentinel lymph node concept in early stage squamous cell vulvar carcinoma. Gynecol Oncol. 2010;116(3):473-7.
4. Moore RG, Robison K, Brown AK, DiSilvestro P, Steinhoff M, Noto R, Brard L, et al. Isolated sentinel lymph node dissection with conservative management in patients with squamous cell carcinoma of the vulva: a prospective trial. Gynecol Oncol. 2008;109(1):65-70.
5. Tamussino K, Bader AA, Regauer S. Do we need immunohistochemistry to evaluate sentinel lymph nodes in vulvar cancer? Gynecol Oncol. 2008;111(1):158-9.
6. e Hullu JA, Oonk MH, Ansink AC, Hollema H, Jager PL, van der Zee AG. Pitfalls in the sentinel lymph node procedure in vulvar cancer. Gynecol Oncol. 2004;94(1):10-5.

1984 – Graduated on Medical Faculty of Zagreb; 1984 – Assistant investigator at Department of Pharmacology, Medical Faculty of Zagreb, professional personnel engaged on joined project of Department of Health, Education and Welfare, Public Health Service (USA) and Medical Faculty of Zagreb: Peripheral Dopaminergic Neuronal System; 1985 – 1986 Surgical Resident, Military Medical Academy, Belgrade, Yugoslavia; 1998 – Postgraduate study in the field of Biomedicine; 1990 – Obstetrician / Gynecologist; 1993 – 1994 working at Department of Gynecological Surgery; 1995 – Mastered at University of Zagreb; 1996 – Started working at Department of Gynecologic Oncology, Zagreb University Hospital Centre; 1997 – Founder and the director of Family Planning and Reproductive Health Course, Inter-University Center, Dubrovnik; 1999 – Active member of New York Academy of Sciences; 1999 – Guest Editor Jour. Gen. Social Issues; 2001 – Coordinator of National Program for Youth; 2012 – Chairman of the Committee for the prevention of cervical cancer Croatian Ministry of Health; 2012 – Gynecologic Oncologist; 2012 – Governing Council Member, University Hospital Dubrava, Zagreb, Croatia; 2012 – Assistant Professor, University of Split Faculty of Medicine; 2013 – Associate Editorial Board Member of the American Journal of Clinical Cancer Research (AJCCR) and the American Journal of Current Medicine (AJCM); 2016 – EU Twinning project HR 14 IB SO 01, Improvement of quality of the National Cancer Screening Programs Implementation (CRO Screening), BC coordinator.

V-Y KLIZAJUĆI FASCIOKUTANI REŽANJ U HIRURŠKOM LEČENJU KARCINOMA VULVE

Prof. Srđan Đurđević

Bivši predsednik udruženja za ginekološku onkologiju Srbije (UGOS)
Načelnik Odeljenja operativne ginekologije u bolnici Genesis, Novi Sad, Srbija

Učestalost karcinoma vulve iznosi oko 3% u odnosu na sve maligne tumore ženskog genitalnog sistema, u Srbiji oko 1,6:100.000. Primarno lečenje karcinoma vulve je uvek hirurško, a potom se u zavisnosti od histopatološkog nalaza primenju dopusnka zračna i hemioterapija. Posle hirurškog uklanjanja velikih i proširenih tumora na vulvi, defekt se pokriva kožno-mišićnim režnjevima koji se dele prema vaskularizaciji i vrsti tkiva (slojevima) koji ulaze u sastav režnja i to na: kožni, fasciokutani, mišićni, složeni i perforantni režanj. Osnovni principi ove hirurgije podrazumevaju: detaljan preoperativni plan u pripremi, pažljivu manipulaciju sa tkivom, zaostalo tkivo mora biti zdravo, zatvaranje tzv. „mrtvih prostora“, korektnu hemostazu, primenu vakuum drenova, šav ivica režnja bez zatezanja i previjanje rane svakih 6-12 sati. V-Y kožni režanj je lokalni fasciokutani režanj koji uključuje kožu i potkožno tkivo i koristi se u pokrivanju primarnih hirurških defekata na koži vulve i perineuma. Slovo “ V “ označava rez ili inciziju u obliku slova V koja se kreira na koži i u dubinu kroz potkožno tkivo do fascije, dok slovo “ Y “ pokazuje kako se koža zatvara pri čemu duža osnova slova Y ostaje na mestu odakle potiče režanj. Odnos dužine horizontalne prema vertikolnoj osovini režnja je 2:1. Ova hirurška tehnika koristi se kada je koža donora dovoljno elastična da prihvati kreirani režanj na mesto defekta. Zarastanje traje 3-6 meseci a režanj može biti eritematozan i edematozan nekoliko nedelja posle operacije. Komplikacije uključuju : razilaženje, dehiscenciju i nekrozu režnja.

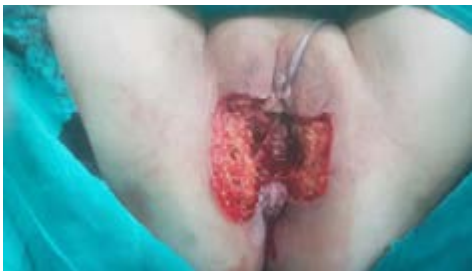
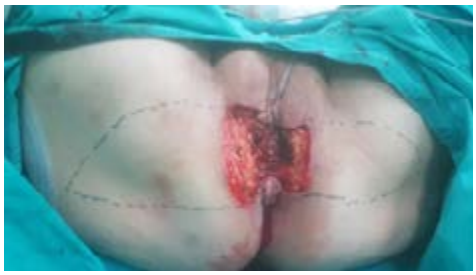
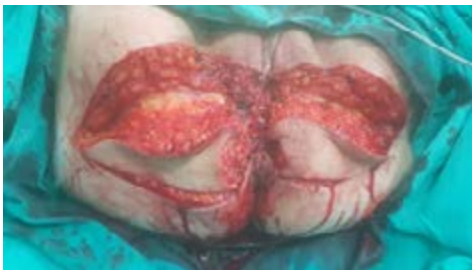
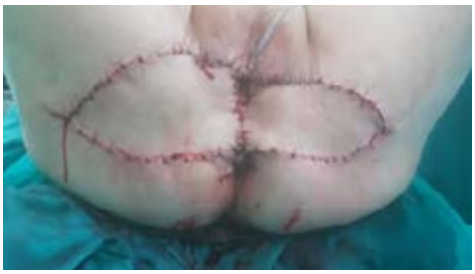
U periodu od 15 godina (2005-2020), kod ukupno 12 pacijentkinja posle radikalne ekscizije tumora na vulvi i perineumu na Klinici za ginekologiju i akušerstvo KC Vojvodine u N.Sadu (9), specijalnoj ginekološkoj bolnici “Genesis“ u N.Sadu (2) i opštoj bolnici u Somboru (1), plasiran je V-Y režanj. Sve pacijentkinje bile su uzrasta od 44-81 godine (prosek 65,5 g.) , dijametar tumora iznosio je od 15-90 mm, široka ekscizija sprovedena je kod 3 (25%) a radikalna vulvektomija kod 9 (75%) pacijenata. Kod 5 (41,6%) pacijentkinja sprovedena je jednostrana ili obostrana ingvinofemoralna limfadenektomija. Prosečno trajanje operacije iznosilo je 128 min. (100-240 min.), prosečan gubitrak krvi bio je 250 ml a od komplikacija zabeležena je parcijalna dehiscencija obostranog režnja kod 2 (16,6%) pacijentkinje. U tabeli broj 1. Prikazani su vrsta oboljenja na vulvi, primena VY režnja sa jedne ili obe strane, pojava recidiva i komplikacija.

Tabela 1. Karakteristike pacijenata

Broj	Oboljenje	V-Y režanj	Limfaden.	Recidiv	Komplikacije
1	Planocel. Ca	Obostrani	DA	DA Exitus	Parcijalna dehiscencija
2	Planocel. Ca	Jednostrani	NE	NE	NE
3	Planocel. Ca	Jednostrani	DA	NE	NE
4	Planocel. Ca Recidiv	Obostrani	DA	DA Exitus	Parcijalna dehiscencija
5	VIN 3 Recidiv	Jednostrani	NE	DA	NE
6	Planocel. Ca	Obostrani	DA	NE	NE
7	m. Paget	Jednostrani	NE	NE	NE
8	Planocel. Ca	Jednostrani	DA	NE	NE

9	VIN 3 Recidiv	Jednostrani	NE	NE	NE
10	m. Paget	Obostrani	NE	NE	NE
11	Verukozni Ca. Recidiv	Jednostrani	NE	NE	NE
12	m. Paget	Obostrani	NE	NE	NE

Legenda: Planocel. – pločastoslojeviti, Ca – karcinom, VIN – vulvarna intraepitelijalna neoplazija, m.Paget – Pdžetova bolest

Literatura

1. Đurđević S, Devaja O, Hadžić B. Malignant potential of gigantic condylomatous lesions of the vulva. Eur J Gynaec Oncol.1999;20(1):63-6.
2. Đurđević S, Hadžić B, Petrović Đ. Radikalna vulvektomija sa ingvinofemoralnom limfadenektomijom u lečenju karcinoma vulve. Med Pregl.2000;53(11-12):607-12.
3. Djurdjevic S, Janjic Z, Hadzic B, Milosevic V. Invasive condylomatous vulvar carcinoma associated with multifocal low genital tract neoplasia. A case report. Eur J Gynaec Oncol.2000;(6):596-98.
4. Đurđević S, Segedi D. Blok disekcija ingvinofemoralnih limfnih žlezda primenom odvojenih ¨S¨ rezova u hirurškom lečenju karcinoma vulve. Med Pregl .2004;57(7-8) :343-48.
5. Djurdjevic S, Curcic A, Bogavac M, Ivanovic Lj. V-Y fasciocutaneous sliding flap in the surgical treatment of invasive vulvar cancer. Helth MED.Vol. 5, No 6, suppl. 1,2011:2010-14.
6. Benedetti Panici P, Di Donato V, Bracchi C et al. Modified gluteal fold advancement V-Y flap for vulvar reconstruction after surgery for vulvar malignancies. Gynecol Oncol. 2014;(132):125-29.
7. Paik-Kwon Lee, Moon Seup Choi, Sang-Tae Ahn et all. Gluteal Fold V-Y Advancement Flap for Vulvar and Vaginal Reconstruction: A New Flap. Plastic and reconstructive Surgery, 2006;118(2):401-6.
8. Fin A, Rampino Cordo E, Guarneri GF et al. Experience with gluteal V-Y fasciocutaneous advancement flaps in vulvar reconstruction after oncological resection and a modification to the marking: Playing with tension lines. Int Wound Jour 2018 ;12997
9. Pantelić M, Đurđević S, Nikolić D, Maksimović M. Hirurško lečenje invazivnog karcinoma vulve. Med Pregl.2012; 65(3-4):97-101.
10. Đurđević S. Osnovni principi hirurškog lečenja karcinoma vulve. Zbornik Radova 1 Kongresa ginekologa I opstetričara republike Srpske sa međunarodnim učešćem. Banja Luka 2016.

Prof. Srđan Đurđević je publikovao 146 stručnih radova , 82 kao prvi autor. Bio je mentor u 5 odbranjenih doktorskih disertacija na Medicinskom fakultetu u Novom Sadu, 6 studentskih radova, koautor u 2 video filma, učesnik u 3 jednogodišnje naučnoistraživačke teme Klinike i saradnik u dva projekta. Rukovodio je sa 2 istraživačke studije na Klinici za ginekologiju i akušerstvo KC Vojvodine 2007/2008. i 2014-2016. Publikovao je monografiju: „Tumorski markeri u ginekološkoj onkologiji" u ediciji DMBJ 1988. Glavni je urednik udžbenika „GINEKOLOŠKA ONKOLOGIJA" 2009. Godine i Monografije – Atlasa : „LAPAROSKOPSKA HIRURGIJA U GINEKOLOGIJI" 2016 godine i udžbenika „GINEKOLOGIJA" za studente medicine na Medicinskom fakultetu u Novom Sadu 2012, 2015 i 2019. Član je ginekološko-akušerske sekcije Srpskog lekarskog društva (SLD), Udruženja za ginekološku onkologiju Srbije (UGOS) i Evropskog udruženja ginekologa-onkologa (ESGO). Od 1.09.2020. stalno je zaposlen kao konsultant u specijalnoj ginekološkoj bolnici "Genesis" (60 %), opštoj bolnici u Somboru (20 %) i privatnom farmaceutskom fakultetu u N.Sadu (20 %).

DA LI SE ONKOGENI POTENCIJAL I GENOTIPSKA PREVALENCA HPV MENJAJU SVAKE GODINE?

Prof. Radomir Živadinović

Klinika za ginekologiju i akušerstvo, Klinički centar Niš,
Medicinski fakultet, Univerzitet u Nišu, Srbija

Distribucija onkogenosti HPV tipova se menja zbog mutacije virusa, prokuženosti populacije odredjenim tipom virisa ili promenama našeg imunološkog odgovora na isti virus . Za anogenitalnu regiju je dtektovano preko 118 tipa HPV. Klinička iskustva su pokazala da oni imaju različiti onkogeni potencija. Tako su podeljeni na: visokorizične 16,18,31,33,39,45,51,52,56,58,59,68,73,82 verovatno visokorizične 26,53,66 i niskorizične 6,11,40,42,43,44,54,61,70 (1).

Iz grupe visoko rizičnih se po stepenu onkogenosti izdvajaju tip 16 i 18 jer je rizik za progresiju i karcinom za ova dva tipa duplo veći u odnosu na sve ostale tipove iove grupe (2).

Prisustvo HPV 16 tipa kod žena starijih od 30 godina života treba shvatiti rizičnim kao da se radi o citološkom ASCUS razmazu. Medjutim HPV 16 tip ima svoje podtipove koji se artzlikuju u odnosu na sekvencu DNA koja menja stepen onkogenosti HPV 16 i deli ga na subtip Evropski , Azijski ,Afrički (3).

Onkogeni potencijal HPV zavisi i od geografske regije , rase , religije. Prva ispitivanja o onkogenom potencijalu i geografskom tropizmu na Jugoistoku Srbije su sprovedena 2017 godine. Tada se tip 56 i 58 izdvojio kao specifični tropizam za ovu regiju . Dalja ispitivanja u narednim godinam do 2020 su pokazala das u se javile promene u distibuciji onkjogenosti u odnosu na godinu ispitivanja.

Svake godine se javlja po neki novi tip koji udje u top 10 a nakon toga ga nema u sledecim godinama. U našoj regiji su to tipovi: 56 , 54 , 59 , 39 . Ako bi se ovi tipovi isključili onda se ipak primećuje pravilnost u distibuciji onkogenog potencijala. Redosled top17 HPV tipova po onkogenosti bi izgledao ovako: 16, 31, 58, 33. 18, 45 i 51.

Poznavanje distibucije onkogenog potencijala je važno zbog : procene onkogenog rizika i potrebe za personalizovanim agresivnijim dijagnostičko terapijskim pristupom trijaže HPV pozitivnih testova i ctološki negativnih HPV + testova procena i izbor najefikasnije HPV vakcine u jednom geografskom području

Literatura

1 . Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Muñoz N. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999; 189: 12-19.

2 . Thomas C . Evaluation of HPV 16 and 18 genotyping for the triage of womwn with high risk HPV pos. Cytology neg .2011 ; 136(4) : 578-86 .

3 . Bosch FX, Burchell AN, Schiffman M, Giuliano AR, de Sanjose S, Bruni L, Tortolero-Luna G Kruger Kjaer S, Mu˜noz N. Epidemiology and Natural History of Human Papillomavirus Infections and Type-Specific Implications in Cervical Neoplasia Vaccine 26S (2008) K.

Radomir Živadinović je vanredni profesor. Zaposlen: Ginekološko akušerska klinika Niš, Medicinski fakultet Niš. Edukacija iz citologije TAK Narodni front Beograd; Edukacija is kolposkopije.GAK Narodni front Geograd; Subspedžijalisacija Ginekološke onkologije . Beograd; Škola ultrasvuka . Beograd.

HUMAN PAPILLOMAVIRUS GENOTYPE-SPECIFIC RISK OF CERVICAL INTRAEPITHELIAL NEOPLASIA AND CANCER

Prof. Goran Dimitrov

President of the MSCPC (Macedonian Society for Colposcopy and Cervical Pathology – member of IFCPC, EFC)
President of Macedonian Medical Association, North Macedonia
University Clinic for Gynecology and Obstetrics, Skopje, North Macedonia

Cervical cancer is the second most common cancer in women living in less developed regions with an estimated 570 000 new cases in 2018 (84% of the new cases worldwide). The main cause of cervical cancer is sexually acquired infection with certain types of HPV. There are more than 100 types of HPV, of which at least 14 are cancer-causing - high risk types. Persistent infection with HR-HPV is considered essential for the development of cervical cancer. The overall prevalence of high-risk human papillomavirus (HR-HPV) increases from 12% in normal cytology, to 89% in cervical cancer.

Globally, HPV 16/18 are the 2 most common genotypes in approximately 70% of invasive cervical cancer cases. The remaining 30% are caused by other HR-HPV types. HPV infections are common among young women and most spontaneously clear within 1–2 years. HPV type-specific prevalence is different between low-grade squamous intraepithelial lesion (LSIL) and malignancy.

HPV 16, 18, and 45 are more frequent in invasive cervical cancer. HPV 51, 52, and 31 are more frequently detected in precancerous lesions. HPV genotypes 16, 52, and 58 were the most common in all age groups according to cervical disease grade.

These HR-HPV types belong to alpha-9 species (HPV 16/31/33/35/52/58/67) and are likely to have biological properties similar to those of HPV 16. HPV types in the alpha-9 species are more persistent and more likely to progress to CIN 3 or worse, compared with HPV types in the alpha-5 (HPV 51), 6 (HPV 53/56/66) and 7 (HPV 18/39/45/59/68) groups.

Time from HPV infection to CIN 3 is shorter than the decades-long time from first development of a CIN 3 lesion to cancer. It takes 15 to 20 years for cervical cancer to develop in women with normal immune systems. It can take only 5 to 10 years in women with weakened immune systems, such as those with untreated HIV infection.

Several previous studies reported a multiple infection rate of 20%–40%. Multiple infections present more frequent in younger women with high-grade CIN and the infection rate decline with increasing age.

A 12-year follow-up study in Denmark showed that the absolute risk of CIN 3 or worse among those infected with HPV 31 was 14.3%, with 14.9% for HPV 33.

In 2020, we evaluated retrospectively all of the patients referred for HPV testing and histological verification to the University Clinic for Gynecology and Obstetrics – Skopje in 2019, 60.5% had HPV 16, 59.3% of them had HSIL and 24.7% had LSIL.

hrHPV testing had a better value in predicting CIN2+ lesions in the ASC-US group than in the LSIL group.

HPV 16, 31, 33, 52, and 58 infections are associated with significant risk of high-grade disease and might play important roles in the development of cervical cancer.

References

1. So KA, Lee IH, Lee KH, Hong SR, Kim YJ, Seo HH, et al. Human papillomavirus genotype-specific risk in cervical carcinogenesis. J Gynecol Oncol. 2019;30(4):e52.
2. Lissenberg-Witte BI, Bogaards JA, Quint WGV, Berkhof J. Estimating the Human Papillomavirus Genotype Attribution in Screen-detected High-grade Cervical Lesions. Epidemiology. 2019;30(4):590-596.
3. Lehtinen M, Lagheden C, Luostarinen T, Eriksson T, Apter D, Harjula K, et al. Ten-year follow-up of human papillomavirus vaccine efficacy against the most stringent cervical neoplasia end-point-registry-based follow-up of three cohorts from randomized trials. BMJ Open. 2017;7(8):e015867.
4. Arbyn M, Xu L, Simoens C, Martin-Hirsch PP. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database Syst Rev. 2018;5(5):CD009069.
5. Kietpeerakool C, Kleebkaow P, Srisomboon J. Human Papillomavirus Genotype Distribution among Thai Women with High-Grade Cervical Intraepithelial Lesions and Invasive Cervical Cancer: a Literature Review. Asian Pac J Cancer Prev. 2015;16(13):5153-8.

