Vaccines that prevent infection with two of the commonest human papillomaviruses associated with cervical cancer are available, and point of care tests for high risk human papillomavirus infection in cervical samples are likely to be available within the next year. Mapping of genetic polymorphisms predisposing to persistent HPV infection and cervical cancer is underway. These initiatives has prompted discussion about the best future approach to prevention of cervical cancer. We need still more information about the natural history of human papillomavirus infection of the cervix, and the genetic and environmental risk factors for progression of infection to cancer, before we can produce evidence based recommendations about optimal cost effective cervical cancer prevention. However, strategies will likely be adopted that involve vaccination as the primary preventative measure, and detection of persisting high risk HPV infection as the first line secondary measure, perhaps with particular focus of secondary screening on women at increased genetic risk. Colposcopically directed cervical biopsy will remain the gold standard for assessment of cervical pathology in women with symptoms, and in women with evidence of persisting HPV infection, though there should be steady reduction over the next 20 years in the need for surgical interventions to prevent cervical cancer.
Title: Epidemiology of Cervical Cancer Worldwide

Cervical cancer is a major cause of mortality and premature death among women in their most productive years in developing countries. Persistent infection with one or more of the oncogenic HPV types has been established as the primary cause of cervical cancer. In the majority of individuals, HPV infections resolve within 2 years. It is not clearly understood why HPV infections resolve in certain individuals and result in cervical intraepithelial neoplasias in others, but several factors are thought to play a role; including individual susceptibility, immune status and nutrition, endogenous and exogenous hormones, tobacco smoking, parity, co-infection with other sexually transmitted agents such as HIV, herpes simplex virus type 2 and Chlamydia trachomatis as well as viral characteristics such as HPV type, concomitant infection with other types, viral load, HPV variant and viral integration. Age-standardized rates less than 5 per 100,000 women were observed in middle-eastern countries, while they ranged between 5-10 per 100,000 in developed countries. High rates exceeding 35 per 100,000 were observed in sub-Saharan Africa and in certain populations in India and Latin America, which lack effective screening programmes. Worldwide, it accounted for an estimated 493,000 incident cases, 1.4 million prevalent cases and 273,000 deaths around 2002, constituting 8% of all cancers among women; four-fifths of this occurred in developing countries. Five-year survival ranged between 60-70% in developed countries and between 20-40% in developing countries. If effective prevention interventions are not implemented, over 1 million new cervical cancer cases will be diagnosed annually by the year 2030.
Diseases induced by Human papillomavirus (HPV) 16 and 18 infections and amenable to primary prevention include most external genital cancers in women (cervical, vulva, vaginal, anal) in men (penile and anal) as well as a fraction of cancers of the oral cavity and the oro-pharynx. In addition HPV 6 and 11 are responsible for the majority (>80 %) of genital warts and the rare cases of respiratory papillomatosis both juvenile and adult onset.

Cancer of the cervix uteri has been historically the number one cancer in women. In spite of the opportunities offered by screening programs still is the second most common cancer among women worldwide, with an estimated 493,000 new cases and 274,000 deaths in 2002. Cancers of the vulva and vagina account globally for some 40.000 new cases per year, cancer of the anus account for close to 100 000 cases of which 60% in women and penile cancer for some 30.000 cases annually. Oral cavity cancers and oro-pharyngeal cancers account for some 400 000 new cases per year in both sexes. In countries with screening programs a number of diagnoses of high grade and are produced, of which some 45-55 % are induced by HPV 16, 18, 6 or 11.

Cervical cancer clusters in developing countries, where 80% of the cases occur and account for at least 15% of all female cancers. In some of these populations the cumulative risk of developing cervical cancer is estimated in the range of 1.5 to 3%, while in developed countries it accounts for 3.6% of all new cancers in women with a cumulative risk of 0.8% up to 65 years of age. In general, the lowest rates (less than 15 per 100,000) are found in Europe (except in many of the Eastern European countries), North America, and Japan. The incidence is particularly high in Latin America (age-standardized incidence rates; ASR 33.5 per 100,000) and the Caribbean (ASR 33.5), sub-Saharan Africa (ASR 31.0), and South-Central (ASR 26.5) and Southeast Asia (ASR 18.3). Moreover, within the developed countries, cervical cancer also clusters in the lower socio economic strata, signalling the lack of appropriate screening as one of the major determinants of the occurrence of the invasive stages of the disease. Predictions based on the passive growth of the population and the increase in life expectancy indicates that the expected number in 2020 will increase by 40 % corresponding to 56% in developing countries and 11% in the developed parts of the world.

