INTERNATIONAL COLPOSCOPY & CERVICAL PATHOLOGY CONFERENCE

November 24-26, 2016
Marriott Budapest Hotel, Hungary

MAIN TOPICS

1. Cervical cancer epidemiology in Europe
2. New tools in cervical cancer screening
3. Practical aspects of colposcopy
4. Primary prevention of cervical cancer-Vaccination
5. Treatment and follow up of CIN

TOPICS PLENARY SPEAKERS

Christine Bergeron (France)
Charles Redman (United Kingdom)
Simon Leeson (United Kingdom)

INTERNATIONAL SCIENTIFIC COMMITTEE

Róbert Koiss (chair)
Gusztáv Adorján
Maggiorino Barbero
Christine Bergeron
Péter Bősze
Drazan Butorac
Goran Dimitrov
Péter Göncze
Balázs Járay
Vesna Kesic
Simon Leeson
László Pálfalvi
Imre Pete
Charles Redman
János Rigó
Špela Smrkolj

SCIENTIFIC ORGANISER

Dr. Robert Koiss Ph.D.
Szent István Hospital, Dept. of Gynecology
H-1096 Budapest, Nagyvárad tér 1.
E-mail: koiss.robert@eszszk.hu

CONGRESS OFFICE

Károly Bagdi (Mr.) - congress organisation
E-mail: kbagdi@convention.hu
Krisztina Barna (Ms.) - registration
E-mail: kbarna@convention.hu
Convention Budapest Ltd
Phone: + 36 1 299 01 84, - 85, -86 • Fax: + 36 1 299 01 87
Mailing: Lajos u. 66., H-1036 Budapest, Hungary
Website: www.convention.hu

MEETING VENUE

Venue: Budapest Marriott Hotel
Address: Apáczai Csere János u. 4., H-1052 Budapest, Hungary
Phone: +36-1-486 5000 • Fax: +36-1-486-5005 • Web: http://www.marriott.com

Thank you for your support

ellman®
A CYNOSURE® Company

ewopharma

MSD
Be well

125 YEARS SINCE 1891

GARDASIL 9
[Humán papillomavírus 9-valens vakcina, rekombináns]

Roche

SYNLAB

SCHMITZ
A Sense of Confidence

Made in Germany

PROGRAM | NOVEMBER 24, 2016 - THURSDAY

19.00 **Welcome Reception**
(Marriott Hotel)

PROGRAM | NOVEMBER 25, 2016 - FRIDAY

10.00–12.00 **STATE OF THE ART LECTURE'S**
Moderators: *Robert Koiss, Peter Bősze*

New methods in cervical screening 30'
Christine Bergeron
Laboratoire Cerba, France

Colposcopy in perspective; its role and quality assurance 30'
Charles Redman
Consultant Gynaecologist, University Hospital of North Midlands, UK
President of the European Federation for Colposcopy

Cervical screening strategy in the UK 30'
Simon Leeson
Consultant Gynaecologist, Oncologist and
Honorary Senior Lecturer to the University of Wales, UK

Discussion 30'

12.00–13.15 **Lunch**

13.15–15.00 **CYTOLOGY**
Moderator: *László Kornya, János Rigó*

Comprehensive cytopathological risk assessment: a new era 20'
Peter Pogany
1st Pathology Department of Semmelweis University, Budapest,Hungary

Pitfalls and benefits of cervical screening-could be implemented new screening methods in Hungary? 20'
László Vass
FIAC Pathology Department of Flór Ferenc Hospital, Kistarcsa, Hungary

Diagnostic value of cytology – already existing precursos versus risk of developing one 20'
Orsolya Bubnó, Károly Pap, Ágnes László
Obstetrics and Gynecology Department of Jósa András Szabolcs-Szatmár Bereg County Teaching Hospital, Nyíregyháza, Hungary

Evaluation of POU4F3 as a new biomarker of cervical precancer and cancer in the triage of high-risk HPV positive women 25'
Márta Benczik[1,2,9], Adrienn Kocsis[1,2], Tibor Takács[1,2,9], Csaba Jeney[2], Zsuzsa Schaff[3], Róbert Koiss[4], Balázs Járay[3], Gábor Sobel[5], Károly Pap[6], István Székely[4], Tamás Ferenci[10], Hung-Cheng Lai[7,8], Miklós Nyíri[1,2]
[1]NEUMANN Diagnostics Ltd., Hungary; [2]Cellcall Ltd., Hungary; [3]2nd Department of Pathology, Semmelweis University, Hungary; [4]Department of Obstetrics and Gynaecology, St. Stephan Hospital, Hungary; [5]2nd Department of Obstetrics and Gynaecology, Semmelweis University, Hungary; [6]Jósa András Regional Central Hospital, Hungary; [7]Department of Obstetrics and Gynecology, Shuang Ho Hospital, Taipei Medical University; [8]Department of Obstetrics and Gynecology, School of Medicine, College of Medicine, Taipei Medical University; [9]Synlab Hungary Ltd. GenoID Molecular Diagnostic Laboratory, Hungary; [10]Óbuda University, Budapest, Hungary