Goran Dimitrov, MD, PhD is associate Professor and specialist in Gynecology and Obstetrics, University Clinic of Obstetrics and Gynecology – Skopje, North Macedonia

Born on the 5th of June, 1963 in Kocani, Republic of Macedonia. Graduated at the Medical Faculty, University "Sts. Cyril and Methodius", Skopje, Republic of Macedonia. Specialized in obstetrics and gynecology. 1995 – employed at the Clinic of Gynecology and Obstetrics, Skopje, Macedonia. 1999 – acquired the title of Teaching Assistant at the University Clinic of Gynecology and Obstetrics, Skopje, Macedonia. 2002 – completed the postgraduate studies in the field of oncogynecology – topic of the MSc thesis: "Epidemiologic risk factors in the genesis of Cervical Intraepithelial Neoplasia". 2010 – Chief of Operative Gynecology Unit 2 (Oncogynecology) of the University Clinic for Gynaecology and Obstetrics, Skopje, Macedonia. 2014 – PhD in the field of oncogynecology – topic of the thesis: "Postoperative risk for Cervical Intraepithelial Neoplasia". 2015 – acquired the title of Assistant Professor (Docent) at the Dept. of Gynecology and Obstetrics, University of Skopje, Macedonia. 2016 – elected and appointed Head of Gynecology and Obstetrics - Educational Department (Katedra) at the Medical Faculty (re-elected October, 2020). 2020 – acquired the title of Associate Professor at the Dept. of Gynecology and Obstetrics, University of Skopje, Macedonia.

Study stays at: Policlinico Umberto I, University Clinic of Ob/Gyn I, University "La Sapienza", Rome – Italy; University Clinic of Obstetrics and Gynecology, University "La Laguna", Santa Cruz de Tenerife – Spain; Department for Gynecologic Oncology, Universitaets Frauenklinik, University "Georg August", Goettingen – Germany; Clinic of Gynecology and Obstetrics, University State Hospital "Maichin Dom", Sofia – Bulgaria; University Clinic of Obstetrics and Gynecology, Faculty of Medicine (Çapa), University of Istanbul – Turkey

General Secretary of the MAGO (Macedonian Association of Gynecologists and Obstetricians – member of FIGO) since April, 2003. President of MHPVS (Macedonian Humanpapilloma Virus Society). General Secretary of MMA (Macedonian Medical Association) since March, 2013. Member of the EXECUTIVE BOARD of European Federation for Colposcopy and Pathology (EFC) 2017 – 2019. President of the MSCPC (Macedonian Society for Colposcopy and Cervical Pathology – member of IFCPC, EFC. President of MMA (Macedonian Medical Association) since March,2015 [re-elected 2019]. Foreign languages spoken: English, Spanish and German.

QUALITY INDICATORS FOR ADVANCED OVARIAN CANCER SURGERY

Asst. Prof. Miljan Ćeranić

Dr. Maja Pavlov, Dr. Stojan Latinčić, Dr. Jovica Vasiljević

Clinic for digestive surgery of First surgical clinic, Clinical Center of Serbia
School of Medicine, University of Belgrade, Serbia

The optimal surgical management of patients with early stages ovarian cancer includes a staging with peritoneal and retroperitoneal assessment, and a complete debulking with removal of all macroscopic tumor for advanced disease. Differences across different institutions in terms of optimal surgical management have been described. Surgical quality control programs constitute a real possibility to ensure and improve the quality of the surgery delivered.

Rates of complete surgical resection, number of cytoreductive surgeries performed per center and per surgeon, number of surgery performed by a gynecologic oncologist or a trained surgeon specifically dedicated to gynecological cancers management, treatment planned and reviewed at a multidisciplinary team (MDT) meeting, minimum required elements in operative reports, center participating in clinical trials in gynecologic oncology, minimum required elements in pathology reports existence of a structured prospective reporting of postoperative complications were proposed quality indicators (QIs).

Development of quality control programs has been shown to improve surgical outcomes for patients with ovarian cancer. Centralization of care for patients with ovarian cancer is associated with better surgical and oncological outcomes.

References

1. Gac MM, Loaec C, Silve J, Vaucel E, Augereau P, Wernert R, Bourgin C, Aireau X, Lortholary A, Descamps P, Priou F, Deblaye P, Bourgeois H, Delecroix V, Empereur F, Campion L, Classe JM. Quality of advanced ovarian cancer surgery: A French assessment of ESGO quality indicators. Eur J Surg Oncol. 2020;11:S0748-7983(20)30695-8.
2. Querleu D, Planchamp F, Chiva L, Fotopoulou C, Barton D, Cibula D, Aletti G, Carinelli S, Creutzberg C, Davidson B, Harter P, Lundvall L, Marth C, Morice P, Rafii A, Ray-Coquard I, Rockall A, Sessa C, van der Zee A, Vergote I, du Bois A. European Society of Gynaecologic Oncology Quality Indicators for Advanced Ovarian Cancer Surgery. Int J Gynecol Cancer. 2016;26(7):1354-63.
3. Fotopoulou C, Concin N, Planchamp F, Morice P, Vergote I, du Bois A, Querleu D. Quality indicators for advanced ovarian cancer surgery from the European Society of Gynaecological Oncology (ESGO): 2020 update. Int J Gynecol Cancer. 2020;30(4):436-440.
4. Brand AH, DiSilvestro PA, Sehouli J, Berek JS. Cytoreductive surgery for ovarian cancer: quality assessment. Ann Oncol. 2017;1;28(suppl_8):viii25-viii29.

Miljan Ćeranić, Klinički centar Srbije, Beograd, Klinika za digestinu hirurgiju – Prva hirurška. Od januara 2011 Projekat Ministrastva za nauku i tehnologiju „Uloga preoperativnog odredjivanja stadijuma bolesti, prognostičkih, terapijskih markera, objektiviziranje funkcionalnih rezultata u odluci o strategiji lečenja karcinoma rektuma, a u cilju unapredjenja onkoloških rezultata i kavaliteta života.“ broj 41033.

Kao stipendista Franucuske vlade za oblast onkologije u martu i aprilu 2005. godine boravio je na stručnom usavršavanju na odeljenju za

digestivnu onkološku hirurgiju Instituta Gustave Rousssy, Villejeuf, Francuska. Dr Dominique Elias, koji je šef digestivne hirurgije ove prestižne onkološke bolnice.

Bio je učesnik ESTRO kursa „Evidence and research in rectal cancer« koji je održan u Beogradu od 20-22. maja 2010. godine i učesnik ETHICON ovog kursa „Biosurgery Innovation Wet Lab Meeting“koji je održan u Zagrebu, 17.06.2011. godine. Završio je Internacionalni kurs Ultrasonographic imaging of pelvic floor disorders koji je održan u Treviso-u, Italija 23-25. novembra 2011. godine. Završio je „Advanced course in laparoscopic colorectal surgery“ Rijeka, Hrvatska, 18-19. sep. 2014. godine. Završio je „THD and gatekeeper: Mini invasive surgery for the treatment of hemorrhoids and faecal incontinence“ 26-26 marta 2015. Roma, Italy. 2016. „ Mini Fellow Ship laparoscopic colorectal surgery –Prof Yves Panis of Hôpital Beaujon” Paris, France. „Advanced Master Class In Minimally Invasive Colorectal Surgery“, koji je održan u Lisabonu, Portugal od 19-21. februara 2018. Godine. „Laparoscopic Colorectal Training Programme for Serbia (LAPSERB)“ 22. November 2018. godine. „Laparoscopic CME Course“ Norderstedt, Germany on Monday 17 – Tuesday 18 December 2018.

PRIMENA MATIČNIH ĆELIJA U ONKOLOGIJI

Prof. Tatjana Božanović

Klinika za ginekologiju i akušerstvo, Klinički Centar Srbije
Medicinski fakultet, Univerzitet u Beogradu, Srbija

Nova saznanja o matičnim ćelijama, uvid u njihove karakteristike i mogućnosti, otvorila su novu eru u shvatanju molekularnih procesa, kako fizioloških tako i patoloških i posle više decenija , omogućila veliki iskorak u lečenju ljudi.

Matične ćelije su detektovane u raznim tkivima i organima. Osnovna podela matičnih ćelija učinjena je prema njihovom potencijalu diferencijacije:

- totipotentne stem ćelije – u ranom stadijumu nastanka embriona i mogu formirati ceo organizam
- pluripotentne stem ćelije – nalaze se u unutrašnjem ćelijskom sloju blastociste i mogu se diferencirati u sva tri klicina lista
- multipotentne – u većini tkiva i mogu se diferencirati u specifičnu vrstu tkiva ili organa
- unipotentne – mogu se diferencirati u samo jednu vrstu ćelijske linije

Adultne somatske stem ćelije su multipotentne i najčešće se, u terapijske svrhe, koriste Mezenhimalne stem ćelije (MSC). One su multipotentne, samoproliferišuće, niske imunogenosti, poseduju mogućnost veoma precizne detekcije lokacije patološkog procesa i zahvaljujući posebnim molekulama, imaju sposobnost brzog dolaska na mesto koje treba terapijski tretirati. Potom mogu da se diferenciraju u različite tipove ćelija ili da vrše reparaciju tkiva, takodje i imunomodulaciju. Danas se smatra da je možda najvažnija uloga matičnih ćelija u popravljanju medjućelijske komunikacije, u čemu najvažniju ulogu imaju male ekstracelularne vezikule Egzozomi. One su veličine manje od 100 nanometera, prenose proteine, lipide i aminokiseline i predstavljaju medijatore za komunikaciju izmedju ćelija.

Terapijski efekat stem ćelija je determinisan njihovom sposobnosti da migriraju na mesto patološkog procesa, gde nakon sagledavanja problema, sekretuju bioaktivne medijatore, kao što su faktori rasta, citokini, egzozomi koji svi zajedno dovode do imunosupresivnih, anti-apoptotičkih, antifibroznih, proangiogenih i anti inflamatornih efekata (1). Brojne in vitro studije su pokazale glavna svojstva MSC, a to je mogućnost precizne migracije na mesto lezije i potom indukcija reparacije. S tim u vezi je evidentan ogroman napredak u oblasti regenerativne medicine, upotrebom matičnih celija. Drugo važno svojstvo MSC je diferencijacija u ćelije ektodermalnog i endodermalnog porekla kao što su neuroni, kardiomiociti, hepatociti, epitelne ćelije (2). Saznanja o mogućnostima upotrebe matičnih čelija u terapijske svrhe su dovela do značajnih rezultata u rešavanju problema ovarijalne insuficijencije (3). kao i brojnih sistemskih poremećaja

Inetrreakcija MSC i mikrosredine oštećenog tkiva ima za posledicu sekreciju medijatora koji učestvuju u stimulaciji i diferencijaciji lokalnih prekursorskih ćelija. Pokazan je jasan efekat u popravljanju postiradijacionog enterokolitisa, intravenskom primenom MSC koja dovodi do aktivacije signalnog puta za proliferaciju intestinalnih stem ćelija (4). Kancerske ćelije se ponašaju slično oštećenom tkivu. Tumor produkuje molekule koji privlače MSC. Najbolje proučen signalni put za migraciju MSC ka tumoru, je CXCL12/CXCR4. To je signalni put za migraciju mezenhimalnih stem ćelija u mikrosredinu tumora (5). Migracija MSC ka kancerskom tkivu je takodje regulisana

drugim medijatorima iz okruženja kao što su citokini IL8, faktori rasta iz trombocita, ekstracelularni matrix u kome je najvažnije prisustvo matriks metaloproteinaze 2 (MMP-2) (6). Nakon pristizanja MSC u kancersku mikrosredinu, dolazi do direktne i indirektne intereeakcije MSC i kancerskih ćelija što za posledicu ima efekat na razvoj tumora. Parakrina funkcija stem ćelija preko razlilčitih medijatora je glavni efekat na kancerske ćelije dejstvom na ćelijski ciklus malignih ćelija, ćelijsko preživljavanje, neoangiogenezu, imunomodulaciju (7). Interakcija MSC sa kancerskim ćelijama dovodi do terapijskog efekta (8). Inhibicijom signalnog puta fosfatidilinozitol 3-kinaza/ protein kinaza B (PI3K/AKT) , MSC može da indukuje ćelijski arest i redukciju kancerskog tkiva (9).

Sa druge strane MSC se mogu diferencirati u kancer udružene fibroblaste (CAF) koji onda direktno stimulišu progresiju kancera (10) Brojni in vitro eksperimenti ukazuju na mogućnost i pro tumorskog i antitumorskog efekta koje imaju MSC. Potrebne su detaljnije studije koje će prevazici različite eksperimentalne uslove, vreme davanja MSC, dozu MSC, lokalne faktore, opšte stanje onkološkog pacijenta koje takodje menja uslove mikrosredine itd (11). Posebno mesto ispitivanja je svakako situacija da adultne normalne MSC budu transformisane u funkciju preživljavanja malignih ćelija. Pretpostavka je da ključnu ulogu imaju kancerske stem ćelije (CSC) čije je otkiriće 2005. godine dovelo do značajnih saznanja o biološkom potencijalu malignih bolesti. Postavlja se pitanje da li je u njima upravo ključna uloga u odbrani malignih tumora i daljem širenju i opstanku, kao i koji sve faktori utiču da kancerska stem ćelija nadjača humanu mezenhimalnu stem ćeliju i programira je za opstanka tumora.

Posebna pažnja se poslednjih godina posvećuje genetskom inženjeringu MSC kojim se koristi sposobnost MSC da brzo i precizno migrira u patološki proces, tako što će preneti tumor supresorske molekule . MSC je u ovom slučaju Trojanski konj koji će ubaciti terapijske supstance direktno u kancersko tkivo. Koristeći nanopartikule u dizajniranju MSC, korišćenjem TRIAL suicidalnog proteina koji je preko MSC ubačen u gliom, dobijeni su odlični rezultati u smislu potpune inhibicije tumora (12). Značajno mesto ima inženjering sa mikroRNA koje imaju antitumorski efekat, njihovim transportom preko MSC dolazi do redukcije tumora (13). Hemioterapeutici inkapsulirani u nanopartikule a potom ugradjeni u MSC dolaze do kancerskih ćelija i vrše direkatan antitumorski efekat, bez oštećenja zdravih ćelija (14). U toku su brojne interesantne studije koje koriste ugradnju biorazgradivih materijala u MSC sa idejom da posle hirurškog otklanjanja tumora, na mestu ekscizije, lokalnim delovanjem, omoguće duži period bez bolesti. Najpoznatiji biomaterijal koji se koristi u onkologiji je Gliadel. Vrši se insercija na mesto ekscizije i deluje tako što polako otpušta antikancerski lek karmustin tokom 2 do 3 nedelje. Ispitivanja su fokusirana na integrativno antikancersko dejstvo biorazgradivih supstanci u kombinaciji sa matičnim ćelijama.

MSC bazirane terapije će omogućiti razvoj visoko efikasne, antikancerske personalizovane terapije.

Literatura

1. Salgado, et al. Adipose tissue derived stem cells secretome: soluble factors and their roles in regenerative medicine. Curr Stem Cell Res Ther. 2010;5:103-10.
2. Garvois, et al. Neurogenic maturation of human dental pulp stem cells following neurosphere generation induces morphological and electrophysiological characteristics of functional neurons. Stem Cells Dev. 2015;24:296-311.
3. Aleksandar Ljubić. Autologous ovarian in vitro activation with ultrasound-guided orthotopic re-transplantation. Am J Clin Exp Obstet Gynecol. 2017; 4(5):51-7.
4. Gong, et al. Mesenchymal stem cells stimulate intestinal stem cells to repair radiation-induced intestinal injury. Cell death Dis. 2016;7:e2387.
5. Kalimuthu, et al. In Vivo tracking of Chemokine Receptor CXCR4-Engineered Mesenchymal Stem Cell Migration bz Optical Molecular Imiging. Stem Cells Int, 2017,808.
6. Bhoopathi, et al. MMP-2 mediates mesenchymal stem cell tropism towards medulloblastoma tumors. Gene Ther. 2011;18:692-701.
7. Rani, et al. Mesenchymal stem cell-derived extracellular vesicles: toward cell free therapeutic applications. Mol Ther.

2015;23:812-23.

8. Fathi, et al. Mesenchymal stem cells in acute myeloid leukemia: a focus on mechanisms involved and therapeutic concepts. Blood Res. 2019;54:165-74.
9. Lu, et al. Bone marrow mesenchymal stem cells suppress growth and promote the apoptosis of glioma U251 cells through downregulation of the PI3K/AKT signaling pathway. Biomed. Pharmacorther.2019:112.
10. Aoto, et al. Complex formation between platelet-derived growth factor receptor beta and transforming growth factor beta receptor regulates the differentiation of mesenchymal stem cells into cancer-associated fibroblasts. Oncotarget. 2018;9:34090-102.
11. Rivera, et al.Aging restricts the ability of mesenchymal stem cells to promote the generation of oligodendrocytes during remyelination. Glia 2019;67:1510-25.
12. Jiang, et al. Nanoparticle engineered TRAIL- overexpressing adipose derived stem cells target and eradicate glioblastoma via intracranial delivery. Proc. Natl. Acad. Sci.USA 2016;113:13857-62.
13. Li X, et al. Human umbilical cord mesenchymal stem cell derived extracellular vesicles inhibit endometrial cancer cell proliferation and migration through delivery of exogenous miR-302a. Stem Cells Int. 2019;81.
14. Moku, et al. Improving payload capacity and anti-tumor efficacy of mesenchymal stem cells using TAT peptide functionalized polymeric nanoparticles. Cancers. 2019;11: e491.

ULOGA PREDIKTIVNIH MODELA U PROCENI ADNEKSALNIH PROMENA

Ass. Zoran Vilendečić

Klinika za ginekologiju i akušerstvo Kliničkog centra Srbije
Medicinski fakultet, Univerzitet u Beogradu, Srbija

Adneksalne promene predstavljaju relativno čest nalaz u ginekološkoj praksi. Većina promena su dobroćudne prirode i mogu se podeliti na funkcionalne ciste i dobroćudne neoplazije jajnika. Iako relativno retki, maligniteti jajnika predstavljaju vodeći uzrok smrtnosti od ginekoloških maligniteta. Patogeneza i faktori rizika nisu do kraja poznati, a često nespecifična klinička slika otežava dijagnozu u ranijim stadijumima bolesti. Niska zastupljenost ranih stadijuma kancera jajnika je posledica nepostojanja metoda za rano otkrivanje, odnosno nepostojanje skrininga, pa su maligniteti jajnika ranog stadijuma uglavnom „slučajni nalaz“ pri operativnom lečenju iz različitih indikacija (akutni abdomen zbog rupture ili torzije adneksalne promene ili operacija zbog drugih hirurških postupaka u maloj karlici i abdomenu). Kao posledica navedenog, uprkos razvoju ginekološke onkologije nije značajnije smanjena smrtnost od maligniteta jajnika.

Najvažniji korak u dijagnostici ovarijalnih tumora je diferencijacija na maligne i benigne tumore jajnika, što ima veliki praktični značaj. Promene koje su benigne se u značajnom procentu slučajeva mogu pratiti ili lečiti minimalno invazivnim procedurama, dok se promene sumnjive na malignitet optimalno tretiraju u specijalizovanim centrima od strane osoblja koje je obučeno za izvođenje opsežnijih hirurških zahvata.

Inicijalna dijagnostička metoda za procenu adneksalnih promena je ultrazvuk, a kao dodatne metode se koriste tumorski markeri i dodatne imidžing metode kao što su magnetna rezonanca ili kompjuterizovana tomografija (1). Subjektivna procena iskusnog kliničara koja uzima u obzir demografske karakteristike pacijentkinje, kao i kliničke i ultrazvučne podatke, predstavlja najbolji pristup sa senzitivnošću od 93% i specifičnošću od 89% (2)(3)(4). Ograničenje ovog pristupa je činjenica da kvalitet subjektivne procene u značajnoj meri zavisi od iskustva dijagnostičara. Uloga tumorskih markera u inicijalnoj klasifikaciji adneksalnih promena je kontraverzna. U široj primeni je određivanje kancer antigena 125 (CA 125) i humanog epididimalnog sekretornog proteina 4 (HE 4).