Mortality rates are substantially lower than incidence. Worldwide, the ratio of mortality to incidence is 55%. The 5- year survival rates vary between regions with good prognosis in developed countries (73% in US registries and 63% in European registries). Because cervical cancer affects relatively young women, it is an important cause of years of life lost. One recent estimate concluded that cervical cancer is the most important single cause of years of life lost (YLL) from cancer in the developing world. In Latin America, the Caribbean and Eastern Europe, cervical cancer makes a greater contribution to YLL than diseases such as tuberculosis or Acquired Immune Deficiency Syndrome (AIDS). It also makes the largest contribution to YLL from cancer in the populous regions of sub-Saharan Africa and South-Central Asia.
Title: Quality Assurance in Colposcopy

Colposcopy was introduced in 1925 as a screening tool for the detection of early cervical cancer, but quickly became established as a screening tool for cervical pre-malignant disease. When cytology was introduced, colposcopy found its place in the assessment of women with abnormal cytology. Some, however, still use it as a primary screening procedure, with or without cytology.

Two questions have to be addressed. First, does Colposcopy increase the accuracy of cytology, and the simple answer is no. As colposcopy becomes more widely used, and its use is encouraged, the second question is "HOW CAN COLPOSCOPY BE IMPROVED?" This is fundamental to the main objective of IFCPC, the promotion of high quality Colposcopy.

How then can IFCPC improve the quality of Colposcopy worldwide?
1 - introduce agreed minimum standards of training for Colposcopy.
2 - introduce agreed guidelines for the management of standard colposcopic problems.
3 - use standard terminology as defined by IFCPC in 2003.
4 - encourage colposcopists to audit their management and outcome of treatment.

The European Guidelines for Quality Assurance in Cervical Cancer Screening (2008) made the following recommendations -
1 - because of its low specificity, colposcopy is not recommended as a screening tool.
2 - colposcopy is an essential triage method for the management of women with abnormal cytology.
3 - colposcopy must be performed prior to the treatment of CIN.
4 - colposcopy should be performed ONLY be trained and experienced colposcopists.
5 - colposcopists should audit their work These principles are gradually being introduced in Europe, and are principles which should form the basis of worldwide colposcopy with the support and encouragement of IFCPC.

The European Guidelines for Quality Assurance in Cervical Cancer Screening can be accessed through the web site of the European Federation for Colposcopy (EFC) www.efc.cx and of the British Society for Colposcopy and Cervical Pathology www.bsccp.org.uk
Title: Immunology for the Gynaecologist

Host immune defences to pathogens are a partnership between innate immunity (phagocytes, soluble proteins e.g. cytokines, complement and epithelial barriers) together with adaptive immunity (antibody, cytotoxic effector cells). Put simply the innate immune system detects the pathogen and acts as first line defence and, it is estimated, clears 90% of microbial insults. Innate responses do not have memory but, critically, innate immunity activates the appropriate adaptive immune response that will kill and clear the pathogen and generate specific memory to the insult. Thus the adaptive, antibody mediated, humoral immune response clear pathogens from body fluids and surfaces and can prevent re-infection by pathogen, those of cell mediated immune (CMI) responses are essential for the clearance of infected cells and the generation of immune memory.
Title: Inequalities in Cervical Cancer Treatment and Survival between Maori and non-Maori Women in New Zealand

Cervical cancer is decreasing in New Zealand, yet significant inequalities exist between Māori and non-Māori women in both incidence and mortality. Improving access to cervical screening for Māori women is a priority given disparities in coverage. However, little is known about disparities in treatment. This study aimed to determine if disparities in survival and treatment exist between Māori and non-Māori women registered with cervical cancer between 1996 and 2006. Cancer registry data was linked to national hospitalisation and mortality (until 2005) data sets. Proportional hazards modelling was used to compare differences in treatment and survival between a cohort of Māori and non-Māori women diagnosed with cervical cancer, adjusted for age and stage. Between 1996 and 2006, 368 Māori and 1,683 non-Māori were registered with cervical cancer. Māori women were more likely to be diagnosed at a later stage of disease and have lower survival than non-Māori women (stage adjusted Hazard Ratio, Māori vs non-Māori 1.6, p<0.05). Survival disparities were found to be decreasing over time. After adjusting for stage, Māori were slightly more likely than non-Māori to receive total hysterectomy and brachytherapy (HR, 1.37 and 1.25 respectively, p<0.05) and slightly less likely to receive radical hysterectomy (HR 0.8, not significant). It is encouraging that survival differences between Māori and non-Māori women are improving. In addition, major disparities in treatment as demonstrated in other areas, are not apparent for cervical cancer. Preventive measures should maintain an inequalities focus in order to reduce disparities in incidence and mortality.
Title: Lessons from Success and Failure from Cervical Cancer Prevention in Japan