Discussion 15'

15.00–15.30 **MSD SYMPOSIUM**
Chair: *Balázs Járay*

HPV prevalence in Hungary 15'
Adrienn Kocsis, Hungary

Prevention and treatment of cervical precancer lesions in Hungary 15'
László Kornya
Department of Obstetrics and Gynaecology, St. Stephan Hospital, Budapest, Hungary

15.30–16.00 **Coffee Break**

16.00–17.50 **HPV-COLPOSCOPY**
Moderators: *Imre Boncz, Maggiorino Barbero*

HPV-based screening for cervical cancer precursors in Italy 25'
Guglielmo Ronco
Centre for cancer prevention (CPO), Turin, Italy

Disease burden and cost-effectiveness of cervical cancer screening 25'
Imre Boncz, director, vice-dean University of Pécs Faculty of Health Sciences Institute for Health Insurance, Pécs, Hungary

Management of women with abnormal cytology 20'
Péter Bősze
Department of Obstetrics and Gynaecology, St. Stephan Hospital, Budapest, Hungary

Role of colposcopy in the management of abnormal smear test and HPV positive patients 20'
Maggiorino Barbero
Dep. Of Obstetrics and Gynecology of University Turin, Italy

Discussion 20'

19.00 **Banquet Dinner**
(Marriott Hotel)

08.30–09.30 **MMKT közgyűlés – Meeting of the Hungarian Society on Colposcopy & Cervix Pathology**

10.00–11.50 **SCREENING STRATEGY**
Moderators: *Goran Dimitrov, Robert Jach*

Cervical cancer screening in Poland 20'
Andrzej Nowakowski
Second Department of Gynaecological Oncology, St. John's of Dukla Regional Cancer Centre, Lublin, Poland
Central Coordinating Centre for Screening Programmes, Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland

Cervical cancer prevention strategy in Serbia 20'
Vesna Kesi
Medical Faculty, University of Belgrade; Department of Obstetrics and Gynecology, Clinical Center of Serbia, Serbia

Croatian cancer screening programme 20'
Drazan Butorac
Clinical Hospital Centre „Sisters of mercy", Zagreb, Croatia

Cervical cancer prevention in Republic of Macedonia 20'
Goran Dimitrov
Chief of GyneOncology Department University Ob/Gyn Clinic, University „Sts Cyril & Methodius" Skopje - MACEDONIA

Cervical cancer prevention strategy in Slovenia
Špela Smrkolj
University Medical Centre Ljubljana, Division of Gynecology, Slovenia

Cervical cancer prevention strategies in Hungary 20'
Robert Koiss
Department of Obstetrics and Gynaecology, St. Stephan Hospital, Budapest, Hungary

Discussion 10'

11.50–12.10 **Coffee Break**

12.10–13.45 **HPV-COLPOSCOPY**
Moderators: *Vesna Kesic, Drazan Butorac*

Are positive cone margins a disadvantage of LLETZ technique? 20′
Škrtić B., Pitner I., Orsag N., Tučkar N., Kuna K., Djakovic I., Butorac D.
University Clinical Hospital Centre 'Sestre milosrdnice' Zagreb, Croatia

Human papilloma virus infection in women with cervical intreaepithelial changes: associations with colposcopic and hystologycal findings 20′
Vaso Korunoski[1], Pavlina Korunoska[1], Goran Dimitrov[2]
[1]Private Doctor's office PZU "Dr Korunoski" – Skopje, Macedonia
[2]University Ob/Gyn Clinic, University Sts Cyril & Methodius – Skopje, Macedonia

Distribution of HPV genotypisation in citology and pathohystology findings at Sisters of Mercy Clinical Hospital 20′
Orsag N., Škrtić B., Pitner I., Čukelj M., Tučkar N., Kuna K., Djaković I., Butorac D.
Clinical Hospital „Sisters of mercy", Zagreb, Croatia

The significance of colposcopy in cervical premalignant lesions during pregnancy 20′
Pitner I., Orsag N., Škrtić B., Čukelj M., Kuna K., Tučkar N., Djaković I., Butorac D.
University Clinical Hospital Center "Sestre Milosrdnice", Zagreb, Croatia

Discussion 15′

13.45 **Closing Remarks, Take Home Message**

14.00 **Lunch**

ABSTRACTS

Evaluation of POU4F3 as a new biomarker of cervical precancer and cancer in the triage of high-risk HPV positive women