U cilju objektivnije procene adneksalnih promena razvijen je veći broj prediktivnih modela koji kombinuju različite parametre, najčešće ultrazvučne karakteristike uočene promene, vrednosti biomarkera i menopauzalni status pacijentkinje. Ultrazvučne karakteristike adneksalne promene i vrednosti biomarkera se u smislu dihotomne klasifikacije (benigno i maligno) mogu koristiti samostalno ili u kombinovanim prediktivnim modelima.

Najzastupljeniji kombinovani prediktivni model je Risk of Malignancy Index (RMI) koji uzima u obzir ultrazvučne parametare, vrednost CA 125 i menopauzalni status pacijentkinje (5). Ultrazvučni skor se dobija na osnovu sledećih parametara: multilokularnost, prisustvo solidnih delova, bilateralnost, prisustvo ascitesa i intraabdominalnih metastaza. Senzitivnost i specifičnost najzastupljenijeg RMI-II modela, koji koristi vrednost od 200 kao cut-off vrednost za malignitet, iznosi 81,1% i 89,6% (6). Nedostatak standardizacije u opisu ultrazvučnog nalaza i niska senzitivnost CA 125 u borderline tumorima i ranim stadijumima invazivnog kancera jajnika predstavljaju ograničenja ovog modela.

Drugi značajan prediktivni model za procenu rizika ovarijalnog karcinoma je ROMA indeks (Risk of Ovarian Malignancy Algorithm) koji uzima u obzir koncentracije CA 125 i HE 4, u kombinaciji sa menopauzalnim statusom. Referentne vrednosti za tumorske markere iznose: CA 125 do 35 U/ml; HE 4 do 70 pmol/l. Za predikciju maligniteta se koristi cut-off vrednost od 11.4% za premenopauzalne i 29.9% za postmenopauzalne pacijentkinje. U postmenopauzalnoj grupi senzitivnost ovog testa je 92,3 % i specifičnost 75%, a u premenopauzalnoj grupi senzitivnost iznosi 76,5%, a specifičnost 74,8% (7). Iako ovaj algoritam ne uzima u obzir ultrazvučne karakteristike promene smatra se korisnim u diferencijaciji benigne i maligne adneksalne patologije, kao i u slučaju dijagnostičkih dilema kod ovarijalnih border-line tumora (8)(9). Rezultati u pogledu dijagnostičke primene ovog biomarkera i ROMA algoritma su obećavajući, ali je za potpuniji uvid u njegove dijagnostičke vrednosti potrebno dalje kliničko ispitivanje, posebno kod pacijentkinja sa ranim stadijumima ovarijalnih maligniteta.

Međunarodna IOTA (International Ovarian Tumour Analysis) grupa je razvila veći broj ultrazvučnih prediktivnih modela, od kojih se po svojoj jednostavnosti i performansama ističe model jednostavnih pravila (IOTA Simple Rules). Ovaj model je i najbolje prihvaćen od strane kliničara. Pravila se baziraju na podeli ultrazvučnih karakteristika na one koje su karakteristične za maligne lezije (M karakteristike) i one koje su karakteristične za benigne lezije (B karakteristike) (10). Model jednostavnih pravila uključuje 5 jasno definisanih ultrazvučnih karakteristika koje ukazuju na benignu promenu (B karakteristike) i to su unilokularnost, solidna komponenta sa najvećim dijametrom do 7 mm, prisustvo akustične senke, pravilan multilokularan tumor sa najvećim dijametrom do 100 mm i promena nije vaskularizovana (kolor skor 1), kao i 5 ultrazvučnih karakteristika koje ukazuju na malignitet (M karakteristike), i to su solidan tumor iregularnih kontura, prisustvo ascitesa, 4 ili više papilarnih projekcija, nepravilan multilokularno solidan tumor sa najvećim dijametrom 100 ili više milimetara i izražena vaskularizacija (kolor skor 4). Prisustvo najmanje jedne M karakteristike i odsustvo B karakteristika klasifikuje promenu kao malignu, i obrnuto prisustvo najmanje jedne B karakteristike i odsustvo M karakteristika klasifikuje leziju kao benignu. Prisustvo i B i M karakteristika daje nekonkluzivan nalaz. Ograničenje ovog modela predstavlja činjenica da se adneksalne promene u jednoj četvrtini slučajeva ne mogu klasifikovati, što zahteva primenu dodatnog postupka koji može biti subjektivna procena iskusnog lekara ili upotreba dodatnih imidžing metoda.

U novije vreme se preporučuje upotreba logističkih regresionih modela koji kombinacijom većeg broja varijabli omogućavaju procenu individualnog rizika od maligniteta. Adnex model (Assessment of Different Neoplasias in the adnexa) (11) uključuje devet varijabli, i to: starost, vrednost serumskog CA-125, tip centra (onkološki centar ili ustanova drugog tipa), maksimalni dijametar lezije, proporcija solidnog tkiva, broj papilarnih projekcija, broj cističnih subjedinica (više ili manje od 10), prisustvo akustične senke i prisustvo ascitesa. Na osnovu ovih parametara promena se svrstava u jednu od sledećih kategorija: dobroćudna promena, border-line tumor, invazivni kancer ranog stadijuma, invazivni kancer uznapredovalog stadijuma i metastatski kancer jajnika. Međutim, rezultati studija koje procenjuju performanse ovog modela su kontraverzne i zahtevaju dalje validacije (12)(13).

Primena prediktivnih modela omogućava bolju inicijalnu procenu benignih i malignih adneksalnih promena, čime se pacijentkinjama može ponuditi optimalniji tretman. Identifikacija pacijentkinja sa niskim rizikom od maligniteta omogućava u značajnom procentu praćenje ili lečenje minimalno invazivnim procedurama, dok s druge strane pravilna identifikacija pacijentkinja sa visokim rizikom od maligniteta omogućava adekvatniju preoperativnu obradu i identifikaciju pacijentkinja koje bi imale korist od primarnog hirurškog tretmana od strane ginekološkog onkologa.

Literatura

1. Republička stručna komisija za izradu i implementaciju vodiča dobre kliničke prakse, [urednik, Ministarstvo zdravlja Republike Srbije; Šternić Čoviković N. NACIONALNI vodič dobre kliničke prakse za dijagnostikovanje i lečenje karcinoma ovarijuma.
2. Meys EMJ, Jeelof LS, Achten NMJ, Slangen BFM, Lambrechts S, Kruitwagen RFPM, et al. Estimating risk of malignancy in adnexal masses: external validation of the ADNEX model and comparison with other frequently used ultrasound methods. Ultrasound Obstet Gynecol. 2017;49(6):784–92.
3. Meys EMJ, Kaijser J, Kruitwagen RFPM, Slangen BFM, Van Calster B, Aertgeerts B, et al. Subjective assessment versus ultrasound models to diagnose ovarian cancer: A systematic review and meta-analysis. Eur J Cancer [Internet]. Elsevier Ltd; 2016;58:17–29. Available from: http://dx.doi.org/10.1016/j.ejca.2016.01.007
4. Glanc P, Benacerraf B, Bourne T, Brown D, Coleman BG, Crum C, et al. First International Consensus Report on Adnexal Masses: Management Recommendations. J Ultrasound Med. 2017;36(5):849–63.
5. Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol [Internet]. 1990 Oct [cited 2018 Nov 5];97(10):922–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2223684
6. Yamamoto Y, Yamada R, Oguri H, Maeda N, Fukaya T. Comparison of four malignancy risk indices in the preoperative evaluation of patients with pelvic masses. Eur J Obstet Gynecol Reprod Biol [Internet]. 2009 Jun [cited 2018 Nov 5];144(2):163–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19327881
7. Moore RG, Scott Mcmeekin D, Brown AK, Disilvestro P, Miller MC, Allard WJ, et al. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. 2010 [cited 2018 Nov 5]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3594094/pdf/nihms-231784.pdf
8. Sölétormos G, Duffy MJ, Suher Othman Abu Hassan Þ, Verheijen RH, Bengt Tholander þ, Bast RC, et al. Clinical Use of Cancer Biomarkers in Epithelial Ovarian Cancer Updated Guidelines From the European Group on Tumor Markers. 2015 [cited 2018 Nov 5]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4679342/pdf/igj-26-043.pdf
9. Gizzo S, Berretta R, Gangi S Di, Guido M, Zanni GC, Franceschetti I, et al. Borderline Ovarian Tumors and Diagnostic Dilemma of Intraoperative Diagnosis: Could Preoperative He4 Assay and ROMA Score Assessment Increase the Frozen Section Accuracy? A Multicenter Case-Control Study. 2014 [cited 2018 Nov 5]; Available from: http://dx.doi.org/10.1155/2014/803598
10. Timmerman D, Van Calster B, Testa A, Savelli L, Fischerova D, Froyman W, Wynants L, Van Holsbeke C, Epstein E, Franchi D, Kaijser J, Czekierdowski A, Guerriero S, Fruscio R, Leone FPG, Rossi A, Landolfo C, Vergote I, Bourne T VL. Predicting the risk of malignancy in adnexal masses based on the Simple Rules from the International Ovarian Tumor Analysis group. Am J Obs Gynecol [Internet]. Elsevier Inc.; 2016;214(4):424–37. Available from: http://dx.doi.org/10.1016/j.ajog.2016.01.007
11. Calster B Van, Hoorde K Van, Valentin L, Testa AC, Fischerova D, Holsbeke C Van, et al. Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign , borderline , early and advanced stage invasive , and secondary metastatic tumours : prospective multicentre diagnostic study. 2014;5920(October):1–14.
12. Szubert S, Wojtowicz A, Moszynski R, Zywica P, Dyczkowski K, Stachowiak A, et al. External validation of the IOTA ADNEX model performed by two independent gynecologic centers. Gynecol Oncol [Internet]. Elsevier Inc.; 2016;142(3):490–5. Available from: http://dx.doi.org/10.1016/j.ygyno.2016.06.020
13. Araujo KG, Jales RM, Pereira PN, Yoshida A, de Angelo Andrade L, Sarian LO, et al. Performance of the IOTA ADNEX model in preoperative discrimination of adnexal masses in a gynecological oncology center. Ultrasound Obstet Gynecol. 2017;49(6):778–83.

FERTILITY PRESERVING SURGERY IN GYNAECOLOGIC ONCOLOGY

Ass. Igor Pilić

Klinika za ginekologiju i akušerstvo, Klinički Centar Srbije
Medicinski fakultet, Univerzitet u Beogradu, Srbija

Oncofertility – nova oblast koja povezuje onkologiju i reproduktivnu medicinu.

Očuvanje fertilnosti u toku i pre započinjanja lečenja maligne bolesti je neophodna usled fenomena odloženog rađanja. Veća incidenca premalignih lezija endometrijuma, grlića i jajnika kod mlađih pacijentkinja. Neophodno je očuvanje fertiliteta bez promene onkološkog ishoda.

Karcinom endometrijuma, karcinom grlića, karcinom jajnika su oboljenja koja mogu biti tretirana endoskopskim procedurama i minimalno invazivnom hirurgijom u cilju očuvanja fertiliteta.

Endometrijalni karcinom – najčešći ginekološki malignitet, jedan od najređih uzroka smrti sa samo 1,3% smrtnih slučajeva od malignih bolesti ukupno. Skoro 80% karcinoma dijagnostikuje u početnom stadijumu bolesti kada je veće preživljavanje (95%). Kumulativni rizik za dijagnozu endometrijalnog kancera je 1,71%, a 3% do 5% pacijentkinja su mladje od 40 godina. Histeroskopija predstavlja zlatni standard! Postoji vizuelna kontrola, ciljana biopsija (kiretaža), provera stanja kavuma posle uzimanja uzorka za HP analizu. Preciznost histerokopije je dovoljna u dijagnostici endometrijalnog karcinoma ili hiperplazije. Senzitivnost je 86,4%, a specifičnost 99,2%. Diseminacija malignih ćelija kroz jajovode tokom histeroskopije nije dokazana u ranim stadijumima meta analizom. Veliki značaj histeroskopske evaluacije

endometrijuma na svakih šest meseci je u konzervativnom tretmanu (najčešće gestagenima ili GnRh analozima) kod mlađih žena sa dobro diferentovanim karcinomom endometrijuma nižeg gradusa u početnom stadijumu tumorske bolesti. Kombinovanje histeroskopske resekcije uz konzervativni tretman ranog stadijuma karcinoma endometrijuma može biti način da se poboljša stopa odgovora i smanjenje recidiva kod žena koje žele da sačuvaju plodnost i da u što kraćem vremenskom periodu postignu remisiju i uđu u reprodukciju.

Na KGA KCS 42 pacijentkinje je konzervativno tretirano, pre svega sa GnRh antagonistima i IUD, 5 sa histeroskopskom resekcijom i kiretažom, praćenje je i dalje u toku, do sada 8 uspešnih trudnoća (4 porođene).

Karcinom jajnika - Fertilnost je jedna od glavnih briga pacijentkinje koja je preživela kancer. Očuvanje fertiliteta je veoma važan aspekt u ginekološkoj onkologiji. Fertility-sparing hirurgija bi morala da bude sigurna u ranom ovarijalnom karcinomu i određenim histološkim subtipovima, u ovarijalnim tumorima niskog malignog potencijala i ovarijalnim malignitetima germinativnih ćelija, zatim ovarian sex cord stromal tumori čak i u odmaklim stadijumima, ukoliko je kontra lateralni jajnik normalan, kao i kod invazivnog epithelialnog ovarijalnog cancera u ranim stadijumima bolesti. Fertility-sparing hirurgija podrazumeva: unilaterana salpingo-oophorectomija sa prezervacijom kontra lateralnog jajnika. Kao opcija u stadijumu IA, G1 ili G2 ovarijalnog karcinoma kao siguran tretman kod pacijentkinja koje su zainteresovane za potomstvo fertility-sparing hirurgija može biti praćena postoperativnom hemoterapijom.

Kod želje za očuvanjem fertilnosti , mlađih pacijentkinja, ranog stadijuma, unilateralna adneksektomija, Staging (citologija, biopsija kontralateralnog jajnika, omentuma, limfadenektomija , biopsija peritoneuma). Mlađe pacijentkinje sa željom za očuvanje fertilnosti sa tumorom ograničen na jedan jajnik, sa nižim gradusom tumora, intaktne kapsule, bez znakova

invazije, pokretan, bez palpabilno uvećanih limfnih čvorova i negativan peritonealni ispirak uz negativnu biopsiju omentuma i peritoneuma, mogu biti kandidati.

Kontraindikacije za poštednu hirurgiju: bilateralna zahvaćenost oba jajnika kod karcinoma jajnika, histološki agresivni tipovi (anaplastični, neuroendokrini), nepovoljnan gradus tumora G3 kod postojanje BRCA mutacije, postojanje sinhronog endometroidnog tumora.

Dijagnostički i terapijski pristup mladim pacijentkinjama sa ginekološkim malignitetom je veoma kompleksan i izazovan i zahteva intenzivni dalji režim praćenja.

U cilju ostvarivanja trudnoće kod većine pacijentkinja kod kojih je malignitet tretiran hemoterapijom ili hirurški gde je ovarijalno tkivo uklonjeno obično su neophodne asistirane reproduktivne tehnike (ARTS), in vitro fertilization (IVF).

Uloga laparoskopije: laparoskopska evaluacija, dijagnoza i stejdžing naizgled ranog stadijuma karcinoma jajnika. Sa preciznim stadiranjem i detaljnim postoperativnim praćenjem, laparoskopska hirurgija može biti prihvatljiva metoda izbora za pacijente sa adneksalnim masama uključujući i rane stadijume.

Karcinom grlića materice - treći kancer po učestalosti u ženskoj populaciji, u Srbiji, učestalost - 4.mesto, smrtnost – 5. mesto. Moderna hirurška onkologija podrazumeva očuvanje funkcije organa, percepcija tela, kvalitet života. Očuvanje organa i njegove funkcije je standardna procedura kod mnogih solidnih tumora. Konzervativne hirurške procedure kod karcinoma grlića materice podrazumevaju konizaciju, amputaciju, prostu trahelektomiju.

Da li su zahvaćena parametrija? Ukoliko nisu, moguć konzervativni pristup.

Radikalna trahelektomija predstavlja uklanjanje cerviksa, parametrija i dela vagine, pri čemu se štedi telo materice i adneksa, a procedura se kombinuje sa pelvičnom limfadenektomijom.

Cilj: očuvanje fertilnosti uz nepromenjen onkološki ishod.

Trahelektomija – Preduslovi: Adekvatna selekcija pacijentkinja (rani stadijum bolesti i pacijentkinja zainteresovana za očuvanje fertilne sposobnosti), adekvatno preoperativno stadiranje (metoda izbora MRI), intraoperativna ex-tempore analiza uzoraka i obučen kadar.

Uporediv ishod - onkološki ishod se ne razlikuje od standardne procedure, stopa recidiva je od 3-6%, a stopa smrtnosti 2-5%. Trahelektomija – Indikacije: Starosna dob ispod 40 (ili 45) godina, veličina Tu do 2 (3 cm), negativni limfni nodusi na preoperativnom imidžingu, povoljan histološki tipa tumora (skvamocelularni karcinom, ređe adenokarcinom), stadijum IA1, IA2, IB1,

adekvatna dužina grlića materice. Ukoliko se intraoperativno utvrdi da nisu ispunjeni uslovi za konzervativni onkološki tretman konverzija u standardnu radikalnu operaciju.

Prednosti abdominalnog pristupa: kraća edukacija operatora, veća radikalnost u resekciji parametrija, ne zahteva veštine u vaginalnom ili laparoskopskom pristupu, jeftinija.

Mane abdominalnog pristupa: rez na trbuhu, duža hospitalizacija, češća cervikalna stenoza (u gotovo 40% slučajeva), stenoza istmusa materice i hematometra, dismenoreja, iregularne menstruacije, limfocela, edem vulve, dispareunija, hronična pelvična bol, češće vaginalne infekcije, recidiv bolesti.

Suštinu svaga predstavlja smanjenje radikalnosti, očuvanje fertilne sposobnosti, smanjenje morbiditeta koji prate radikalnu hirurgiju. U perspektivi su potrebne nove i pouzdane studije (naš problem je praćenje pacijentkinja). Potencijalno redefinisanje standarda za tretman ranih

stadijuma cervikalnog kancera (45 god, adenotip, tumor do 3 cm, dubina invazije u stromu), a sve to u cilju postizanja boljeg kvaliteta života pacijentkinja.

References

1. Clark TJ, Voit D, Gupta JK, Hyde C, Song F, Khan KS. Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. JAMA. 2002 Oct 2;288(13):1610-21.
2. Takac, et al. Office hysteroscopy and risk for extrauterine spreading of endometrial carcinoma. Gynecol oncol. 2007.
3. Arendas K, Aldossari M, Kipolla A, Lider A, Leiland NA. Hysteroscopic resection in the

management of early-stage endometrial cancer: report of 2 cases and review of the literature. J Minim invazivna Obstet. 2015;22(1): 34-9.

4. Shigeko S, Hiroaki K, Yoko M, Mika M, Fumitaka K, Shiho A, et al. Unexpected ovarian malignancy found after laparoscopic surgery in patients with adnexal masses –a single institutional experience. Nagoya J Med Sci. 2014;76(1-2): 83–90.
5. Novak F. Radical abdominal subcorporeal exttirpation of the cervix with bilateral pelvic nodes dissection in cancer in situ of cervix uteri. Acta Med Iugoslav. 1952;6:59-71.
6. Shepherd JH. Cervical cancer. Best Pract Res Clin Obstet Gynaecol. 2012;26(3):293-309.

KARCINOM TELA MATERICE – GENETSKA KLASIFIKACIJA I NOVI PRISTUP LEČENJU

Ass. Lazar Nejković

Potpredsednik udruženja za ginekološku onkologiju Srbije (UGOS),
Ginekološko-akušerska klinika Narodni Front, Univerzitet u Beogradu, Srbija

Karcinom endometrijuma je najčeši ginekološki malignitet koji se globalno povećava i po učestalosti i po smrtnosti u celom svetu. Prema procenama Američkog udruženja za rak očekuje se 65 620 novih slučajeva u 2020. godini i 12 590 smtrnih slučajeva. Najčešče pogađa postmenopauzalne žene, oko 62 godine života (1).