Márta Benczik[1,2,9], Adrienn Kocsis[1,2], Tibor Takács[1,2,9], Csaba Jeney[2], Zsuzsa Schaff[3], Róbert Koiss[4], Balázs Járay[3], Gábor Sobel[5], Károly Pap[6], István Székely[4], Tamás Ferenci[10], Hung-Cheng Lai[7,8], Miklós Nyíri[1,2]

[1]NEUMANN Diagnostics Ltd., Hungary
[2]Cellcall Ltd., Hungary
[3]2nd Department of Pathology, Semmelweis University, Hungary
[4]Department of Obstetrics and Gynaecology, St. Stephan Hospital, Hungary
[5]2nd Department of Obstetrics and Gynaecology, Semmelweis University, Hungary
[6]Jósa András Regional Central Hospital, Hungary
[7]Department of Obstetrics and Gynecology, Shuang Ho Hospital, Taipei Medical University
[8]Department of Obstetrics and Gynecology, School of Medicine, College of Medicine, Taipei Medical University
[9]Synlab Hungary Ltd. GenoID Molecular Diagnostic Laboratory, Hungary
[10]Óbuda University, Budapest, Hungary

Aims: The ongoing TRACE prospective, multicenter study recruited over 6,000 women aged 18 or older and aimed to provide a clinical evaluation of the CONFIDENCE™ assay, which comprises an HPV DNA test (CONFIDENCE™ HPV) and a human epigenetic biomarker (CONFIDENCE™ Marker) test.

Method: Liquid based cytology, hrHPV DNA detection and single target host-gene methylation test of the promoter sequence of the POU4F3 gene by quantitative methylation specific PCR were performed from the same LBC sample. The current analysis is focused on the baseline cross-sectional clinical results of 5,384 LBC samples collected from subjects aged 25 years or older.

Results: The performance of the CONFIDENCE™ HPV test was found to be comparable to the cobas® HPV test with good agreement. Applying the CONFIDENCE™ Marker test alone in hrHPV positives showed significantly higher sensitivity with matching specificity compared to LBC based triage. For CIN3+ histological endpoint in the age group of 25-65 and 30-65, the methylation test of POU4F3 achieved relative sensitivities of 1.74 (95% CI: 1.25-2.33) and 1.64 (95% CI: 1.08-2.27), respectively after verification bias adjustment. In comparison of LBC and POU4F3 both combined with HPV16/18 genotyping, methylation based triage was found to be significantly more specific with comparable sensitivity for CIN2+ in crude analysis.

Conclusion: On the basis of our findings, POU4F3 methylation as a triage test of hrHPV positives appears to be a noteworthy method. We can reasonably assume that its quantitative nature offers the potential for a more objective and discriminative risk assessment tool in the prevention and diagnostics of high-grade CIN lesions and cervical cancer.

Keywords: cervical cancer, high risk HPV, POU4F3 biomarker, epigenetics, host-gene methylation

Diagnostic value of cytology – already existing precursos versus risk of developing one

Orsolya Bubnó[1], Károly Pap[1], Ágnes László[2]
[1]Szabolcs-Szatmár-Bereg Megyei Kórházak és Egyetemi Oktatókórház Jósa András Oktatókórház, Szülészet-Nőgyógyászati Osztály, Nyíregyháza, Hungary
[2]Szabolcs-Szatmár-Bereg Megyei Kórházak és Egyetemi Oktatókórház Jósa András Oktatókórház, Pathológiai Osztály, Nyíregyháza, Hungary

With the introduction of cytology-based cervical cancer screening, the incidence and mortality of cervical cancer has decreased substantially. However, cervical cancer still remains the third most common cancer and fourth leading cause of death among women. Pap smear per se lacks accuracy and misses disease in identifying precancerous lesions. In order to improve diagnostic safety, additional tests should be added to the current screening techniques, including conventional cytology and colposcopy.

Our aim was to evaluate the correlation between the abnormal cytological and subsequent histological tissue diagnoses (obtained by punch biopsy, LEEP or cone biopsy) in cervical pathology. 663 women aged 18-59 screened between 2012-2016 with atypical cytology were recruited in the study for assessment of the diagnostic accuracy. The initial results have been compared with the follow-up histopathologic diagnoses taken 3 monts after the first smears. The histological verification of CIN 1-2 confirmed the same grade of dysplasia in less than 50% of the cases, in several patients more severe atypia existed. In 162 cytological findings of ASCUS, LSIL, CIN 1 we performed punch biopsy, out of which in 124 cases we interpreted equivalent results, in 19 and 19 cases negative or higher grade of neoplasia, respectively. Histologically confirmed cervical intraepithelial neoplasisa grades 2 and 3 were treated with cone biopsy, in which cases the results of the histological examination correlated with the former results of punch biopsies.