Histološki tip tumora i gradus tumora zajedno sa stadiranjem stepan zahvaćenosti bolesti predstvljalo je do sada osnovni princip u pristupu lečneja karcinoma endometrijuma. Odlike kao što su starost pacijentkinje, dubina invazije miometrijuma, prisustvo limfovaskularne invazije, zahvaćenost strome grlića meterice i limfnih čvorova preciznije određuju primenu dodatne zračne, hemioterapije ili obe (2). Međutim, dosadašnja iskustva su pokazala da ovakav pristup nije dovoljno uspešan u lečenju žena obolelim od karcinoma endometrijuma jer kod pacijetkinja koje pripadaju istoj grupi postoje različiti ishodi u preživljavanju i recidivu bolesti (3).

Istraživanjem molekularnih mutacija, poslednih godina došlo je do velikog pomaka u razumevanju karcinoma endometrijuma. Izučavanje genomskog atlasa karcinoma (TGGA) karcinom endometrijuma je na osnovu genetskih informacija o promeni broja somatskih kopija i mutacija podeljen na četiri podgupe sa različitim genskim aberacijama.

Prvoj molekularnoj podgrupi (*polymerase ε exonuclease (POLE) ultramutated*), pripadaju kopije brojno stabilnih, ali ultramutiranih endometrijalnih karcinom sa mutacijama u eksonukleazi DNK polimeraze epsilon (POLE) gena koji učestvuje u nukleranim replikacijama i popravkama DNK-a. Ovi tumori imaju visoku frekvencu somatskih mutacija, preko 100 po megabazi, histološki su slični endometroidnom podtipu karcinoma endometrijuma i imaju relativno povoljnu prognozu(4).

Drugoj podgrupi (*hypermutated/microsatellite unstable subgroup*) pripadaju hipermutirani podtipovi sa mikrosatelitskom nestabilnošću zbog nefunkcionalnosti proteina za popravak I to MLH1, PMS2, MSH, MSH6 (5). Ovoj grupi pripada Lynch sindrom.

Trećoj molekularnoj podgrupi (*copy number low/microsatellite stable subgroup*) pripadaju genomski relativno stabilni tumori koji imaju umeren broj mutacija uglavnom unutar PI3K/Akt puta, pozitivni na estrogenske i progesteronske receptore.

Četvrtoj podgrupi (*copy number high-Serous like*) pripadaju tumori veoma slični seroznom karcinomu jajnika i odlikuje ih TP53 mutacija u oko 92%.

Cilj nove klasifikacije poboljšati dosadašnji sistem patohistološke I kliničke klasifikacije radi boljeg pristupa i lečenja, tačnije izbeći slučajeve koji su “nedovoljno stadirani ili “prestadirani” te takve pacijetkinje nisu dobijale adekvatnu terapiju što je rezultiralo Ili smanjenim intervalom preživljavanja ili nepotrebnom izloženošću štetnim efektima dodatne terapije. Ukoliko bi se u dijagnostičkim postupcima pre operacije (eksplorativna kiretaža) mogla primeniti molekuralna kaslifikacija to bi omogućilo da se u najranijem trenutku, preopartivno napravi plan lečenja što bi dodatno poboljšalo ishod u odnosu na lečenje nakon operacije. Ovo se posebno odnosi na 14%

mladih žena ispod 50 godina I 5% ispod 40 godina života obolelh od karcinoma endometrijuma koje žele da rađaju (6).

Dodatno razumevanje molekularne osnove ćelija tumora omogućava primenu molekularno ciljanih citiotoksičnih lekova, koji za razliku od konvencionalnih, mogu da razlikuju ćelije raka od normalnih i ihibiraju puteve neoplastične proliferacije i metastaze. Karakteristike molekularnih podgrupa prema TGGA kalsifikasciji to i dokazuju. Tako su ćelije kancera u okviru *POLE ultramutated* podgrupe pokazale pojačani citotoksični odgovor T-ćelija, što rezultuje povećan br CD8 limfocita koji infiltišu tumor te je za ove karcinome idealna primena lekova koji su inhibitori imunih kontrolnih tačaka. Tumori sa velikim brojem somatskih mutacija usled mikrosateliteske nestabilnosti takođe mogu biti podložni blokadi imunološke kontrolne tačke. Lekovi koji sprečavaju promena na nivou PI3K/Akt idelani su za treću podgrupu molekulerne klasifikacije tumora endometrijuma. A kako su u četvrtoj podgrupi tumori sa sličnim karkteristikama seropapilarnom karcinomu jajnuka molekulrana terapija koja se primenjuje za karcinom jajnika bi bila terapija izbora za ovu grupu karcinoma (7).

Prilagođeni nadzor, prilagođen individualnim rizicima pacijenata umesto jedinstvenog protokola poboljšao bi njihovo lečenje. Očekuje se da integracija nove molekularne kalsifikacije postane svakodnevni deo prakse u pristupu i lečenju karcinoma endometrijuma.

Literatura

1. American Cancer Society. Cancer facts & figures 2020. Atlanta:American Cancer Society; (2020).
2. Colombo N, Preti E, Landoni F, et al. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi33-8.
3. Bendifallah S, Canlorbe G, Collinet P, et al. Just how accurate are the major risk stratification systems for early-stage endometrial cancer? Br J Cancer. 2015;112:793–801.
4. Rayner E, van Gool IC, Palles C, et al. A panoply of errors: polymerase proofreading domain mutations in cancer. Nat Rev Cancer. 2016;16:71–81.
5. Shinbrot E, Henninger EE, Weinhold N, et al. Exonuclease mutations in DNA polymerase epsilon reveal replication strand specific mutation patterns and human origins of replication. Genome Res. 2014;24:1740-50.
6. Eggink FA, Van Gool IC, Leary A, et al. Immunological profiling of molecularly classified high-risk endometrial cancers identifies POLE-mutant and microsatellite unstable carcinomas as candidates for checkpoint inhibition. Oncoimmunology. 2017;6:e1264565.
7. Mohammed A, Samir Al H, Orwa E, Sameera R, Ajayeb D M H Al-N. Classification of Endometrial Carcinoma: New Perspectives Beyond Morphology. Adv Anat Pathol. 2019;26(6):421-27.
8. Takashi M, Peixin D, Kei I, Masataka K, Hidemichi W. Molecular-targeted therapies and precision medicine for endometrial cancer.Jpn J Clin Oncol. 2019;49(2):108-20.

SOLO 2 RESULTS: MAINTENANCE THERAPY WITH LYNPARZA EXTENDS SURVIVAL IN RELAPSED EPITHELIAL OVARIAN CANCER (EOC)

Dr. Marijana Milović Kovačević

Clinic for Medical Oncology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

Germline alterations in breast cancer 1 (*gBRCA1*) and breast cancer 2 (*gBRCA2*) genes have been identified in up to 17% of women diagnosed with EOC, and somatic mutations are found in an additional 7% (1). Approximately 41-50% of EOCs are estimated to exhibit homologous recombination deficiency (HRD) involved in repair of DNA damage and replication. The introduction of poly(ADP-ribose) polymerase inhibitors (PARPis) has led to major change in the approaches to EOC management across the treatment life cycle. In 2014, the US Food and Drug Administration (FDA) approved the first PARPi, olaparib, as a treatment of *gBRCA* EOC for patients who had received ≥ 3 prior lines of chemotherapy. Rucaparib received FDA approval for treatment of *g/sBRCA* recurrent disease in 2016. Approval for niraparib and, subsequently, olaparib as maintenance therapy for women with complete or partial response to platinum-based chemotherapy was granted in 2017. Since then, the FDA has expanded the regulatory approval of PARPis, thereby allowing more patients to benefit from these agents and access the drugs earlier in treatment. Recent studies have confirmed that the efficacy of PARPis is enhanced not only in *g/sBRCA* EOC but also in cancers in which HRD is caused by other underlying etiologies. The applications of PARPis in the management of EOC are complex and all approvals to date are predicated on the absence of prior exposure to PARPis.

Platinum sensitivity and high-grade histology predict patients with homologous recombination repair deficiency HRD is a key determinant of platinum sensitivity in high-grade serous ovarian cancer, and sensitivity to platinum agents is reported to correlate with sensitivity to olaparib (2). The most profound deficit in the homologous recombination repair (HRR) pathway is seen in tumours with a BRCAm.

Olaparib (Lynparza capsule formulation) received approval based on the results from Study 19 [ClinicalTrials.gov identifier: NCT00753545]. Study 19 was a randomized, placebo-controlled, phase II trial enrolling 265 patients who were clinically enriched for markers associated with a response to PARP-inhibitor treatment [i.e. patients with high-grade serous platinum-sensitive relapsed (PSR) ovarian cancer who had received at least two platinum-based chemotherapy regimens and were in complete or partial response to their most recent regimen]. Olaparib treat-ment improved PFS in Study 19 in the overall population [hazard ratio (HR) 0.35, 95% confidence interval (CI) 0.25–0.49; p< 0.0001 for olaparib versus placebo]. A planned, retrospective analysis of BRCAm status was performed and information was obtained for 96% of the overall population. In the BRCAm population, the benefit of olaparib versus placebo was even greater (HR 0.18, 95% CI 0.10–0.31; p < 0.0001) than in the non-BRCAm population (HR 0.54, 95% CI 0.34–0.85; p = 0.0075); After a median follow up of 6.5 years (79% data maturity), there was a clinically significant improvement in OS in the overall population of Study 19 (HR 0.73, 95% CI 0.55–0.95; nominal p = 0.021) and in patients with a BRCAm (HR 0.62, 95% CI 0.42–0.93; p = 0.021) (3). Although the criterion for statistical significance (p < 0.0095) was not reached for OS.

Consistent across BRCAm and non-BRCAm subgroups, approximately 10% of patients experienced a durable benefit from olaparib maintenance monotherapy for at least 6 years.

The full dose for the originally approved olaparib formulation was 400 mg b.i.d. administered as eight 50 mg capsules; (4) because of the high administration burden of the capsules, an alternative tablet formulation was developed. The capsule and tablet formulations are not bioequivalent, therefore an adaptive study, Study 24 [ClinicalTrials.gov identifier: NCT00777582] enrolling patients with advanced solid tumours, including patients with BRCAm ovarian and breast cancer, was performed to determine the optimal dose of the tablet formulation for use in phase III trials. This study determined that the olaparib 300 mg b.i.d. (2 × 150 mg) tablet for-mulation matched or exceeded the exposure of 400 mg b.i.d. capsules; the 300 mg b.i.d. tablet regimen was also shown to be non-inferior to 400 mg b.i.d. capsules in terms of tumour shrink-age (5), which led to 300 mg b.i.d. tablets being assessed in phase III trials of olaparib. The SOLO2 [ClinicalTrials.gov identifier: NCT01874353] study of olaparib was designed to evaluate the tablet formulation (300 mg b.i.d.) and to confirm the efficacy of olaparib in a phase III trial of patients with BRCAm, PSR ovarian cancer who were in complete or partial response to their most recent platinum-based regimen. It confirmed the efficacy of olaparib in this patient population with a significant improvement in both the investigator-assessed (primary endpoint) and blinded, independent central review (BICR; sensitivity analysis) PFS following olaparib treatment versus placebo (investgator-assessed median PFS: 19.1 versus 5.5 months, respectively; HR 0.30, 95% CI 0.22–0.41; $p < 0.0001$; BICR median PFS: 30.2 versus 5.5 months; HR 0.25, 95% CI 0.18–0.35; $p < 0.0001$) (6).

In summary, PARP inhibitors were developed with the intention of treating patients with HRD, specifically for patients with tumours that harbour a BRCAm. Evidence from clinical trials to date has demonstrated that patients with a BRCAm derive the greatest benefit from PARP inhibitors. However, there is a clear body of evidence showing that PARP inhibitors also benefit ovarian cancer patients without a BRCAm and the approval of olaparib, niraparib and rucaparib by the FDA and EMA in all PSR ovarian cancer populations who are in response to platinum sup-ports this. Long-term tolerability and efficacy of olaparib have been demonstrated in patients both with and without a BRCAm through Study 19, with patients receiving maintenance treatment for 6 years or more, which is unprecedented in the relapsed ovarian-cancer setting. Further studies should be performed to elucidate which non-BRCAm patients are deriving benefit, and what HRD molecular processes are enabling this, so that patients continue to receive optimal treatment for their disease.

References

1. Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res. 2012;72:5588-99.
2. Fong PC, Yap TA, Boss DS, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol. 2010;28:2512-19.
3. Friedlander M, Matulonis U, Gourley C, et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. Br J Cancer. 2018;119:1075-85.
4. AstraZeneca. Lynparza tablets receive EU approval for the treatment of platinum-sensitive relapsed ovarian cancer [press release], 2018.
5. Mateo J, Moreno V, Gupta A, et al. An adaptive study to determine the optimal dose of the tablet formulation of the PARP inhibitor olaparib. Target Oncol. 2016;11:401-15.
6. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18:1274-84.

Prim. dr sci. med. Marijana Milović-Kovačević rođena je 1972. godine. Zaposlena je u službi Medikalne onkologije u okviru Instituta za onkologiju i radiologiju Srbije.

Dr sci. med. Marijana Milović-Kovačević – Profesionalne klasifikacije

Diploma Medicinskog fakulteta sa prosečnom ocenom 9.17; Univerzitet u Beogradu. 1997.

Magistarska teza »Praćenje nefrotoksičnog efekta različitih aminoglikozida u toku febrilne neutropenije izazvane citotoksičnom terapijom» ; april 2004.g. Beograd

Specijalizacija iz interne medicine, jul 2005.g. Beograd

Doktorat PhD 2010.g. „Uticaj nivoa ekspresije ercc1 proteina na rezistenciju na platinske režime u karcinomu ovarijuma“

INNOVATIONS IN SYSTEMIC TREATMENT FOR ADVANCED ENDOMETRIAL AND CERVICAL CANCER

Prim. Ljiljana Stamatović

Direktor Klinike za medikalnu onkologiju, Institut za onkologiju i radiologiju Srbije, Beograd, Srbija

Although early-stage endometrial carcinoma is associated with a favorable 5-year relative survival rate (96%), the rate is only 18% in patients with distant metastases. The majority of patients with advanced or recurrent endometrial cancer will be candidates for systemic palliative therapy. The choice between hormonal treatment and chemotherapy relies on several factors, including histopathological and clinical features of the individual patient. Hormonal therapy it is the preferred front-line systemic therapy for patients with hormone receptor-positive tumors grade 1 or 2 and without rapidly progressive disease. The progestogens, MPA 200 mg or MA 160 mg, are traditionally recommended, obtaining response rate of ~25% and PFS of 3 months when used in front-line. Other endocrine therapies, antiestrogens (tamoxifen, fulvestrant) and aromatase inhibitors, have also demonstrated activity among patients with advanced or recurrent endometrial cancer, with response rates of ~10% in second-line, usually after administration of a progestin. Patients with visceral involvement and rapidly progressive disease are not candidates for hormone therapy, and chemotherapy should be considered. Endometrial cancer is a relatively chemo-sensitive disease, with anthracyclines, platinum-based drugs and taxanes shown to be the most active. When chemotherapy is indicated, the standard of care is 6 cycles of three-weekly paclitaxel and carboplatin (TC), as randomized trial GOG209 showed similar efficacy and less toxicity of TC compared to the triplet of paclitaxel/cisplatin/doxorubicin (TAP). Evidence supporting the use of second-line chemotherapy after platinum-containing therapy in patients with endometrial cancer is very limited, and no specific regimen can be recommended as a standard of care for second-line chemotherapy (1,2).

Although endometrial endometrioid adenocarcinomas are hormone-dependent endocrine treatment with an AI is well established, the efficacy of AI is modest. Targeting cell-cycle checkpoints is an increasingly used treatment modality. Cyclin (CDK) is involved in the transition from G1 to S phase of cell cycle. Its activity can be inhibited by palbociclib, a selective inhibitor of the CDKs 4/6. This is a rationale to conduct the ENGOT-EN3/NSGO-PALEO study, the first global randomised trial to evaluate the efficacy of a CDK4/6 inhibitor in combination with an AI in patients with advanced or recurrent ER-positive endometrial cancer, after progression on ≥1 prior systemic therapy. Compared with placebo plus letrozole, the combination of palbociclib plus letrozole demonstrated clinically meaningful improvement in PFS (median PFS 3.0 vs 8.3 months, HR 0.56, p=0.0376), with manageable toxicity of palbociclib plus letrozole combination and no detrimental effect on quality of life (3).

Over the last 15 years, the knowledge in the field of molecular biology of endometrial cancer has expanded significantly, and recently the The Cancer Genome Atlas (TCGA) Research Network performed an integrated genomic characterisation of endometrial carcinoma. Results of TCGA classified endometrial cancers into four categories: POLE ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high, with the POLE subtype associated with the best and copy-number high subtype with the worst prognosis. Although there are a large number of specific gene abnormalities and aberrant signaling pathways that appear to

be promising targets, the results with PI3K and mTOR inhibitors, as well as with tyrosine kinase inhibitors – antiangiogenic agents in recurrent endometrial carcinoma are disappointing.

Recently, the scope of immunotherapy in endometrial cancer has been intensively investigated. Immune checkpoint inhibitors, PD-1/PD-L1 inhibitors, have been shown active in metastatic mismatch-repair deficiency (MMRd) cancers in first clinical studies. In KEYNOTE-028 study, pembrolizumab (a monoclonal antibody targeting programmed cell death receptor 1 (PD-1)) demonstrated a favorable safety profile and durable antitumor activity (ORR 36%, PR 13%) in a subgroup of patients with heavily pretreated advanced PD-L1-positive EC. In GARNET study, dostarlimab (anti-PD-1) demonstrated clinically meaningful response rates regardless of MSI status, with an ORR of 30% (49% in the MSI-H cohort and 20% in the MSS cohort) in patients with advanced or recurrent endometrial carcinoma.

Levantinib is an orally available multikinase inhibitor of VEGFRs 1-3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT. In KEYNOTE-146/Study 111, the combination of lenvatinib plus pembrolizumab showed very promising antitumor activity in patients with advanced endometrial carcinoma who have experienced disease progression after prior systemic therapy, regardless of tumor MSI status (4). These result supported the FDA approval for the combination of pembrolizumab plus levantinib for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. KEYNOTE-775, a randomized, open-label, phase 3 study, is currently being conducted to evaluate efficacy and safety of pembrolizumab plus lenvatinib combination vs treatment of physician's choice in patients with advanced/recurrent endometrial carcinoma. Based on the very promising activity of immune checkpoint inhibitors in patients previously receiving systemic therapy for advanced stage of endometrial carcinoma, phase 3 double-blind AtTEnd study was initiated to evaluate the efficacy of atezolizumab in combination with paclitaxel and carboplatin as front-line therapy in patients with advanced/recurrent endometrial carcinoma.

Uterine serous carcinoma (USC) is a clinically aggressive type of uterine cancer, responsible for a disproportionate incidence of advanced stage disease, recurrences and deaths. Serous endometrial cancers are characterized by alterations of HER2 gene and 25-30% of patients with USC have HER2-positive disease. Addition of trastuzumab to chemotherapy carboplatin/paclitaxel increased PFS and OS in women with advanced/recurrent HER2-positive USC, with the greatest benefit seen for the treatment of stage III to IV disease (5).

Although uncommon at initial diagnosis, metastatic disease will develop in 15-61% women with cervical cancer, usually within the first two years of completing treatment. Recurrent and/or metastatic cervical cancer remains a significant cause of mortality in women. Metastatic or recurrent cervical cancer is usually a symptomatic and devastating situation for the patient and the main objective of systemic therapy is to relieve symptoms and improve quality of life. For two decades, cisplatin was standard of care as it is considered the most active cytotoxic agent in cervical cancer; however, the global efficacy was disappointing due to a low response rate (20%), short median PFS (2.8–3.2 months) and OS (6.2–8.0 months). Cisplatin-based doublets with topotecan or paclitaxel have demonstrated superiority to cisplatin monotherapy in terms of response rate and PFS, but only a large randomised phase 3 trial GOG204, comparing four different cisplatin-based doublets, definitely established cisplatin/paclitaxel as preferred chemotherapy regimen in recurrent and metastatic cervical cancer (6). Addition of the antiangiogenics drug

bevacizumab to chemotherapy enabled improvement in response rate (ORR 50%) and overall survival in GOG 240 study, and in 2014. the FDA approved bevacizumab for women with advanced cervical cancer. Updated OS analysis demonstrated the sustained clinically meaningful survival benefit of bevacizumab-based therapy over chemotherapy only (median OS 13.3 vs 16.8 months; HR 0.765, p=0.0068) (7). Thus, paclitaxel and cisplatin combined with bevacizumab is considered the preferred first-line regimen in metastatic or recurrent cervical cancer based on the balance between efficacy and toxicity profile.