Our resulst, in concordance with the international findings, imply the issues of the 'limited' exfoliative cytology. The currently available diagnostic strategies, cytology with colposcopy, provide inconclusive results with modest predictive value. In favour of increasing the sensitivity of our screening programmes, predicting the biological potential of the cervical intraepithelial lesions with more certainty, new methods are needed.

Croatian cancer screening programme

Drazan Butorac
Clinical Hospital Centre „Sisters of mercy", Zagreb, Croatia

Cervical cancer is a significant public health problem in the world as well as in Croatia. Cervical cancer by the incidence is the second cancer site in Croatia among women aged 40 to 49, third among women aged 30 to 39.

During 2011, 321 women in Croatia (rate 12.4/100 000) were affected by this disease, and 111 women (rate 3.5/100 000) died.

On the other hand, cervical cancer is one of the rare neoplasms that, if detected at early stage, can be completely cured, and with primary prevention even prevented.

Opportunistic PAP - smear tests have been done in Croatia for the last 60 years. The main disadvantage of this approach is that in many women PAP- smear test is unnecessarily repeated, while others never approach the test.

The Croatian cervical screening programme is the third national programme launched in Croatia and has been carried out since November 2012.

The main method of screening for cervical changes is the conventional PAP-smear test.

The programme is intended for all women in the Republic of Croatia between the age of 25 and 64, including those with health insurance and those without it.

The programme is being conducted in three- year cycles. The invitations are sent every three years to all the women who havent't done a PAP- smear test at their chosen gynecologist's during that period of time. A total of 1 262 065 women were sent the invitations.

The programme goals are:

– to include 85% of the target population in the early stage cervical cancer screening programme during the three years from the beginning of the programme
– to reduce the number of new cases of women suffering from cervical cancer by 60% in the age group 25- 64 during the 8 years from the beginning of the programme
– to reduce invasive cervical cancer mortality rate by 80% in the age group 25- 70 during the 13 years from the beginning of the programme

In implementing the programme we are faced with a number of organizational and implementational challenges, such as insufficient availability of gynecological primary health care teams, incomplete teams in the country's public health institutes, non- compliance to the gynecological society guidelines, and the invitation base taken from The Croatian Health Care System which has revealed certain deficiencies.

At this time the results for the first three years of the programme are not available.

Human papilloma virus infection in women with cervical intreaepithelial changes: associations with colposcopic and hystologycal findings

Vaso Korunoski[1], Pavlina Korunoska[1], Goran Dimitrov[2]
[1]Private Doctor's office PZU "Dr Korunoski" – Skopje, Macedonia
[2]University Ob/Gyn Clinic, University Sts Cyril & Methodius – Skopje, Macedonia

The aim of the study was to determine the prevalence of human papillomavirus (HPV) types 16 and 18 in women with cervical intraepithelial changes caused by high-risk HPV in relation to colposcopic and histological findings.

Material and Methods: A prospective study of 195 women with cervical cytologic changes confirmed by the Papanicolaou test was undertaken from 01.09.2014 to 01.09.2015. HPV-positive women underwent genotyping for types 16 and 18. Colposcopy and biopsy were done in 150 (76,9%) and 96 women (49,2%), respectively. The results were analyzed by age groups.

Results: Of all the women with cervical intraepithelial changes, 46,1% were positive for HR HPV, and 53,8% were positive for HPV types 16 and 18. HPV types 16 and 18 were detected in 30,7% of women with ASC-US/AGUS/ASC-H, 17,4% of women with LSIL, and 54 % of women with HSIL. After confirmation of any histological and colposcopic changes, HPV types 16 and 18 were detected in 70.0% of women.

Conclusions: Despite the high prevalence of HPV types 16 and 18 testing for these genotypes together with the Papanicolaou test did not improve the diagnosis of high-grade cervical intraepithelial lesions. Without biopsy and histological verification can not come to correct diagnosis and can not be planned suitable treatment in these patients.

Cervical cancer screening in Poland

Andrzej Nowakowski
Second Department of Gynaecological Oncology, St. John's of Dukla Regional Cancer Centre, Lublin, Poland
Central Coordinating Centre for Screening Programmes, Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland

Both cervical cancer (CC) incidence and mortality have been decreasing for several decades in Poland. In 2013, 2909 and 1669 women were diagnosed and died of CC giving age-standardized ratios of 9.3 and 4.6/100 000 respectively which are average in Europe. Opportunistic screening has been present for several decades but an organized programme was implemented in 2006/2007. Screening test is conventional cytology, target age group is 25-59 years of age and screening interval is three years. Written invitations were sent to most eligible women for the first ten years but were stopped in 2016. Cytology results are presented in a modified Bethesda system. Repeated cytology and colposcopy with/without biopsy is used for triage of abnormal results. The administration of the programme is financed by the Ministry of Health from the funds of the National Programme for Fight Against Cancer. The costs of medical procedures are reimbursed by the National Health Fund – the only national health insurance institution. The programme is coordinated by the central coordination centre and is supervised by the Ministry of Health. Some quality assurance measures have been implemented but some are still lacking. Data on all procedures performed in the programme are collected in a central database with an internet-based access to all participating service providers. Unfortunately, the usefulness of the system is limited due to legal and technical constrains. The main obstacle in the organised programme is its low coverage ~ 20-25%. At the same time a high volume of opportunistic screening takes place reaching 70-80% of the female target population according questionnaire-based data. The Polish organised cervical screening programme is only partially adherent to evidence-based European Guidelines for Quality Assurance in Cervical Cancer Screening (EuG) in various aspects of its organization and execution. Very recent data indicate a possible impact of the programme on acceleration of the decreasing trend in CC incidence without a significant impact on mortality trends yet. Changes with special focus on increasing coverage, development of information systems and assessment of quality are required to increase programme adherence to EuG and to measure its effectiveness.

Distribution of HPV genotypisation in citology and patohystology findings at Sisters of Mercy Clinical Hospital

Orsag N., Škrtić B., Pitner I., Čukelj M., Tučkar N., Kuna K., Djaković I., Butorac D.
Clinical Hospital „Sisters of mercy", Zagreb, Croatia

Introduction: Human papillomavirus (HPV) has become recognized in 1970s as an important causative agent of cervical neoplasms. [1, 2] More than a hundred types and subtypes of HPV have been identified, and are classified into low-risk (LR HPV) and high-risk (HR HPV) groups based on their association with cervical cancer.[3] Among these HPV 16 is the most carcinogenic, followed by HPV 18.[1,4] Together, they account for approximately 70% of cervical cancers. [1,3]

Goal: To examine the HPV virus distribution in cytology and pathohistology findings in patients at Sisters of mercy Clinical Hospital in the time period from 2014 to 2016.

Methods: A retrospective study included 440 patients that came to our clinic. Patients were divided into 4 groups, depending on HPV genotypisation: HPV 16 positive, HPV 18 positive, HR HPV positive, and HPV negative group. Within the subgroups, citology and pathohistology exams were conducted and reviewed.

Results: A total of 440 patients from our hospital were included in the study.

Positive HPV 16 and HPV 18 were found in 95 (21.59%), and 28 (6.36%) patients, respectively. Furthermore HR HPV was found in 242 (55.0%) patients, while HPV negative group consisted of 75 (17.05%) patients.

Within the HPV 16 subgroup, PAP smear showed LSIL in 21 (22.11%) patients, HSIL in 57 (60.0%), while malignant epithelial carcinoma or CIS in 1 (1.05%) patient. After colposcopy, in 69 patients a biopsy was performed. Biopsy showed LSIL in 8 (11.59%) patients, HSIL in 43 (62.32%), and epithelial carcinoma in 2 (2.90%) patients. In HPV 18 subgroup PAP smear was positive for LSIL and HSIL in 9 (32.14%) and 16 (57.14%) patients, respectively. Epithelial carcinomas and CIS were not found in this group. Biopsy after colposcopic exam unveiled LSIL in 3 (21.43%) patients, HSIL in 7 (50.0%), and epithelial cervical cancer in 1 (7.14%) patient. In HR HPV subgroup PAP smear was positive for LSIL and HSIL in 86 (35.54%) and 116 (47.94%) patients, respectively. Epithelial carcinomas and CIS were found in 3 (1.24%) patients. After colposcopic biopsy exam uncovered LSIL in 19 (18.63%) patients, HSIL in 64 (62.74%), and epithelial cervical cancer in 3 (2.94%) patient. HPV negative subgroup had positive PAP smear for LSIL and HSIL in 21 (28%) and 17 (22.67%) patients, respectively. Epithelial carcinomas and CIS were not found in this group. Biopsy done after colposcopic exam showed LSIL in 8 (45%) patients, HSIL in 1 (5%) patient, and epithelial cervical was not found in biopsy results.

In all patients included in our study, PAP smear was HSIL positive in 116 (47.94%) patients within the HR HPV group, and in 57 (60.0%) and 16 (57.14%) within the HPV 16 and 18 groups, respectively. Negative HPV group had HSIL in 17 (22.67%) patients. Cervical cancer was found in 3 (1.24%) patients in HR HPV group, in 1 (1.05%) patient in HPV 16 group, and there was no cancer found in PAP smear in HPV 18 or HPV negative group.