Further research was aimed at answering whether it was immunotherapy the next frontier in cervical cancer. KEYNOTE-158 is a phase 2 basket study investigating the antitumor activity and safety of pembrolizumab in multiple cancer types. In patients with previously treated advanced cervical cancer, pembrolizumab was associated with an ORR of 14.6% (CR 3%) with responses observed only in patients with PD-L1–positive disease (8). On the basis of these results, showing that pembrolizumab monotherapy demonstrated durable antitumor activity and manageable safety in patients with advanced cervical cancer, FDA granted accelerated approval of pembrolizumab for patients with advanced PD-L1–positive cervical cancer who experienced progression during or after chemotherapy. In CheckMate 358 phase 1/2 study in patients with HPV-associated tumors, nivolumab has demonstrated promissing efficacy (ORR 26.3%) in patients with metastatic cervical cancer who had received prior systemic therapy for metastatic disease (9).

Tisotumab vedotin is an investigational antibody-drug conjugate directed to tissue factor (TF) and covalently linked to the microtubule-disrupting agent MMAE via a protease-cleavable linker. TF is highly prevalent in cervical cancer and is associated with poor prognosis. Tisotumab vedotin has multiple anti-tumor effects. In InnovaTV 204 study patients with recurrent or metastatic cervical cancer with disease progression on or after doublet chemotherapy with bevacizumab and ≤2 prior systemic regimens received tisotumab vedotin until disease progression or unacceptable toxicity. The results were presented at ESMO2020 virtuel congress: Tisotumab vedotin demonstrated compelling (ORR: 24%; CR: 7%) and durable (median DOR: 8.3 months) antitumor activity in recurrent and/or metastatic cervical cancer previously treated with doublet chemotherapy with bevacizumab (if eligible); median PFS (4.2 months) and OS (12.1 months) are encouraging; tisotumab vedotin had a manageable and tolerable safety profile (10). Thus, tisotumab vedotin is a potential novel treatment for women with previously treated recurrent and/or metastatic cervical cancer.

In conclusion, there are limited standard treatment options in women with advanced or recurrent endometrial and cervical cancer. However, knowledge and therapeutic options that could improve outcomes in patients with advanced or recurrent endometrial and cervical cancer are rapidly increasing and progress is underway.

References

1. Colombo N, Creutzberg C, Amant A et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016;27:16–41.
2. Brooks R, Fleming G, Lastra R et al. Current recommendations and recent progress in endometrial cancer. CA Cancer J Clin. 2019; 69:258-79.
3. Mirza MR, Bjørge L, Marmé F et al. A randomised double-blind placebo-controlled phase II trial of palbociclib combined with letrozole in patients with oestrogen receptor-positive advanced/recurrent endometrial cancer ENGOT-EN3/NSGO-PALEO. Ann Oncol. 2020;31 Suppl 4: S1142-S1215.
4. Makker V, Taylor MH, Aghajanian C et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. J Clin Oncol. 2020;38:2981-92.
5. Fader A, Roque D, Siegal E et al. Randomized phase II trial of carboplatin-paclitaxel compared with carboplatin-paclitaxel-trastuzumab in advanced stage (stage III-IV) or recurrent Uterine Serous Carcinoma that overexpress HER2/Neu (NCT01367002): Updated overall survival analysis. Clin. Cancer Res. 2020;26:3928-35.

6. Marth C, Landoni F, Mahner S et al. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28 Suppl 4: iv72–iv83.
7. Tewari K, Sill M, Penson R et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet 2017;390:1654-63.
8. Chung HC, Ros W, Delord JP et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: Results from the Phase II KEYNOTE-158 Study. J Clin. Oncol. 2019; 37:1470-78.
9. Naumann RW, Hollebecque A, Meyer T et al. Safety and efficacy of Nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar Carcinoma: Results from the Phase I/II CheckMate 358 Trial. J Clin Oncol. 2019;37:2825-34.
10. Coleman RL, Lorusso D, Gennigens C et al. Tisotumab vedotin in previously treated recurrent or metastatic cervical cancer: Results from the phase II innovaTV 204/GOG-3023/ENGOT-cx6 study. Ann. Oncol.2020;31 Suppl 4:S1142-S1215.

Ljiljana Stamatovic, MD, PhD, is senior medical oncologist at the Institute for Oncology and Radiology of Serbia, specialising in breast and gynecological cancer research and treatment. Currently she serves as the Head of Medical Oncology Department for breast and gynecological cancers. Dr Stamatovic participates in the regular (on every-day basis) and expert committees for breast and gynecological cancers. Her research interests include targeted and investigational therapeutics in the treatment of breast and gynecological tumors. She was invited lecturer on ESO, ESMO, ESGO courses and many national oncology meetings with international participation. She has notably experience in conducting numerous international clinical trials. Dr Stamatovic is a member of several societies, including European Society for Medical Oncology, American Society of Clinical Oncology, European Society of Gynecological Oncology and Association of Clinical Research Professionals. She participated in the development of national Clinical Practice Guidelines for breast, cervical and ovarian cancer, under the guidance of Ministry of Health of Serbia. Dr Stamatovic has contributed to more than 120 publications, of which 40 are peer-reviewed, and she is an author of several chapters in national monographs.

UROGYNECOLOGY & RECONSTRUCTIVE SURGERY

POSTERIOR COMPARTMENT PELVIC DISORDERS

Prof. Adolf Lukanovič

President of the Slovene Association of Gynecologists and Obstetricians
Chairman of the Division of Gynecology and Obstetrics, Ljubljana University Medical Center
Faculty of Medicine, University Medical Centre Ljubljana, Slovenia

Posterior pelvic floor compartment disorders generally refer to functional anorectal disturbances that by definition are symptom-based rather than anatomical defect–based. They represent a range of functional disorders that frequently occur in adult women, with a significant burden on the quality of life, and their incidence tends to increase in line with the expected aging of the population. Pelvic floor dysfunctions can manifest as incontinence, constipation, and prolapsed pelvic organs. The pelvic floor is divided into three anatomical compartments—anterior, middle, and posterior—connected by structures responsible for pelvic support. Craniocaudally, these are the endopelvic fascia, the pelvic diaphragm, and the urogenital diaphragm. The pelvic floor works as a single entity, and pelvic weakness is frequently generalized, affecting more than one compartment. Although prolapses may coexist with relaxation or laxity of the pelvic support structures, and themselves may induce functional disorders from external compression, pelvic prolapses can be independent from functional disorders (1). Because pelvic floor weakness is frequently generalized and clinically underdiagnosed, imaging evaluation is of major importance, especially prior to surgical correction.

Posterior vaginal prolapse, also known as a rectocele, occurs when the wall of fibrous tissue that separates the rectum from the vagina weakens. When this happens, tissues or structures just behind the vaginal wall—in this case, the rectum—can bulge into the vagina. Rectoceles become important when they are symptomatic, being responsible for incomplete evacuation and obstruction. Small rectoceles may be entirely asymptomatic in as many as 80% of patients. Known risk factors include vaginal birth trauma, as well as constipation with chronically increased abdominal pressure (2). With dynamic cystoproctography it is possible to determine the frequency of associated urinary, genital, and anorectal abnormalities in women with pelvic floor dysfunction. Although patients may present with symptoms that involve only one compartment, a multicompartment prolapse is usually revealed on dynamic cystoproctography. Of the patients with pelvic floor dysfunction, 95% had abnormalities in all three compartments. If the posterior vaginal prolapse causes few or no symptoms, simple self-care measures—such as performing Kegel exercises to strengthen the pelvic muscles—may provide relief. A vaginal pessarya - plastic or rubber ring inserted into the vagina to support the bulging tissues—may also relieve the unpleasant symptoms.

Surgery is indicated if the prolapse is causing pain, if there are problems with the urinary bladder and bowel, or if the prolapse make it difficult for the patient to do activities she enjoys. An organ can prolapse again after surgery. Surgery in one part of the pelvis can exacerbate a prolapse in another part (3).

Although posterior vaginal compartment prolapse and defecatory dysfunction are highly prevalent conditions in women with pelvic floor disorders, the relationship between anatomy and symptoms, specifically obstructed defecation, is incompletely understood and remains debatable. A clinically useful classification system for defecatory dysfunction is justified. Tools for measuring symptoms, physical findings, and imaging in women with posterior compartment

prolapse are obligatory. However, it is well recognized that pelvic floor symptoms originating from one compartment do not imply absent pathology in another compartment. Furthermore, symptoms associated with one disorder (such as constipation related to functional obstructed defecation) can be causative in the sequential development of other pelvic floor disorders, such as a urogenital prolapse syndrome, which may further exacerbate symptoms. In addition, it has been found that treatment that corrects one problem may improve, worsen, or even predispose to other symptoms from another compartment. Consequently, although the concept of global pelvic floor dysfunction has emerged, the traditional single-specialty referral and evaluation of pelvic floor problems continues to foster potentially segregated management strategies that can overlook the relevance of concomitant symptomatology.

The main dilemmas proposed for future exploration are dealing with the association between posterior vaginal wall prolapse and defecation symptoms. They are divided into three topics: 1) Does prevalence of defecation symptoms increase along with posterior wall prolapse severity? 2) Is postoperative symptom improvement greater in women that underwent posterior compartment procedures in comparison with those that did not? and 3) Is symptom improvement related to the symptom's correlation with the degree of prolapse?

The stage of posterior wall prolapse (stage 2 vs. stage 0) is correlated with splinting, straining, incomplete evacuation, fecal incontinence of liquid stool, pain during defecation, fecal urgency, and anorectal prolapse. Obstructed defecation symptoms (splinting, straining, and incomplete evacuation) improved more in women undergoing posterior compartment surgery compared with women undergoing repair for other compartments (4).

For women presenting with posterior wall prolapse, these symptoms can be expected to improve after surgery. Other defecation symptoms also improve after pelvic organ prolapse surgery, but they are not as specific to posterior wall anatomy as obstructed defecation symptoms.

MR defecography allows a noninvasive, radiation-free, multiplanar dynamic evaluation of the three pelvic compartments simultaneously and with high spatial and temporal resolution. Both static/anatomic and dynamic/functional findings are important because pelvic disorders can manifest as whole pelvic floor weakness/dysfunction or as an isolated or single compartment disorder. Imaging has a preponderant role in accessing pelvic floor disorders, and dynamic MR defecography is a reliable option, being able to evaluate the entire pelvic floor for optimal patient management before surgery (5).

The evaluation and treatment of posterior pelvic compartment disorders needs to assume an individualized but multidisciplinary therapeutic approach. Given the variation in surgical approaches described to correct anatomical integrity of posterior pelvic compartment deficits, a consensus on optimal management has yet to be achieved. Therefore, it is critical that outcome measures following surgery be clearly defined. Treatment is to a great extent dictated by functional severity and the impact that symptoms have on quality of life. Long-term follow-up should ensure that the potential for complications is minimized and that satisfactory bowel, bladder, and sexual function is maintained (6).

Although this compartmentalization is relevant to systematize these conditions, it is also in part responsible for the frequent therapeutic failure associated with these surgical procedures because the pelvic floor functions as a single entity, and pelvic weakness is frequently generalized, affecting more than one compartment even though it may be clinically silent. In addition, clinical evaluation still underestimates or misdiagnoses pelvic organ prolapses in as many as 45 to 90% of cases (1, 6).

This becomes even more important when surgical intervention is considered, especially when a single compartment correction is done. Recurrence rates range from 10 to 30% in these patients, mostly related to other pelvic compartments that were not initially assessed or repaired. It is estimated that 30% of all surgeries performed in these women are reoperations after unsuccessful treatments. Nowadays, the surgical approach is to perform all the necessary corrections in one intervention (7, 8) in order to prevent future relapse or exacerbation of other pelvic dysfunctions that may initially be associated. One of these attempts is laparoscopic rectopexy, in which the prolapsed uterus or vaginal vault and rectocele are corrected in one surgery. The posterior half of the Y mesh is divided into two arms, and the posterior arm is fixed onto the anterior rectal wall.

To conclude, let us recall what the famous American gynecological surgeon Richard W. Te Linde observed late in his career: “Every honest surgeon of extensive and long experience will have to admit that he is not entirely and absolutely satisfied with his long-term results of all his operations for prolapse and allied conditions” (1966).

References

1. Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol. 1997; 89(4):501–6.
2. Luber KM, Boero S, Choe JY. The demographics of pelvic floor disorders: current observations and future projections. Am J Obstet Gynecol. 2001;184(7):1496–503.
3. Nygaard IE, Kreder KJ. Complication of incontinence surgery. Int Urogynecol J. 1994;5:353–60.
4. Mortele KJ, Fairhurst J. Dynamic MR defecography of the posterior compartment: indications, techniques and MRI features. Eur J Radiol. 2007;61:462–72.
5. Maglinte DD, Kelvin FM, Fitzgerald K, Halo DS, Benson JT. Association of compartment defects in pelvic floor dysfunction. AJR Am J Roentgenol. 1999;172:439–44.
6. Pannu HK, Javitt MC, Glanc P, et al. ACR appropriateness criteria pelvic floor dysfunction. J Am Coll Radiol. 2015;12:134–42.
7. Fielding JR. Practical MR imaging of female pelvic floor weakness. Radiographics. 2002; 22:295–304.
8. Fengler SA, Pearl PK, Prasad ML, et al. Management of recurrent rectal prolapse. Dis Colon Rectum. 1997;40:832–34.

.

Adolf Lukanovič has been employed by the Gynecology and Obstetrics Division at the Ljubljana University Medical Center since 1982. He has been a gynecology and obstetrics specialist since 1986. In 1988 he became the head of the division’s Urogynecology Department, and in 2006 he became the head of its Gynecology Department. Between 2008 and 2020 he was medical director of the Gynecology and Obstetrics Division at the Ljubljana University Medical Center.

He received his master’s degree in urogynecology at the University of Zagreb School of Medicine with the thesis Mikcijske motnje in urodinamske spremembe po radikalni histerektomiji (Micturition Disorders and Urodynamic Changes after Radical Hysterectomy). In 1988 he defended his doctoral dissertation, Pomen ultrazvočne preiskave v diagnostiki in zdravljenju stresne urinske inkontinence (The Importance of Ultrasound Examination in Diagnosing and Treating Stress Urinary Incontinence), and he was awarded a medical doctorate in gynecology.

In 2000 the Slovenian Ministry of Health conferred upon him the title of adviser for his professional, organizational, teaching, and research contributions to the field, and in 2019 he

was awarded the title of senior medical adviser. In 2017 he was promoted to full professor of gynecology and obstetrics at the University of Ljubljana Faculty of Medicine.

Adolf Lukanovič's research deals with new methods for surgical treatment in gynecology, especially in terms of introducing minimally invasive surgical procedures, urological complications following radical gynecological surgery, and, first and foremost, new methods of treating urinary incontinence in women, including the use of laser photothermal therapy, which has been his most recent interest. He introduced the TVT procedure into routine clinical practice for treating urinary incontinence in women in Slovenia, as well as the use of synthetic mesh in reconstructive surgery for treating pelvic organ prolapse.

He has lectured as a visiting professor at medical schools in Sarajevo, Belgrade, Skopje, Rijeka, Udine, Novara, Pleven, London, Doha, and Bahrain.

Adolf Lukanovič is the chairman of the Slovenian Association of Gynecologists and Obstetricians. In 2004 he founded the Slovenian Urogynecology Society and he became its first chairman the same year. Since 2007 he has been a board member of the Slovenian Menopause Society, he has served two terms as chair of the Slovenian College of Gynecology and Obstetrics, he has served two terms as a member of the medical board, and since 2015 he has been a member of the professional advancement committee at the Ministry of Health. Since 2019 he has been the chairman of the Ljubljana University Medical Center's Ethics Committee and an external member of the Slovenian Medical Ethics Committee.

He is a founding member of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) and a member of the International Urogynecological Association (IUGA), where he served one term as the representative for Europe on the international advisory board. He is a founding member of the Mediterranean Incontinence and Pelvic Floor Society (MIPS) and chairman of its Training Committee. He has been the general secretary of the MIPS since December 2015. Since 2019 he has been the chairman of the accreditation committee at the European Urogynaecology Association (EUGA). He is a member of the Slovenian Medical Association (SZD), European Congress of Obstetrics and Gynaecology (EBCOG), International Continence Society (ICS), European Society of Gastrointestinal Endoscopy (ESGE), and European Association of Gynaecologists and Obstetricians (EAGO).

UROGYNECOLOGY IMPLANTS: COMPLICATIONS AND RECOMMENDATIONS

Ass. Dr sci Sveto Pantović

Klinika za ginekologiju i akušerstvo Kliničkog centra Srbije

Transvaginal mesh is a medical device implanted into women's pelvic areas through the vagina to treat weakened pelvic muscles resulting from pelvic organ prolapse, known as POP, and stress urinary incontinence, known as SUI. The development of mesh took decades since the 1950's. In 2008. , FDA announced that complications for both POP and SUI are rare. In the following years. this data was reevaluated.

The procedure is usually performed transvaginally. In 2010, 75 % of POP surgery has been completed transvaginally, as well as 80 % of SUI surgery.

Several basic principles of mesh are:

- Restore anatomy of the pelvis
- Return normal function of pelvic organs
- Improve quality of life for patients

Mesh has its complications, and the most common are urinary retention or prolonged voiding disorder exposure of the device, pelvic pain, fistulas etc. The data consists of over 190 articles reporting complications after the use mesh in gynecologic surgery from 1993 to 2019.

The number of complications resulted in different types of mesh, concerning the material used for its productions as well as pore size in the mesh. Investigators concluded that mesh design, its material, route of implantation, surgical experience are the most valuable factors in reducing the number of procedure complications.

Therefore, patients should be adequately informed regarding the potential success rate and mesh-related adverse events compared with non-mesh alternatives, and should be engaged in the decision-making process.

Dr Sveto Pantović, specijalista ginekologije i akušerstva, rodjen je 1965. godine. Diplomirao je 1990. na Medicinskom fakultetu u Beogradu, Zaposlen je na Klinici za ginekologiju i akušerstvo Kliničkog centra Srbije od 1992.godine. Specijalistički ispit položio je sa odličnim uspehom 1996.godine. Magistarsku tezu pod nazivom – »Primena ekscizije LOOP dijatermijom i lečenju premalgnih promena grlića materice« odbranio je na Medicinskom fakultetu u Beogradu 1999. godine. Doktorsku disertaciju pod nazivom – »Značaj hirurškog postupka u lečenju karcinoma jajnika« odbranio je 2004. godine na Medicinskom fakultetu u Beogradu.

Na mesto načelnika operacionog bloka Klinike za ginekologiju i akušerstvo KCS postavljen je od 2005. godine. Član je Konzilijuma za uroginekološke bolesti KGA KCS od 2005. godine. Nosilac je i koautor više radova objavljenih na domaćim i medjunarodnim stručnim skupovima, najviše iz oblasti ginekološke onkologije i ginekološke urologije.

KOMPARACIJA ISHODA LEČENJA POP-A SA I BEZ APLIKACIJE MESH-A (NATIVE TISSUE VS MESH REPAIR)

Prim. Snežana Buzadžić

Potpredsednik Srpske Uroginekološke asocijacije (SUGA)
Klinika za ginekologiju i akušerstvo, Klinički Centar Srbije, Srbija

Kod spada vaginalnih zidova u donju polovinu vagine, vaginalna histerektomija sa reparacijom spada prednjeg i zadnjeg vaginalnog zida neće dati zadovoljavajuće rezultate u pogledu dubine vagine i neće sprečiti ponovnu pojavu prolapsa vaginalnih zidova. U takvim slučajevima neophodno je primeniti postupak koji će obezbediti suspenziju svodova vagine kao što je transvaginalna sakrospinalna kolpopeksija i MESH (kao tercijerna tehnika).

Indikacije za suspenziju svodova vagine su prolaps prednjeg ili zadnjeg vaginalnog zida, totalni prolaps genitalnih organa, everzija vagine posle vaginalnih i abdominalnih histerektomija (kod 0,5% pacijentkinja).

Rizik od operacije i reoperacije javlja se zbog slabosti pelvičnog tkiva koja je uzrokovana genetskim, traumatskim i mehaničkim faktorima koji su udruženi sa seksualnom aktivnošću, nezavisno od starosne dobi. U opštoj ženskoj populaciji se javlja kod 11% pacijentkinja. Neuspeh prve operacije tokom 5 godina je 29% (13-56% o.ž.p.).

Za aplikaciju MESH-a, kao tercijerne tehnike, se odlučujemo da bi se uradila adekvantna rekonstrukcija, obnovila anatomija male karlice, povrati normalna funkcija karličnih organa, sprečiti recidive POP i urinarne probleme i poboljšati kvalitet života pacijentkinja.

Krajem devedesetih ugradni materijal (MESH Anterior et Posterior) ulazi u upotrebu u uroginekologiji. Prva upozorenja o komplikacijama, zbog upotrebe polypropylen-a, javlja se posle 2008. godine. Smanjenje teče polako. U mnogim zemljama je trend da se koriste gde ne postoji druga opcija i da postoji individualni pristup prema pacijentu.

Ugradni materijal na KGA KCS u upotrebi u uroginekologiji od 2006. godine.

Komplikacije MESH su retencija urina, poremećaj pražnjenja i obstruktivni simptomi, MESH ekspozicija – asimptomatska i simptomatska, erozija mokraćne bešike i rektuma, bol, hematom, dispareunia, disfunkcija creva, fistula, sacral osteomyelitis or discitis, rekurentni POP, potpune seksualne i fiziološke disfunkcije, stalna bol koja se pojačava u toku seksualnog kontakta, narušavanje intime i privatnog života.

Evropska komisija 2015. godine je zaključila da se mrežice koriste kada klasična hirurgija nema uspeha. Australija i Novi Zeland 2017. godine su zabranili upotrebu ugradnog materijala. Nacionalni Institut za zdravlje Velike Britanij objavio je 2017. godine da bi mrežice trebalo zabraniti jer nisu garancija za trajno rešenje, a komplikacije su veoma ozbiljne. Ministarsvo zdravlja Škotske, septembar 2018. godine, napravljen protokol za upotrebu MESH-a.

Američka organizacija za hranu i lekove, april 2019. godine, zabranila upotrebu ugradnog materjala zbog stalnog bola. Problem inkontinencije ostao je bez rešenje. Sada je na istraživačima da nađu neka nova rešenja.

Literatura

1. Ow LL, Lim YN, Dwyer PL, Karmakar D, Murray C, Thomas E, Rosamilia A. Native tissue repair or transvaginal mesh for recurrent vaginal prolapse: what are the long-term outcomes? Int Urogynecol J. 2016 Sep;27(9):1313-20.
2. Ow LL, Lim YN, Dwyer PL, Karmakar D, Murray C, Thomas E, Rosamilia A. Native tissue repair or transvaginal mesh for recurrent vaginal prolapse: what are the long-term outcomes? Int Urogynecol J. 2016 Sep;27(9):1313-20.
3. Dallas KB, Rogo-Gupta L, Elliott CS. What Impacts the All Cause Risk of Reoperation after Pelvic Organ Prolapse Repair? A Comparison of Mesh and Native Tissue Approaches in 110,329 Women. J Urol. 2018 Aug;200(2):389-396.
4. Jonsson Funk M, Visco AG, Weidner AC, Pate V, Wu JM. Long-term outcomes of vaginal mesh versus native tissue repair for anterior vaginal wall prolapse. Int Urogynecol J. 2013 Aug;24(8):1279-85.
5. Allègre L, Callewaert G, Alonso S, Cornille A, Fernandez H, Eglin G, de Tayrac R. Long-term outcomes of a randomized controlled trial comparing trans-obturator vaginal mesh with native tissue repair in the treatment of anterior vaginal wall prolapse. Int Urogynecol J. 2020 Apr;31(4):745-53.

Snežana Buzadžić je Primarius i specijalista ginekologije i akušerstva; subspecijalista onkologije; šef odseka za uroginekologiju; Načelnik Odeljenja intenzivne nege; Klinika za ginekologiju i akušerstvo, Klinički centar Srbije.

Visiting doctor u Hopital de Latur, Dept. Gynecologie/Obstretique, 3 Ave J.D. Maillard, Meyrin, Geneve, Suisse u Operativnom bloku opšte hirurgije, ginekologije i laparoskopske hirurgije u tri perioda: 11.02 - 11.04.99/ 15.04 - 15.06.00/ 20.12- 20.02.01.

A COMBINED APPROACH FOR TREATING URINARY INCONTINENCE: MAGNETIC STIMULATION AND ER: YAG LASER TREATMENT

Asist. David Lukanović

Division of Gynecology and Obstetrics, University Medical Center Ljubljana, Slovenia

Uncontrolled leakage of urine, or urinary incontinence (UI), is a pelvic floor dysfunction (PFD) and is defined as any involuntary urine leakage. The etiology of incontinence is multifactorial and is based on the basic pathophysiological mechanisms that cause it. The condition is roughly divided into stress, urge, mixed, and overflow incontinence. Stress urinary incontinence (SUI) is a common complaint in women after childbirth. It affects their quality of life (QoL) and sexual satisfaction, and it is one of the major reasons for gynecological surgery. Our department emphasizes stepwise treatment and the importance of conservative and non-surgical treatment. Surgery is recommended only after all conservative treatment options have been exhausted.

The pelvic floor is a highly complex structure made up of skeletal and striated muscles, support and suspensory ligaments, fascial coverings, and an intricate neural network. In order to maintain good pelvic floor function, this elaborate system must work in a highly integrated manner. One must also be aware that diagnosing different kinds of UI is not particularly clear and accept the fact that more than one-third of UI is mixed UI. When treating patients with SUI with magnetic stimulation, the targets are the pelvic and pudendal nerves, and consequently the external sphincters and the pelvic floor muscles. Many published studies have shown a decrease in UI symptoms and an improvement in individual patients' QoL. This method can also be used for conservative treatment of patients with UI that may not be motivated to perform regular exercises to strengthen their pelvic floor muscles. The most recent meta analysis, which was carried out in 2019 by Qing He et al., concludes that treatment with magnetic stimulation is an effective therapeutic option for patients with UI.

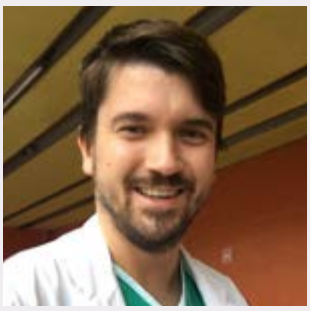
In addition to strengthening the pelvic floor muscles, laser treatment can also be included in the overall treatment of patients with SUI. In 2019, Health Canada was the first government health agency in the world to approve laser treatment for SUI, vulvovaginal atrophy, and genitourinary syndrome of menopause. Altered collagen/elastin in the vaginal connective tissue may result in loose insertions of the striated muscles involved in the pelvic floor closure mechanism, preventing their isometric contraction, and therefore efficient functioning of the closure, causing stress incontinence. Collagen content is diminished in incontinent women. Temporarily increasing the temperature of collagen induces collagen shrinkage and initiates neocollagenesis, leading to contraction and shrinkage of the irradiated bulk tissue and an overall improvement of its tightness and elasticity. Non-ablative Er:YAG laser treatment for SUI is a fast, simple, and well-tolerated procedure that effectively improves incontinence-related QoL and sexual function. It is a promising minimally invasive treatment option for SUI that, after further optimization, could reduce the need for surgery. Although many studies have confirmed both subjective and objective improvement in patients with SUI, the IUGA still cautions against the use of laser treatment in everyday clinical practice because of a lack of high-quality evidence in the form of multicenter, randomized, placebo-controlled studies.

The rise in publications in journals on the topic of pelvic floor dysfunction and its treatment with magnetic stimulation and laser suggests that such treatments are increasingly recognized

as an important new nonsurgical approach. It is hoped that advances in understanding the epidemiology and pathophysiology of PFD, as well as the development of new patient-friendly therapies, will lead to advances in prevention, management, and therapy for patients with any kind of UI.

References

1. Downey A, Inman RD. Recent advances in surgical management of urinary incontinence. 2019. F1000Research, 8, F1000 Faculty Rev-1294.
2. Burkhard FC, (Chair) Bosch JLHR, Cruz F, et al. EAU guidelines on urinary incontinence in adults. 2020.
3. Blaganje M, Šćepanović D, Žgur L, Verdenik I, Pajk F, Lukanović A. Non-ablative Er:YAG laser therapy effect on stress urinary incontinence related to quality of life and sexual function: a randomized controlled trial. Eur J Obstet Gynaecol Reprod Biol. 2018; 224:153-8.
4. He Q, Xiao K, Peng L, Lai J, Li H, Luo D, Wang K. An effective meta-analysis of magnetic stimulation therapy for urinary incontinence. Sci Rep. 2019; 9(1):9077
5. Kunič T, Lugovski S, Lukanović D, Cvetkov D, Barbič M. Magnetic stimulation in the treatment of urinary incontinence in gynecological practice. Akušerstvo i ginekologija. 2017;56(10):24-30.
6. Phillips C, Hillard T, Salvatore S, Toozs-Hobsone P, Cardozo L. Lasers in gynecology. Eur J Obstet Gynecol Reprod Biol. 2020;251:146-55.



David Lukanovič is resident of gynecology and obstetrics at Division of Gynecology and Obstetrics, Ljubljana University Medical Center, Ljubljana, Slovenia. Scientific Field of Expertise: Ovarian cancer, Pelvic floor dysfunction.

As a young researcher, he is involved in main research projects of the department mostly dealing with pelvic floor dysfunction and ovarian cancer. He was a member of pioneer group evaluating the use of magnetic stimulation for the treatment of female and male urinary incontinence and pelvic pain in Slovenia and in the South-East Europe region. Beside this, I am currently member of the European International research group evaluating the use of Er-YAG laser for the treatment of stress urinary incontinence and vaginal rejuvenation.

Member of programme council Interdisciplinary doctoral programme in BIOMEDICINE, University Ljubljana. Member of commission for doctoral degree, Faculty of Medicine, University Ljubljana. Coordinator of Doctors – Interns in University Medical Center, Ljubljana.

MESH OR MESS? CONTROVERSY IN GRAFT VAGINAL SURGERY

Dr. Miloš Radović

Vice President of Serbian Urogynecological association (SUGA)
Head of one day surgery department, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia

MESH vaginal surgery is surgical procedure resolving POP pathology with prevention of recurent postoperative apical prolapse. There are aprox. 60 diferent types/modifications of mesh surgery interventions all arround the world.

Seventeen years of patient clinical folow up in combined retrospective and prospective study. Including 463 mesh and sling SUI procedure and 551 vaginal colposuspension! Investigating wich is the best and safest way to perform an aplication of mesh? With description of surgical procedures performed on KGA KCS. Determining is there a necessity of involving mesh in every surgical procedure resolving POP pathology?

Statistic data in our study has shown that anterior mesh singnificantly decreases the risk of recurent postoperative cystocela and apical prolaps! Burch Tanago and other ventero/ligamento fixation procedures with abdominal approach are most invasive. Laparoscopic mesh sacrocolphysteropexy is moderatly invasive. But it is time consuming and most expensive.

Vaginal approach is of course minimally invasive, shortest, simple to perform, with best cost/benefit ratio and with lowest percent of intra/post-operative complications! (Prof But, Prof Stark, Prof Kovak, Prof Bartoš, dr Radovic). Traditional Sacrospinal colpopexy has become the first choice surgical metod for eversion of vagina and for enterocella.

Aplication of mesh in anterior vaginal compartment and suburetral sling procedures are the safest surgical POP graft procedures associated with prevention of recurent postoperative apical/vaginal prolapse and resolving SUI pathology. Anterior mesh is an operative method of choice for large cystocella (stage 3 and 4) and should be always included in, recurent prolapses and postmenopausal (older) patients with poor tissue quality.

Posterior mesh procedure shows a high rate of complications and does not conclusively improve clinical outcomes over traditional non-mesh repair.

References

1. Rizvi RM, Chughtai NG. Graft and mesh use in vaginal surgery. J Pak Med Assoc. 2017 Dec;67(12):1895-900.
2. Morling JR, McAllister DA, Agur W, Fischbacher CM, Glazener CM, Guerrero K, et al. Adverse events after first, single, mesh and non-mesh surgical procedures for stress urinary incontinence and pelvic organ prolapse in Scotland, 1997-2016: a population-based cohort study. Lancet. 2017 Feb 11;389(10069):629-40.
3. Glazener CM, Breeman S, Elders A, Hemming C, Cooper KG, Freeman RM, et al. Mesh, graft, or standard repair for women having primary transvaginal anterior or posterior compartment prolapse surgery: two parallel-group, multicentre, randomised, controlled trials (PROSPECT). Lancet. 2017 Jan 28;389(10067):381-392.
4. Syed KK, Consolo MJ, Gousse AE. Anterior Vaginal Wall Prolapse Repair and the Rise and Fall of Transvaginal Mesh. Did We Come Full Circle? A Historical Perspective. Urology. 2020 Aug 20:S0090-4295(20)30998-5.

FREE COMMUNICATIONS

CYTOGENETIC STUDY IN COUPLES WITH RECURRENT IN VITRO FERTILIZATION (IVF) FAILURE

Dr. Milica Komnenić Radovanović, Dr. Bojana Petrović

Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade

Dr. Oliver Stojković

School of Medicine, University of Belgrade, Serbia

Constitutional chromosome abnormalities contribute to infertility leading to reproductive failure. Recurrent *in vitro* fertilization (IVF) failure is defined as the inability to establish pregnancy despite high quality embryo transfer (ET) after application of at least two consecutive IVF/intracytoplasmic sperm injection (ICSI)-ET procedures.

The aim of this study was to evaluate the incidence and type of chromosomal abnormalities that occurred in infertility patient population with recurrent in vitro fertilization (IVF) failure.

We evaluated karyotyping data collected from 50 couples (100 samples) who had undergone two or more unsuccessful IVF/ICSI cycles without the establishment of pregnancy. Chromosomal abnormalities were found in 9 (9%) cases. In five patients (5%) reciprocal (balanced) translocation was found, in three patients (3%) deletion of sex chromosome, and in one (1%) small supernumerary marker chromosome. In 5 female patients we found karyotype 45, XX, der(13;14)(q10;q10); 46, XX, t(1;6)(p24;p25); 46, XX, t(2;6)(q21;q21); mos 46, X, del(X)(q22 – q24)(46) / 46, XX(54); 46, X, del(X)(q26) and in 4 male patients karyotype 46, XY, t(1;2)(p34;p21); 46,XY, t(5;14)(q31.1;q32.1); 46, X, del(Y)(q11.2); 47, XY + sSMC. In 3 cases (3%) pericentric inversion of chromosome 9 was found.

Karyotyping is recommended as part of the work-up for repeated implantation failure in assisted reproduction. Moreover, we recommend chromosome analysis as a first step in an infertile couple evaluation. In chromosomally abnormal couples, there is a high likelihood of producing an embryo with chromosome abnormalities. Treatment options include further IVF trials, preimplantation genetic diagnosis, or oocyte donation, tailored according to the type of chromosomal change.

References

1. Ramasamy R, Besada S, Lamb DJ. Fluorescent in situ hybridization of human sperm: diagnostics, indications, and therapeutic implications. Fertil Steril. 2014 Dec;102(6):1534-9.
2. Mozdarani H, Meybodi AM, Zari-Moradi S. A cytogenetic study of couples with recurrent spontaneous abortions and infertile patients with recurrent IVF/ICSI failure. Indian J Hum Genet. 2008 Jan;14(1):1-6.
3. Kumar R, Tanwar M, Ammini AC, Kumar R, Gupta NP, Sharma RK, Dada R. Robertsonian translocation and their role in pathogenesis of recurrent in vitro fertilization failure. Med Sci Monit. 2008 Dec;14(12):CR617-20.
4. Raziel A, Friedler S, Schachter M, Kasterstein E, Strassburger D, Ron-El R. Increased frequency of female partner chromosomal abnormalities in patients with high-order implantation failure after in vitro fertilization. Fertil Steril. 2002 Sep;78(3):515-9.
5. Stern C, Pertile M, Norris H, Hale L, Baker HW. Chromosome translocations in couples with in-vitro fertilization implantation failure. Hum Reprod. 1999 Aug;14(8):2097-101.

KLINIČKA SLIKA APENDICITISA U PUERPERIJUMU KOD COVID-19 POZITIVNE PACIJENTKINJE

Dr Milan Lacković[1]

Prof. Vladimir Đukić[1,2], Ass.Predrag Savić[1,2], Dr Ivana Filipović[1], Ass. Slađana Mihajlović[1,2]

1 KBC "Dr Dragisa Misovic – Dedinje"
2 Medicinski Fakultet, Univerzitet u Beogradu, Srbija

Klinički simptomi apendicitisa u toku trudnoće i postpartalnog perioda su atipični i često se mogu preklapati s simptomima i znacima drugih oboljenja, poput infekcije mokraćnog sistema, torzije adneksa, tubo- ovarijalnog apscesa, tromboze vena jajnika, septični tromboflebitis karlice, pijelonefritis, holecistitis i puerperalnog endometritisa.

Drugorotka, starosti 33 godine, hospitalizovana je osam dana nakon porođaja u Bolnicu za Ginekologiju i akušerstvo KBC "Dr Dragiša Mišović - Dedinje" zbog povišene telesne temperature do 38.7 °C, kašlja i epidemiološkog podatka da je bila u kontaktu sa COVID-19 pozitivnom osobom. Iz medicinske dokumentacije dobijeni su podaci da je pacijentkinja rodila žensko novorođenče težine 4020 grama nakon pet sati porođaja. Na prijema pacijentkinja se žalila na nelagodnost u predelu trbuhu, mučninu, visoku temperaturu i suv, neproduktivan kašalj. Po prijemu pacijentkinja je u potpunosti klinički, labaratorijski i ultrazvučno ispitana i pregledana. Uzet je bris na COVID-19 infekciju. Ginekološkim pregledom utvrđena je blaga bolna osetljivost materice i Douglas-ovog prostora. Nije bilo adneksalne bolne nadražljivosti. Trbuh je bio lokalno bolno osetljiv, ali nije bilo znakova akutnog abdomena. Ultrazvuk male karlice otkrio je proširenost kavuma materice do 17 mm sa sadržajem ultrazvučnih karakteristikama suspektnih na postojanje rezidualnog tkiva i bez patoloških vaskularnih krvotoka. U Douglas-ovom prostoru vizualizovana je formacija veličine 130 × 85 mm bez vaskularnih protoka. Konsultovan je abdominalni hirurg koji je isključio postojanje akutnog apendicitisa. 24 časa nakon prijema u bolnicu pristigli su pozitivni rezultati briseva na COVID-19 infekciju. Pacijentkinja je upućena na radiografiju pluća, koja nije ukazivala na znakove pneumonije. Labaratorijske analize ukazivale su na znakove infekcije i anemije. Obzirom na ultrazvučni nalaz male karlice učinjena je instrumentalna revizija kavuma materice i ordinirana trojna antibiotska terapija. U toku narednog dana parametri infekcije i inflamacije dramatično su porasli, pacijentkinja je imala dijareju i navodila je konstantan abdominalni bol. Ponovljen je ultrazvučni pregled male karlice i konstatovano uvećanje formacije u Douglas-ovom prostoru. Obzirom na kliničku sliku, labaratorijske parameter i ultrazvučni nalaz, doneta je odluka da se učini eksplorativna laparoskopija. Eksploracijom abdomena i male karlice vizualizovan je perforirani apendiks kao i naslage gnoja i fibrinskih depozita među crevima, po utersu i u Douglas-ovom prostoru. Pozvan je abdominalni hirurg u konsultaciju i učinjena je apendektomija. Pacijentkinja je tretirana antibiotskom terapijom sedam dana nakon operacije. Petog postoperativnog dana ponovljeni su brisevi na COVID-19 infekciju i rezultati su bili negativni. Pacijentkinja je otpuštena osmog postoperativnog dana.