Pathohystologic findings following biopsy of the cervix were found HSIL positive in 64 (62.74%) patients in HR HPV group, in 43 (62.32%) patients in HPV 16 group, and in 7 (50.0%) patients in HPV 18 group. Cervical cancer in PH finding after biopsy was detectedin 3 (2.94%) patients within HR HPV group, in 2 (2.90%) patients within HPV 16 group, and in 1 (7.14%) patient within HPV 18 group. HPV negative group had 1 (5.0%) patient with HSIL, and no patients with cervical cancer.

Comparing PAP smear and PH findings, we found that groups HPV 16 and 18 had similar prevalence in HSIL and cervical cancer, as well as HR HPV group. HPV negative group had greater diversity within results.

Conclusion: Colposcopy is a procedure where lower genital tract organs are examined through a magnifying device. Based on the visual detection, a biopsy can be taken from the changed areas for further diagnostic.

Cervical HSIL lesions are caused by HPV virus infection from different subtypes. HPV types 16 and 18 are most cancerous of them all, causing around 70% of all cervical cancers.

Malignant and premalignant lesions were caused in the same prevalence within the HPV 16 and 18 subgroups ($P<0.01$), and within the HR HPV subgroup ($P<0.05$). Negative HPV genotypisation was found as a significant mark for negative prevalence of cervical cancer.

Comparing the results between PAP smear and PH findings, we found that HPV genotypisation is a good indicator for differentiation of premalignant and malignant lesions.

References:

1. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S,Human papillomavirus and cervical cancer. Lancet. 2007;370(9590):890–907.
2. Zekan J, Sirotković SM, Skerlev M (2011) Oncogenic aspect of HPV infections of the female genital tract //DNA replication-current advances/ Seligmann H (ur.). New York: In Tech. 595 – 612.
3. Stanley M, Pathology and epidemiology of HPV infection in females. Gynecol Oncol. 2010 May;117.
4. Ronco G, Franceschi S, Segnan N.: HPV16 and HPV18 genotyping in cervical cancer screening, Lancet Oncol. 2011 Sep;12(9):831-2.

The significance of colposcopy in cervical premalignant lesions during pregnancy

Pitner I., Orsag N., Škrtić B., Čukelj M., Kuna K., Tučkar N., Djaković I., Butorac D.
University Clinical Hospital Center "Sestre Milosrdnice", Zagreb, Croatia

Introduction: Croatia does not have national register for human papillomavirus (HPV) infections.

HPV is the most common sexually transmitted infection globally. In the USA 50% of infected population are women aged 15-24 years with the highest rate of infection between 20-24 and 25-30 years (1). As this is the main age when women get pregnant , Pap smear should be performed if the last one is more than 2 years old (2).

When atypical cells are found in Pap smear during pregnancy, main aim of colposcopy is identification of invasive cervical cancer. During pregnancy CIN lesions are usually stable or regress (3).

Results: In our study we present results of 41 pregnant women who underwent colposcopy in the period from 2011-2012.

According to Pap-smear test results LSIL was found in 22%, HSIL in 73% and AGC-US in 5%.

Colposcopy showed G1 changes in 39%, G2 in 46%, suspected on invasive lesion in 5% and in 10% colposcopy was inadequate.

In patients where HPV typing was made, 56% of them, in 44% HPV-HR was found, in 7% HPV 16, and in 5% HPV infection was not found.

In 5% biopsy was made.

51% of patients after delivery had normal Pap smear result. 8 weeks after delivery cytological regression was found in 64% of patients, progression in 2,4% and in 34% changes persisted.

In 15 patients in which colposcopaly quided biopsy was performed 8 weeks after delivery in 13% was found LSIL, in 73% HSIL, and carcinoma invasivum in 7%.

Conclusion: We confirmed high regression rates of Pap smear and colposcopy results.

Pap smear with colposcopy is the method of choice in detection and evaluation of premalignant changes in pregnancy. Although conservative management of such changes is advisable, it should not miss the recognition of invasive cervical cancer.

1. Weinstock H, Berman S, Cates W Jr. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. Perspect Sex Reprod Health. Jan-Feb 2004;36(1):6-10
2. Selleret L , Mathevet P. Precancerous cervical lesions during pregnancy: diagnostic and treatment. J Gynecol Obstet Biol Reprod (Paris). 2008 Feb;37 Suppl 1:S131-8.
3. Mariella Mailath-Pokorny, Richard Schwameis, Christoph Grimm, Alexander Reinthaller, and Stephan Polterauer. Natural history of cervical intraepithelial neoplasia in pregnancy: postpartum histopathologic outcome and review of the literature. BMC Pregnancy Childbirth. 2016; 16: 74.

Comprehensive cytopathological risk assessment: a new era

Peter Pogany
1st Pathology Department of Semmelweis University, Budapest,Hungary

In this presentation we will address questions like: Why is the sensitivity of cytology so low? What is the explanation of the high false positivity rates? How can this be improved? We will discuss the importance of communication between the gynaecologist and the cytopathologist, and refer to some diagnostic methods (CINtec Plus, L1 protein detection, DNA methylation), which may help stratify patients into risk categories, and ultimately to choose the optimal treatment strategy.

HPV-based screening for cervical cancer precursors in Italy.

Guglielmo Ronco
Centre for cancer prevention (CPO), Torino, Italy

In Italy organised, population based cervical screening with cytology as primary test started in the 1990s. Surveys of activity and process indicators are published yearly. In 2014 67% of the national target population was actively invited. In 2002 a large randomised controlled trial comparing HPV to cytology-based screening started in 9 Italian centres. Based on the results up to the second screening round, showing earlier detection of high-grade CIN and reduced incidence of invasive cancer, some pilot programmes started from 2010. In 2012 a Health Technology Assessment report, based on a systematic review of the literature, recommended moving to screening based on stand-alone DNA testing for high-risk HPV types as primary test, starting at 30-35 years of age and with 5 years intervals. In 2013 progressive conversion to HPV with this protocol was recommended by the Ministry of Health. In 2015 16% of all women invited for cervical screening, were invited for HPV. Participation on average increased after shift to HPV. The Italian protocol recommends reflex cytology for HPV-positive women. Those ≥ASC-US are immediately referred to colposcopy. Those with normal cytology are invited for new HPV testing after 1 year and referred to colposcopy if still positive. The proportion of HPV-positive women referred to immediate colposcopy varied strongly between programmes (from 20% to 57%) showing high variability in criteria of interpretation. However, the proportion of screened women referred to colposcopy immediately or at 1 year repeat was around 3.6% with little variation between programmes. At the first screening round with HPV, the age-adjusted detection of histologically confirmed CIN3+ was on average 1,6 fold that observed with cytology in the same centres before the shift, confirming a remarkable increase in sensitivity.

Are positive cone margins a disadvantage of LLETZ technique?

Škrtić B., Pitner I., Orsag N., Tučkar N., Kuna K., Djakovic I., Butorac D.
University Clinical Hospital Centre 'Sestre milosrdnice'

Introduction: LLETZ (Large Loop Excision of the Transformation Zone) is a procedure that removes the entire cervical transformation zone with low voltage diathermy loop.[1]

Simplified, the indications for LLETZ are HSIL changes with satisfactory colposcopic evaluation without any sign of malignant disease.[2]

The loops are available in a variety of sizes, allowing individualization and avoidance of excessive ecxision. The advantages of this technique are simplicity, speed and low price accompanied with good performance and a low rate of complications.[3]

In literature, the status of cone margins is often cited as an indicator of intervention success, but it is also a subject of disagreements in decisions of control.[4]

The goal: The comparison of efficiency of LLETZ and cold knife conization in relation to the incidence of positive cone margins in patohystological analysis of the cervical cone in University Clinical Hospital Centre 'Sestre Milosrdnice'.

Methods: The study is a prospective analysis of the data obtained from 568 female patients who had cone biopsy due to cervical changes in the University Clinical Hospital Centre 'Sestre Milosrdnice', in the period from 2012 until 2015. They are divided into two groups according to the type of conization.

First group includes patients operated using LLETZ technique and the other group consists of patients who had cold knife cone biopsy. Patohystological analysis for both groups was perfomed in the same laboratory of University Clinical Hospital Centre and classified according to WHO guidelines.

Results: 234 patients (41%) had cold knife biopsy and 334 patients (59%) had LLETZ conization.

In the period from 2012 to 2015 we can find a permanent increase in using LLETZ conization versus cold knife cone biopsy.

LLETZ was a method of choice in 59% of our cases, i.e. 334 patients, opposed to cold knife cone biopsy, which was used in 41% of the cases, i.e. 234 patients.

The percentage of positive cone margins was much higher with LLETZ technique, even 39% (131 patients), compared to 20% for cold knife cone biopsy.

We can also note a declining trend of occurrence of positive cone margins from 2012 when the percentage was 42%, compared to 2015 when the patohystological analysis confirmed 35% positive cone margins obtained by LLETZ technique.

In contrast, cold knife cone biopsy maintains more or less constant incidence of positive cone margins. The incidence of positive edges was 13% in 2012 and 12% in 2015.

Conclusion: The succes of surgical conization depends on the quality of technical equipment within the health facilities, on the training operators and on the medical opinions of actors.

Excision of the entire transformation zone is a diagnostic and therapeutical procedure for women with cervical neoplasia. The technique and cone configuration should be individualized, depending on the specifics of lesions. The transformation zone is not always removed during one procedure by cone biopsy.

According to our results, cold knife cone biopsy has a lower percentage of positive cone margins by almost 50% compared to LLETZ conization.