Mimikrija kliničke slike infekcije COVID-19 i gore navedenih simptoma upale slepog creva, kao i narušen imunološki balans u toku trudnoće i COVID-19 infekcije, otežavaju pravovremeno otkrivanje apendicitisa i otvaraju pitanje da li akutna virusna infekcija poput COVID-19 može pokrenuti akutnu appendicitis, obzirom da je etiologija oboljenja i dalje nerazjašnjena u potpunosti. Dijagnostikovanje apendicitisa i dalje predstavlja izazov u urgentnoj medicine u

postpartalnom period i u nejasnim kliničkim manifestacijama hirurški minimalno invazivni pristup je dijagnostičko- terapijski metod izbora.

Literatura

1. Mojhová M, Mikysková I, Dubová O, Homolková E, Mašek M, Zikán M. A case report of acute apendicitis in puerperium. Ceska Gynekol. 2019;84(5):341-4.
2. Wadhawan D, Singhal S, Sarda N, Arora R. Appendicitis in Postpartum Period: A Diagnostic Challenge. J Clin Diagn Res. 2015;9(10):QD10-1.
3. Moltubak E, Landerholm K, Blomberg M, Redéen S, Andersson RE. Major Variation in the Incidence of Appendicitis Before, During and After Pregnancy: A Population-Based Cohort Study. World J Surg. 2020;44(8):2601-8.

PRIMENA INDEKSA OPTIMALNOSTI U VANBOLNIČKOM PORODILIŠTU ROŽAJA

Dr Azra Lukač

Dom zdravlja Rožaje sa vanbolničkim porodilištem Rožaje

Dr Nenad Šulović[1], Dr Aleksandra Ilić[2]

1 Klinika za ginekologiju i akušerstvo, Medicinski fakultet, Univerzitet u Prištini sa sedištem u Kosovskoj Mitrovici
2 Institut za preventivnu medicine, Medicinski fakultet, Univerzitet u Prištini sa sedištem u Kosovskoj Mitrovici

Da bi se pripremili i stekli najbolji uslovi za vaginalni porođaj, praćenje, priprema, ocena i na kraju odluka o načinu završetka porođaja zahteva izuzetnu posvećenost pacijentu. Trudnoća nije patološka kategorija, ali jeste fiziološki izmenjeno (drugo) stanje i da bi taj period prošao što svrsishodnije potrebna je povećana kontrola stanja kako trudnice tako i ploda, kao i apsolutna saradnja i poverenje pacijenta i akušera. Iz praktičnih razloga, u svrhu praćenja i kontrole trudnoće koriste se opšta pravila, protokoli, algoritmi, upitnici, indeksi koji u znatnoj meri olakšavaju ovaj posao.

Brojna udruženja u svetu podržavaju mogućnost izbora da se žene, koje to žele, porode u vanbolničkim porodilištima ili čak u svom domu. Istovremeno lekari pozivaju na oprez jer sigurnost deteta i majke niko unapred ne može garantovati, čak i nakon uredne trudnoće. Procena potrebe i onoga što bi se moglo okarakterisati kao porođajni potencijal jeste osnova za donošenje pravilne odluke o porođaju i predstavlja početak pravilne medicinske zaštite.

Dok se većina porodjaja odvija u bolnickim centrima ili apartmanima za porodjaj, mali procenat (1,8% na nacionalnom nivou) odvija se u vanbolnickim centrima sa babicama.

Osnovu na kojoj bi se baziralo prećanje stanja pacijentkinje pre i tokom trudnoće, u toku i nakon porođaja, kao i stanje ploda i neonatusa predstavljao bi indeks optimalnosti (OI). Nastao je u Sjedinjenim Američkim Državama (SAD – USA), devedesetih godina XX veka, a modfikovan je 2001. i 2006. godine kakav se i danas koristi uz petogodišnje ažuriranje. U upotrebi je najviše u SAD i Velikoj Britaniji i Skandinavskim zemljama. Podrazumeva i gaji koncept optimalnosti koji je različit od stanja normalnog.

Cilj ove studije je bio da se upotrebom indeksa optimalnosi koji se upotrebljava u Americi (OI-US) inicira mogućnost stvaranja adekvatne baze podataka za trudnice manjeg i srednjeg rizika u vanbolničkom porodilištu i da se na osnovu dobijenih podataka iz indeksa optimalnosi proceni izvodljivost i eventulna njegova primena u cilju što optimalnijeg načina završavanja trudnoće.

Studija se bazira na prospektivnom praćenju trudnica i porodilja koje su kontrolisane i porođene u vanbolničkom porodilištu Rožaje (100). Da bi se obezbedila približna homogenost odabrane pacijentkinje klasifikovane su po kriterijumima manjeg i srednjeg rizika. Upoređivani su parametari koji se nalazio u OI (modifikovani OI-US koji je podrazumevao interpartalne i postpartalne komponente). Osim deskriptivne statistike primenjena je višestruka logistička regresija za model gde je zavisna varijabla od mesto porođaja.

Rezultati ove studije, na osnovu upoređivanih osnovnih komponenti i ukupnog *Optimality Index*-a, potvrđuju prednosti intrapartalnog i neonatalnog ishoda, porođaja završenog u vanbolničkim uslovima. Primena logističke regresione analize takođe je potvrdila da su pojedine komponente iz intrapartalnog i neonatalnog perioda te koje najviše doprinose značajno boljem totalnom optimalnom indeksu u vanbolničkim porodilištu.

Nega i porođaj u vanbolničkim uslovima pružaju višestruke prednosti, kako za porodilju tako i za novorođenče.

Literatura

1. Hermus MAA, Hitzert M, Boesveld IC, van den Akker,van Marle ME, Dommelen PV, et al. Differences in optimality index between planned place of birth in a birth centre and alternative planned places of birth, a nationwide prospective cohort study in The Netherlands: results of the Dutch Birth Centre Study. BMJ Open. 2017;16;7(11):e016958.
2. Birthplace in England Collaborative Group, Brocklehurst P, Hardy P, Hollowell J, Linsell L, Macfarlane A, McCourt C, Marlow N, Miller A, Newburn M, Petrou S, Puddicombe D, Redshaw M, Rowe R, Sandall J, Silverton L, Stewart M. Perinatal and maternal outcomes by planned place of birth for healthy women with low risk pregnancies: the Birthplace in England national prospective cohort study. BMJ. 2011;343:d7400.
3. Hutton EK, Reitsma A, Simioni J, Brunton G, Kaufman K. Perinatal or neonatal mortality among women who intend at the onset of labour to give birth at home compared to women of low obstetrical risk who intend to give birth in hospital: A systematic review and meta-analyses. EClinicalMedicine. 2019;14:59-70.
4. American College of Obstetricians and Gynecologists Planned home birth. committee opinion no. 697. Obstet Gynecol. 2017;129:e117–e122.
5. Reitsma A, Simioni J, Brunton G, Kaufman K, Hutton EK. Maternal outcomes and birth interventions among women who begin labour intending to give birth at home compared to women of low obstetrical risk who intend to give birth in hospital: A systematic review and meta-analyses. E Clinical Medicine. 2020;21:100319.

KLINIČKE KARAKTERISTIKE TRUDNICA OBOLELIH OD COVID-19 INFEKCIJE

Ass. Slađana Mihajlović[1,2]

Dr Milan Lacković[1], Dr Ivana Filipović[1], Dr Jelena Kubat[1], Dr Tijana Kosanović[1], Prof. Vladimir Đukić[1,2]

1 KBC "Dr Dragisa Misovic – Dedinje"
2 Univerzitet u Beogradu, Medicinski Fakultet

Dosadašnji podaci u literature ukazuju da trudnice ne predstavljaju populaciju koja je osetljivija prema infekciji izazvanoj COVID-19 virusom, ali da zbog promena imunološkog sistema u trudnoći, kao i promena kardiovaskularnog, respiratornog i hemostatskog sistema tokom trudnoće mogu imati teže forme bolesti.

U okviru ove retrospektivne kohortne studije uključeno je 93 trudnica sa potvrđenom COVID-19 infekcijom, koje su od marta 2020. godine, hospitalizovane i lečene u Bolnici za ginekologiju i akušerstvo KBC "Dr Dragisa Misovic – Dedinje". Svi analizirani podaci preuzeti su iz istorija bolesti pacijentkinja I bolničkog elektronskog informacionog sistema. U statističkoj analizi podataka korišćeni su x2 test, t-test, univarijantna i multivarijantna logistička regresiona analiza.

Od 93 trudnice sa potvrđenim COVID-19, skoro jedna četvrtina (23,5%) je imala potvrđenu pneumoniju. Dijagnoza pneumonije je postavljena nalazom nativne radiografije pluća ili primenom komjuterizivane tomografije, u zavisnosti od kliničke slike, stanja pacijentkinje i gestacijske starosti trudnoće. Trudnice sa potvrđenom COVID-19 infekcijom i pneumonijom su značajno češće bile starije od 35 godina, imale su bar jedan od komorbiditeta, od kliničkih simptoma gušobolju, kašalj, kratak dah, bolove u mišićima i zglobovima, gubitak čula ukusa i malaksalost, kod njih je češće dolazilo do progresije bolesti, češće su u toku hospitalizacije bile u jedinicama intezivne nege, češće su razvile akutni respiratorni distres sindrom i čečće su bile hospitalizovane duže od 8 dana. Skoro sve trudnice su bile na antibiotskoj terapiji, a najčešće korišćeni antibiotici su bili cefalosporini treće generacije i linkozamidi. Pored primene antibiotika, u toku procesa standardizacije terapisjkog režima, a u skladu sa aktuelnim terapijskim vodičima za lečenje COVID-19 infekcije, manje od 10% trudnica sa pneumonijom dobijalo je antiretroviralnu terapiju za HIV (Lopinavir/ Ritonavir), pri čemu je dužina primene ove terapije bila 13 odnosno 11 dana, retrospektivno. Manje od 2% trudnica je dobijalo hlorokin u trajanju 10 odnosno 5 dana, retrospektivno. Probiotik je koristila svaka druga trudnica sa pneumonijom i svaka treća bez pneumonije. Među trudnicama sa potvrđenom COVID-19 infekcijom i pneumonijom četvrtina pacijentkinja se porodila prevremeno, a manje od 15% pacijentkinja je imalo pobačaj u toku prvog trimestral trudnoće. Trudnice sa COVID-19 infekcijom i pneumonijom su značajno češće rađale decu sa manjom telesnom masom (1945,00 ± 75,94 gr) i dužinom (42,25 ± 0,50 cm), u odnosu na trudnice bez pneumonije (3315,73 ± 592,51 gr; 51,20 ± 3,86 cm). Na početku hospitalizacije, trudnice sa pneumonjom, u odnosu na trudnice bez pneumonije, su imale značajno veće prosečne vrednosti sledećih biohemijskih parametara: CRP, D-dimer, MCH, MCHC, eozinofili, GGT i feritin. Prosečne vrednosti leukocita su bile značajno veće kod trudnica bez pneumonija nego kod trudnica sa pneumonijama. Prema rezultatu multivarijantne logističke regresione analize nezavisni značajni faktori koji mogu da ukažu na razvoj pneumonije su vrednosti GGT koje su veće od referentnih za određen trimestar trudnoće (OR=19,6; 95CI=1,6-250,0; p=0,019) i gušobolja (OR=15,1; 95CI=1,1-200,0; p=0,045).

Pravovremena hospitalizacija, primena adekvatnih terapijskih mera, kontinuirani perinatološki nadzor i pravovremeno planiranje porođaja nad trudnicama obolelim od COVID-19 infekcije mogu da pomognu u ostvarivanju boljih maternalih, fetalnih i neonatalnih ishoda, naročito kada su u pitanju visokorizične trudnoće tj. trudnoće komplikovane komorbiditetima majke.

Literatura

1. Castro P, Matos AP, Werner H, Lopes FP, Tonni G, Araujo Júnior E. Covid-19 and Pregnancy: An Overview. Rev Bras Ginecol Obstet. 2020;42(7):420-6.
2. Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, Choolani M, Mattar C, Su LL. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020;222(6):521-31.
3. Covid-19 and pregnancy. BMJ. 2020;369:m1672.
4. Rajewska A, Mikołajek-Bedner W, Lebdowicz-Knul J, Sokołowska M, Kwiatkowski S, Torbé A. COVID-19 and pregnancy - where are we now? A review. J Perinat Med. 2020;48(5):428-34.

SONOGRAPHIC MARKERS OF CHROMOSOMOPATHY ON ROUTINE SECOND TRIMESTER SCAN

Dr. Bojana Petrović

Dr. Milica Komnenić Radovanović, Dr. Ljubinka Nikolić, Dr. Jelena Stamenković

Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade

Second trimester sonographic examination for risk assessment of chromosomal abnormalities remains an important component of prenatal evaluation.

We conducted a retrospective study to evaluate the efficiency of ultrasonographic screening for chromosomal aberrations and to classify ultrasonographic markers according to the aberration they were found with.

Over a 10 years period we performed 620 karyotype analysis of fetal blood taken by cordocentesis after detection of fetal anomaly on second trimester scan in unselected population and 216 samples of peripheral blood of neonates having phenotypic features suspected for chromosomopathies. Ultrasonographic and clinical data were obtained from the laboratory data base.

Chromosomal abnormalities were found in 36 (5,8%) fetuses with anomalies. Most frequently chromosomal aberrations were detected in fetuses with multiple anomalies (13,3%), hart anomalies (11,5%), short femur (12,5%) and polyhydramnios (7,7%). The success of sonographic examination in detection of Down syndrome was 85%, and in detection of sex chromosome trisomy's 80%. Trisomy 18, trisomy 13 and polyploidy were found prenatally in 100% each. Nearly 42% of trisomy 21 fetuses had hart anomaly, 35,3% polyhydramnios and 17,7% short femur. Trisomy 18 fetuses had polyhydramnios in 87,5%, CNS anomalies in 62,5% and symmetrical IUGR in 50% of cases. All 100% of fetuses with monosomy X had short femur. Ultrasonographic evaluation is the most sensitive screening method for the identification of fetuses having high risk for chromosomal abnormalities in a low risk population.

References

1. Rao R, Platt LD. Ultrasound screening: Status of markers and efficacy of screening for structural abnormalities. Semin Perinatol. 2016;40(1):67-78.
2. Sonek J, Croom C. Second trimester ultrasound markers of fetal aneuploidy. Clin Obstet Gynecol. 2014;57(1):159-81.
3. Souter VL, Nyberg DA, Benn PA, Zebelman A, Luthardt F, Luthy DA. Correlation of second-trimester sonographic and biochemical markers. J Ultrasound Med. 2004;23(4):505-11.
4. Ginsberg Y, Khatib N, Weiner Z, Beloosesky R, Bronshtein M. The recurrence of sonographic 'soft markers': ominous sign or 'just' genetics? Prenat Diagn. 2017;37(5):469-472.
5. Shanks AL, Odibo AO, Gray DL. Echogenic intracardiac foci: associated with increased risk for fetal trisomy 21 or not? J Ultrasound Med. 2009;28(12):1639-43.
6. Beulen L, Faas BHW, Feenstra I, van Vugt JMG, Bekker MN. Clinical utility of non-invasive prenatal testing in pregnancies with ultrasound anomalies. Ultrasound Obstet Gynecol. 2017;49(6):721-28.

POROĐAJ I ANESTEZIJA PACIJENTKINJA SA INFEKCIJOM COVID-19

Dušan Milenković[1]

Tatjana Ilić Mostić[1,2], Danka Mostić Stanišić[1], Jelena Gunjić[1], Žana Ivanković[1], Aleksandra Suvajdžić[1], Stefan Dugalić[1]

1 Klinika za ginekologiju i akušerstvo Klničkog Centra Srbije
2 Medicinski fakultet Univerziteta u Beogradu

Trenutna pandemija pneumonije izazvana bolešću korona virusom 2019 (Coronavirus COVID-19), uzrokovana teškim akutnim respiratornim sindromom korona virusa 2 (SARS-CoV-2) se širi globalno ubrzanom stopom, sa bazičnim reproduktivnim brojem (R0) koji se kreće od 2-2,5.(1) To znači da jedan pacijent zarazi 2-3 osobe. Ozbiljna opasnost po javno zdravlje, posebno je smrtonosna kod vulnerabilnih grupa i u društvima čiji zdravstveni sistem nije spreman da se nosi sa infekcijom.(1) Trudnice i njihovi fetusi predstavljaju visokorizičnu populaciju u toku širenja infekcije. Fiziološke i anatomske promene u trudnoći dovode do povećane sklonosti ka infekcijama generalno, a posebno kada je opterećen kardiorespiratorni sistem što pospešuje brzu progresiju respiratorne insuficijencije kod trudnica. Nadalje, trudnoća favorizuje dominaciju ćelijskog imunog odgovora T-2 limfocitima (eng. Thymus- T-cells) koji štite fetus, ostavljajući majku vulnerabilnom na virusne infekcije koje se efikasnije suzbijaju T-1 sistemom. Ovi jedinstveni izazovi zahtevaju integrisani pristup trudnoćama pogođenim SARS-CoV-2.(2)

Utvrditi specifičnosti primene anestezije u populaciji trudnica sa COVID-19 infekcijom. Takođe, prepoznati potencijalne rizike po zdravlje trudnica, ali i lekara i medicinskog osoblja, prilikom zbrinjavanja porodilja.

Retrospektivno je analizirano i prikazano 18 slučajeva trudnica sa COVID-19 infekcijom u periodu od maja do oktobra 2020. godine. Uvid u istorije bolesti i prikupljanje podataka izvršeno kod pacijentkinja koje su testiranjem imale pozitivan PCR (eng. Polymeraze Chain Reaction). Test obuhvata lančanu reakciju polimeraze koja je visoko specifičan i veoma senzitivan test uzet pre završetka porođaja vaginalnim putem ili carskim rezom, a kod kojih je u tu svrhu primenjen neki vid anestezije. Anlizirane su kliničke slike pacijentkinja, vrsta primenjene anestezije i ishod lečenja, kao i bezbednost medicinskog osoblja. Dobijeni podaci su obrađeni statističkim i deskriptivnim metodama.

Utvrđeno je, da je kod svih pacijentkinja dijagnostičko terapijski pristup bio u skladu sa lokalnim i međunarodnim preporukama.(3) Sve pacijentkinje su imale blaži oblik bolesti, osim jedne sa naglašenim bronhovaskularnim nalazom, ali bez hipoksije i pneumonije. Prema indikacijama, pacijentkinje su porađane vaginalno ili carskim rezom. Kod najvećeg broja pacijenkinja (94,6%) primenjena je regionalna (spinalna) anestezija za carski rez, a samo je kod jedne pacijentkinje primenjena opšta anestezija zbog prisutnog HELLP sindroma (eng. Hemolysis, Elevated Liver enzymes, Low Platelet count Sy). Zbrinjavanje nakon vaginalnog porođaja je u najvećem procentu (81.7%) bilo u lokalnoj anesteziji a 18.3% uz primenu opšte intravenske anestezije. Sva novorođena deca su imala dobru adaptaciju sa prosečnim Apgar skorom 8,9. 17 pacijentkinja je otpušteno sa Klinike dobrog opšteg stanja, bez temperature, respiratornih smetnji, hipoksije i ostalih karakteristika COVID-19. Jedna pacijentkinja je prevedena nakon porođaja u ustanovu za covid pacijente, ali i ona sa pozitivnim krajnjim ishodom lečenja. Nije zabeležen slučaj vertikalnog prenošenja infekcije sa majke na plod. Niko od medicinski radnika koji su bili uključeni u tretman pacijentkinja nije zaražen u ovom periodu.

Trudnice i porodilje su posebna i jedinstvena vulnerabilna grupa u kontekstu infektivnih bolesti, uzimajući u obzir izmenjenu fiziologiju i imuni sistem. Trenutno se ne može reći da su trudnice u povišenom riziku od teške infekcije korona virusom, iako postoje posebno osetljive grupe i u populaciji gravidnih žena. Anesteziolozi su pod povišenim rizikom od ekspozicije virusu u toku endotrahealne intubacije COVID-19 inficiranih pacijenata. Stoga, strategije primene anestezije treba usmeriti ka tehnikama regionalne anestezije, kako bi se izbegla opšta anestezija kod trudnica iole sumnjivih na COVID-19. Lična zaštitna oprema dokazano štiti od virusnih infekcija sve medicinske radnike uključene u dijagnostičko terapijske procedure, te je ona imperativ.