Due to the differences in the indications stated by current guidelines, different aproaches and different cone biopsy techniques, we can justify the differences in the state of cone margins.

The real succes of cone biopsy technique can be measured only by the appearance of the relapse frequency during a long period of time with a great number of patients.

1. Prendiville W Large loop excision of the transformation zone.Clin Obstet Gynecol. 1995 Sep;38(3):622--39.
2. Moss EL, Appleyard TL, Winning JM, Jones PW, Luesley DM. Indication and outcome of repeat large loop excision biopsies of the cervix J Low Genit Tract Dis. 2011 Apr; 15(2): 89--92.
3. Kenwright D, Braam G, Maharaj D, Langdana F. Multiple levels on LLETZ biopsies do not contribute to patient management. Pathology; 2012 Jan;44(1):7--10.
4. Treacy A, Devaney D, Mulligan NJ, Boyd W, O'Keane JC. Can a more detailed evaluation of excision margins refine cytologic follow--up of women post--LLETZ for high--grade dysplasia? Int J Gynecol Pathol; 2010 Sep;29(5):479--82.

Cervical cancer prevention strategy in Slovenia

Špela Smrkolj[1], Urška Ivanuš[2], Maja Primic Žakelj[2]
[1]University Medical Centre Ljubljana, Division of Gynecology, Slovenia
[2]Epidemiology and Cancer Registry, Institute of Oncology Ljubljana, Slovenia

Introduction: Cervical cancer, the second most common cancer in women, develops through well-defined precursor lesions with potential to progress to invasive disease if not properly detected and eradicated. In Slovenia National cervical cancer screening programme ZORA (NP ZORA), which is organised, population-based, nationwide screening programme was launched in 2003. Before that, two pilot programmes were implemented in two Slovenian regions in 1998 and 2001. Before the implementation of organised screening, the opportunistic screening was available to Slovenian women since the 1960□s.

Cervical cancer prevention strategy in Slovenia: In NP ZORA all female residents of the Republic of Slovenia aged from 20 to 64 may request an appointment for screening from their personal gynaecologist once every three years (+/– 3 months) without an invitation or referral. If a woman does not attend the examination on time, she is invited by her personal gynaecologist; if a woman does not respond, she is invited again. If the central screening registry ZORA does not record a Pap smear in four years, she is invited to an examination by the registry with central invitation; if she does not respond, she is invited again. Women finally determined as non-responsive are those who reply in writing that they do not want to attend for screening, and those who did not respond to two consecutive invitations from the screening registry. A woman loses the status of nonrespondent if a new smear is registered, or when she expresses her wish to attend for screening.

Programme providers are gynaecological teams at the primary, secondary and tertiary levels; cytopathology and histopathology laboratories; HPV triage test laboratories; regional offices of the National Institute of Public Health and the ZORA programme and registry department at the Institute of Oncology Ljubljana.

One of the most important conditions to be fulfilled for the effective operation of screening programmes is a good coverage of the target population by the screening test (coverage). Coverage represents a proportion of women with at least one smear among all the women in the target population (residents of Republic of Slovenia aged 20-64 years). The targeted three-year coverage is 70 %. If we compare Slovenian results with countries with well organised screening programmes from abroad which have a five-year screening interval, such as Finland and the United Kingdom, the five-year coverage in Slovenia is above 80%, which places Slovenia among the countries with the highest coverage in Europe.

The most important achievement of the ZORA programme is undoubtedly the desired reduction in the incidence of cervical cancer; from the introduction of the programme in 2003 until 2015, the incidence fell by almost 50%. In 2003 crude incidence rate was 20,7 and age standardised (world standard) 15,3 per 100.000 women, in 2015 these rates were 11,1 and 7,4 per 100.000 women. Praise goes to the gynaecological teams who regularly invite women to their screening exams, which certainly contributes to a good coverage which is one of the key factors for the success. Women that do not respond to invitations (non-responders) are mostly older (50–64 years old) and some of them don't have a selected gynaecologist. Although this group of women is smaller, more than half of all new cases of cancer are diagnosed within it, and the number has even grown in recent years. Other countries are developing different ways to include non-responders in screening programmes – either by special invitations or by offering them self-sampling at home. Slovenia follows these examples and in 2014 Institute of Oncology, the responsible institution for NP ZORA, has started a self-sampling pilot project in two Slovenian regions, aimed at increasing the examination rate in this group of women.

Conclusions: In Slovenia National cervical cancer screening programme ZORA (NP ZORA) was launched in 2003. Slovenian women well received NP ZORA and more than 70% of them regularly attend examinations. The most important achievement of the ZORA programme is undoubtedly the desired reduction in the incidence of cervical cancer; from the introduction of the programme in 2003 until 2015, the incidence fell by almost 50%.