Reference

1. Dashraath P, Wong JLJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020;222(6):521-531. doi:10.1016/j.ajog.2020.03.021
2. Masmejan S, Pomar L, Lepigeon K, Favre G, Baud D, Rieder W. COVID-19 et grossesse [COVID-19 and pregnancy]. Rev Med Suisse. 2020;16(692):944-946.
3. Covid-19 and pregnancy. BMJ. 2020;369:m1672. Published 2020 May 4. doi:10.1136/bmj.m1672

GENERAL SPONSOR

INPHARM

Roche

GOLD SPONSOR WITH COMMERCIAL LECTURE

AstraZeneca

GOLD SPONSOR

Hemofarm
STADA GRUPA

SILVER SPONSORS

MERCK

ИНСТИТУТ ВИНЧА
СПОЉНОТРГОВИНСКИ ПРОМЕТ

BRONZE SPONSOR

B BRAUN
SHARING EXPERTISE

CONGRESS PLATFORM SPONSOR

AMICUS
a Swixx BioPharma company

SOCIAL MEDIA SPONSOR

Medtronic

EXHIBITORS

INPHARM

AstraZeneca

Hemofarm
STADA GRUPA

MERCK

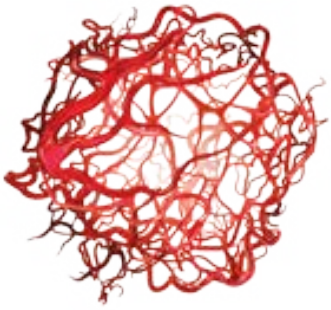
ИНСТИТУТ ВИНЧА
СПОЉНОТРГОВИНСКИ ПРОМЕТ

Dräger

COMMERCIAL PRESENTATION

E-DONORS

E-ADVERTISERS



AVASTIN®

bevacizumab

AstraZeneca

* Poly (ADP ribose) polymerase • ** Breast Cancer Gene mutations
Lynparza®, kapsula, tvrda 50 mg; 4×112 kom. • Broj dozvole: 2030/17/401-6734 od 11.10.2017.
Režim izdavanja: Lek se može upotrebljavati u stacionarnoj zdravstvenoj ustanovi, izuzetno lek se može izdavati i uz Rp, u cilju nastavka terapije kod kuće, što mora biti naznačeno i overeno na poleđini Rp. • Datum poslednje revizije Sažetka karakteristika leka: Jul 2019.
Detaljne informacije dostupne u odobrenom Sažetku karakteristika leka

SAMO ZA STRUČNU JAVNOST.

AstraZeneca
Predstavništvo AstraZeneca UK Ltd
Milutina Milankovića 1i, Beograd - Novi Beograd
Tel: 011 3336 900 • Fax: 011 3336 901

RS-1339 Novembar 2020.

Hemomycin®

prašak za rastvor za infuziju, **500 mg**

Godinama

jedinstven

Lek se može upotrebljavati u zdravstvenoj ustanovi.
Nosilac dozvole: Hemofarm AD Vršac, Beogradski put bb Vršac
Broj i datum poslednje obnove dozvole: 515-01-03214-17-001 od 30.07.2018. za lek Hemomycin, prašak za rastvor za infuziju, 1 x 500 mg
Datum poslednje revizije teksta Jul, 2018

Hemofarm
STADA GRUPA

Poverenje je važno
kada stvarate porodicu

RS-FERT-00001

Merck d.o.o.
Omladinskih brigada 90v
11070 Novi Beograd
Tel: 011 217 57 61

MERCK

BULKAMID®

Prva linija terapije
stres-urinarne inkontinencije kod žena

Bulkamid Academy
https://bulkamidacademy.com

AMICUS
a Swixx BioPharma company

PM-RS-2020-11-1428

contura

MOĆ KRVI JE U GVOŽĐU.

ŠTA JE VAŠA SUPERMOĆ?

- Brzo i efikasno koriguje nivo hemoglobina[1]
- Odlično se podnosi[2]
- Visoka efikasnost uporediva sa efikasnošću intravenskog gvožđa[1]

Ne zaboravite na značaj uravnotežene ishrane i zdravog načina života.
Dodatak ishrani namenjen svim stanjima povećanih potreba za unosom gvožđa, kao i nadoknadi njegovih smanjenih rezervi u organizmu.
Dodaci ishrani nisu zamena za raznovrsnu i izbalansiranu ishranu i zdrav način života.

Reference:
1. Shankar P Nagaraju, Adam Cohn, Ayub Akbari, Janet L Davis and Deborah L. Zimmerman Heme iron polypeptide for the treatment of iron deficiency anemia in non-dialysis chronic kidney. Nagaraju et al. BMC Nephrology 2013, 14:64
2. Frykman, E, et al, Side effects of iron supplements in blood donors: Superior tolerance of heme iron, J Lab Clin Med 1994; 123(4):561-4.

Nosilac upisa u bazu podataka Ministarstva zdravlja: PharmaSwiss d.o.o. Batajnički drum 5a, Beograd, tel. +381(11) 2050-200
Broj rešenja: 14539/2019 od 01.07.2019.

PHARMASWISS


LABTEH
Vaš partner u laboratoriji

MACMIROR® COMPLEX

nifuratel + nistatin

KANDIDA

TRIHOMONAS

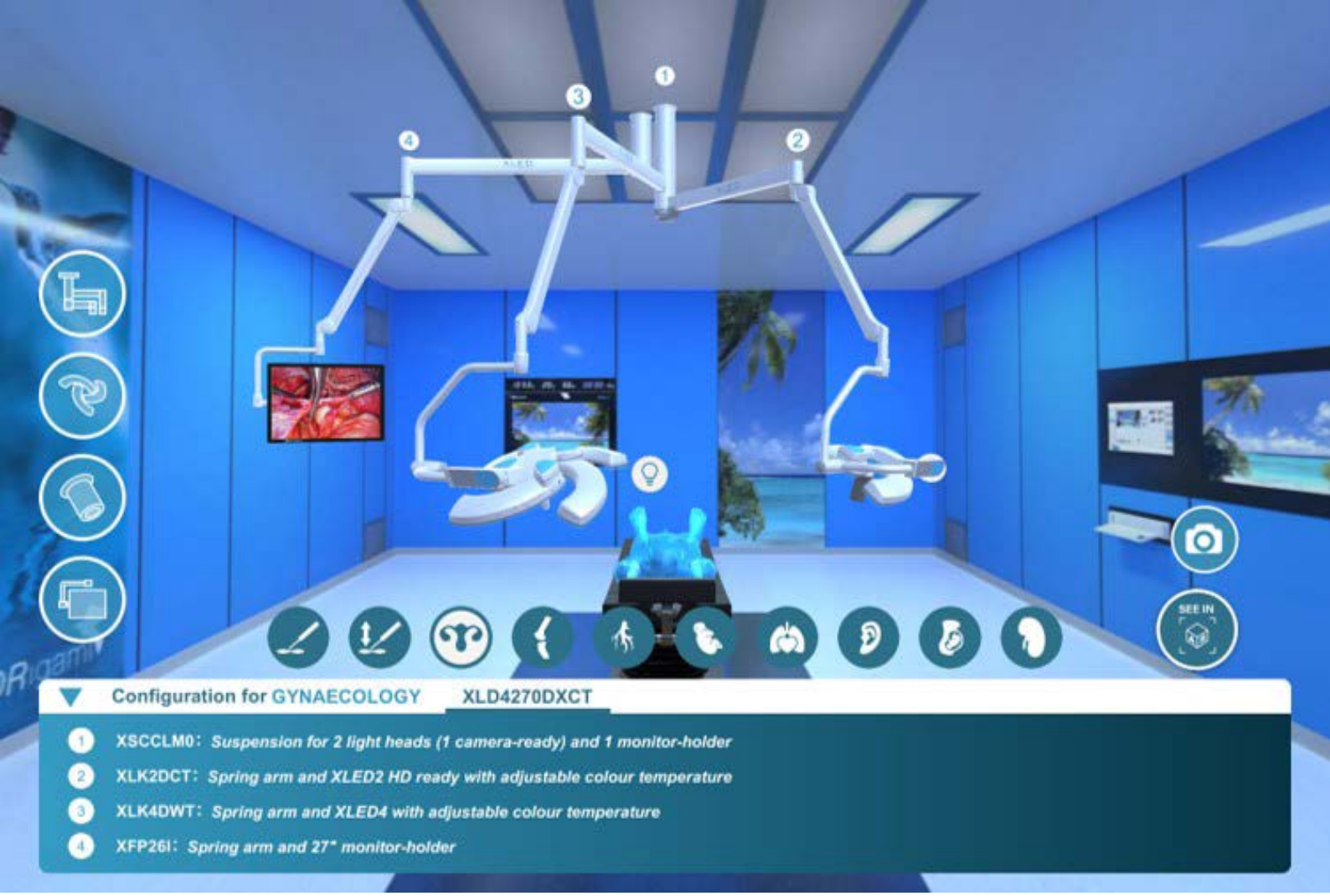
MEŠOVITA INFEKCIJA

BAKTERIJSKA VAGINOZA

NAJŠIRI SPEKTAR DEJSTVA U TERAPIJI VULVOVAGINALNIH INFEKCIJA

Bonifar doo, Novi Beograd

Bulevar Zorana Đinđića 87/1 • 011 313 25 33 • office@bonifar.com



neomedica
a Brain company

PRIČAJMO O **DIJABETESU**

Želite da saznate više o terapiji
i zdravim životnim navikama
koje Vam mogu pomoći da držite
svoj **dijabetes** pod kontrolom?

Posetite vebsajt
PRIČAJMO O **DIJABETESU**
i saznajte više.

www.dijabetes.rs

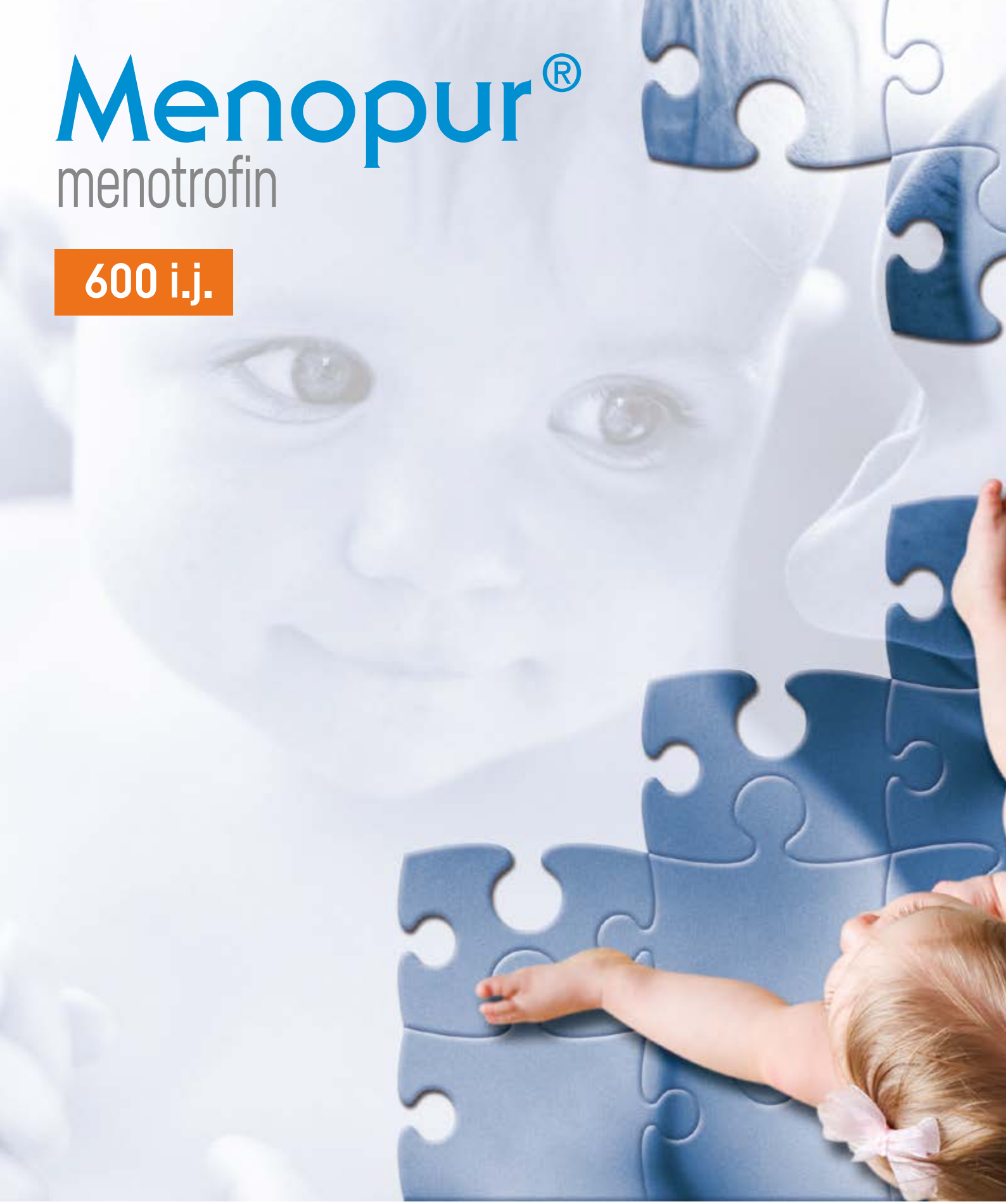
novo nordisk®

SM20NNG00023

Menopur®

menotrofin

600 i.j.



SAMO ZA STRUČNU JAVNOST

Proizvođač: Ferring-Lečiva a.s., K.Rybniku 475, Jasenice - Prag, Češka
Nosilac dozvole za lek: Ferring Pharmaceuticals d.o.o. Beograd - Stari Grad
Broj i datum dozvole: 515-01-03660-18-001od 20.06.2019.
Režim izdavanja leka: Lek se može upotrebljavati u stacionarnoj zdravstvenoj ustanovi, izuzetno lek se može izdavati i uz Rp, u cilju nastavka terapije kod kuće, što mora biti naznačeno i overeno na poleđini Rp.
Datum revizije Sažetka karakteristika leka: Jun, 2019.
Promotivni materijal odobren rešenjem broj: 515-08-00482-19-001

FERRING
PHARMACEUTICALS

MEN-SRB-002/2019

PreMama^duo

- **11** vitamina
- **10** minerala
- **Omega 3** masne kiseline

Zadovoljava povećane potrebe organizma za hranljivim materijama:

– *kod žena koje planiraju trudnoću*
– *tokom trudnoće*
– *tokom dojenja*

1 tableta +
1 kapsula dnevno

Tablete i kapsule PreMama Duo obezbeđuju preporučen unos folne kiseline, vitamina D i omega 3 masnih kiselina zajedno sa ostalim vitaminima i mineralima važnim za pravilan tok trudnoće, rast i razvoj ploda i bebe.

Dnevni unos od 400 mcg folne kiseline smanjuje rizik od nastanka defekta neuralne cevi.

Povećan unos omega 3 masnih kiselina u toku trudnoće značajan je za razvoj mozga, centralnog nervnog sistema i za pravilan razvoj očiju i funkcije vida. Povezan je sa povećanom težinom na porođaju, obimom glave i dužinom novorođenčeta.

Nancy L. Morse: Nutrients 2012,4 (7), 799-840 Review: Benefits of Docosahexaenoic Acid, Folic Acid Vitamin D and Iodine on Foetal and Infant Brain Development and Function Following Maternal Supplementation during Pregnancy and Lactation.

ALKALOID
SKOPJE

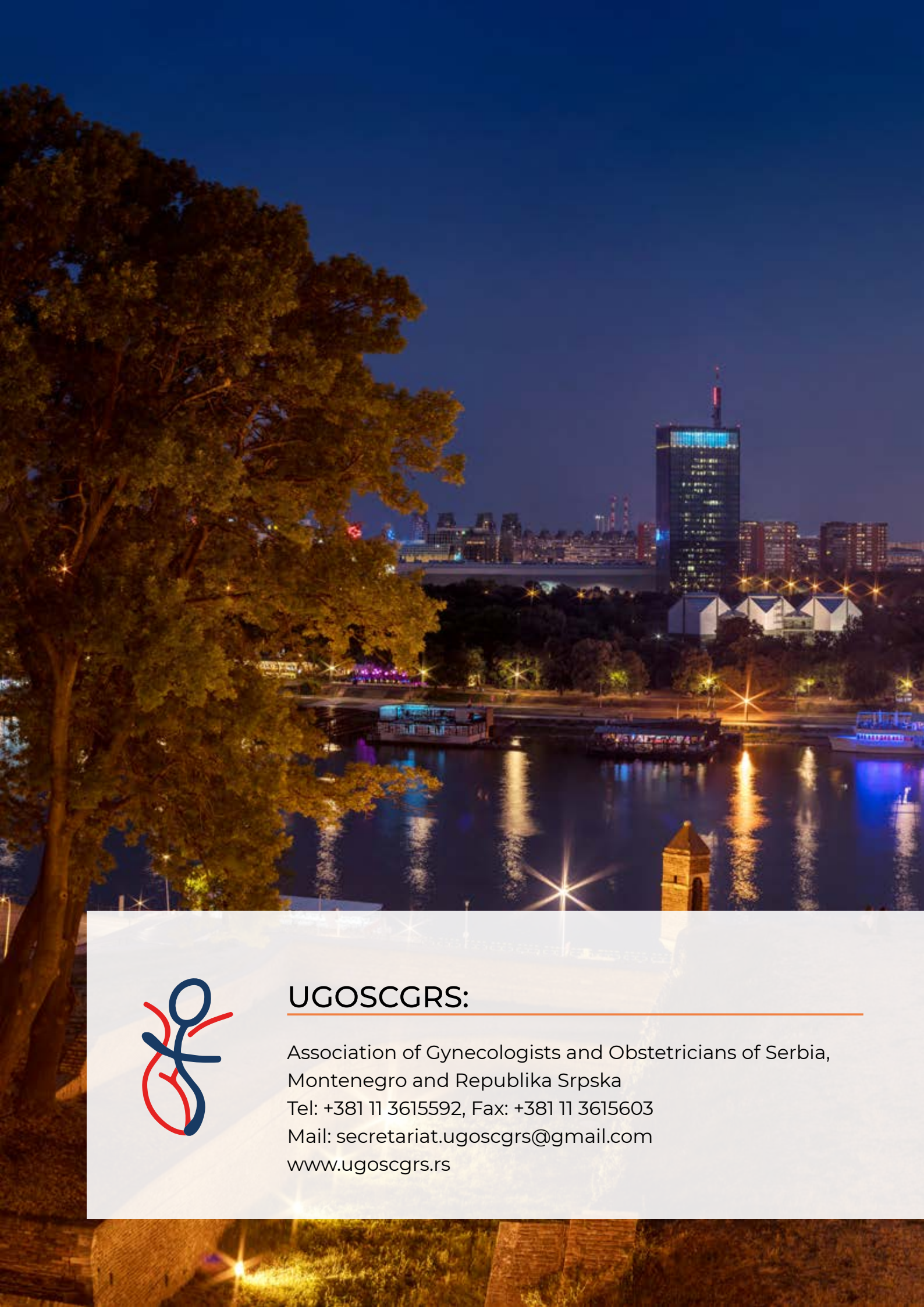
B|BRAUN

SHARING EXPERTISE

ELISA testovi za određivanje antitela na virus SARS-CoV-2 klase IgM i IgG

Za bezbednost:

Začeća
Trudnoće
Porođaja
Novorođenčeta
In vitro fertilizacije
Intervencije



UGOSCGRS:

Association of Gynecologists and Obstetricians of Serbia,
Montenegro and Republika Srpska
Tel: +381 11 3615592, Fax: +381 11 3615603
Mail: secretariat.ugoscgrs@gmail.com
www.ugoscgrs.rs