The cervical cancer screening program was introduced in the late 1950s and enacted as a national program in 1982 in Japan. The age-adjusted mortality rate of uterine carcinoma fell from 21.3% in 1960 to 5.3% in 1993. The cytological screening for the detection of cervical cancer demonstrated a sensitivity of 94.7%, specificity of 98.9% and a false negative rate of 5.3%. Cervical cancer screening program was successful to reduce the incidence and the mortality until 1995 in Japan. In 1997, poorly informed mass media reports claimed that mass screening for cervical cancer might not be effective. Furthermore, the Japanese national government stopped specific funding for cancer screening in 1998 for financial reasons, stating that local governments, not the nation, should provide funding for cancer screening. Since funding by the regional government is not provided in full, women have to make an out-of-pocket payment of 10-30% of the total cost of the screening. Recent coverage of cervical cancer screening is lowest among 22 OECD countries (Japan 23.7%). Because there is not enough reproductive health education in schools, adolescent and young women do not have the knowledge about cervical cancer or cervical cancer screening. Coverage between 20-39 aged women is only 7%. Older women have continued participation but remarkably fewer younger women participate in screening programs which may explain the increase in the incidence and mortality rate among young women. Low screening coverage must be due to insufficient knowledge of cervical cancer screening and less financial support by government. There are many problems facing the prevention of cervical cancer in Japan, such as low screening coverage, no HPV vaccine and a less political strategy for cost-effectiveness. In Japan, it is now urgent to educate people, doctors and the government on how to prevent cervical cancer. Public funding for school-based mandatory vaccination and high coverage of cervical cancer screening are most important for cervical cancer prevention. We should learn a lesson from the success and the failure afterwards in cervical cancer screening, and we are straightening the strategy for cervical cancer prevention in the near future.
Promoting Cervical Screening Following Implementation of the HPV Vaccine in Queensland

There have been significant reductions in incidence and mortality from cervical cancer in Australia since the introduction of an organised approach to cervical screening in 1991. These reductions are dependent upon women’s participation in regular screening using the Pap smear, however, participation rates in Queensland are consistently amongst the lowest in the country.

Queensland recently implemented a social marketing campaign to promote cervical screening particularly to women who are unscreened and underscreened for cervical cancer. A computer-assisted telephone interview (CATI) survey was conducted in June 2008 to assess the reach and recall of this campaign and gather information to inform future strategies to be undertaken within the Queensland Cervical Screening Program to increase women’s participation in cervical screening.

A random sample of 1,000 women aged 20-69 years who had not had a hysterectomy and who were resident in Queensland were surveyed to determine their knowledge of cervical screening, cervical cancer and human papillomavirus (HPV) and their knowledge and attitudes towards the HPV vaccine. Preliminary findings of this study will be discussed.

Within the context of the National HPV Vaccination Program, significant changes are anticipated to the National Cervical Screening Program in Australia. An in-depth understanding of women’s current knowledge of cervical screening, cervical cancer and human papillomavirus (HPV) and their knowledge and attitudes towards the HPV vaccine will inform future policies and health promotion activities in Queensland, Australia.
Title: Why the Introduction of Sensitive Vaccines Require Different Approaches in Indigenous Communities

Introduction: This Australian study examined the attitudes of Aboriginal Health Workers (AHWs) toward mass immunisation with the human papillomavirus (HPV) vaccine in one remote and one urban Aboriginal region. In Australia HPV vaccine mass immunisation was targeted to females between ages 9 to 26 years. Its introduction was considered highly sensitive in some cultural groups and raised challenging issues for those who administer, and those who are offered the vaccine. The HPV vaccine is particularly pertinent in Australian Aboriginal communities where there is a higher incidence of cervical cancer incidence and deaths than non-Aboriginal communities. The initial uptake of the third dose was low in some Australian regions.

Methods: Participants for the Aboriginal cultural group’s qualitative focus group discussions were purposively selected according to Aboriginal descendency, gender (female only), and AHW status. The sample is not representative of the wider cultural group in Australia. As one group cannot speak for another the results are not generalisable between communities. Recruitment was through Aboriginal health associations and clinics; and the Aboriginal Reference Group that advised the study. AHWs were educated about HPV vaccine prior to the study and disseminated the knowledge to their communities.

Results: The findings from AHWs demonstrated that the national introduction of sensitive vaccines cannot be generalised to Indigenous populations. Whilst there were similarities in attitudes toward support for the vaccine; adolescent behaviours; concerns about vaccine safety and efficacy there were significant differences in how communities should be educated; age of vaccination; stigma; perceived risk of promiscuity and infrastructure needs.

Discussions: By understanding the perspectives and development needs from two Aboriginal communities for culturally appropriate HPV vaccine information, education and resourcing, it enable insights into what is required for optimum and culturally sensitive delivery of the HPV vaccine. Global mass immunisation strategies need to consider specific issues relevant to Indigenous communities for high uptake.
**Title:** Compliance to Self-Collection for Hybrid Capture II for the Screening of Cervical Cancer and its Precursors in a Poor Community in Rio de Janeiro – Brazil – A Randomized Clinical Trial

**Introduction:** Pap smear has major limitations on its sensitivity and coverage, which limits the greatest reduction in mortality rates of cervical cancer. For these reasons, molecular diagnostic methods such as Hybrid Capture have been mentioned as a possible substitute of primary screening of cervical cancer.

**Objective:** to examine the compliance of a female population, living in the community of the Morro dos Macacos, Vila Isabel, Rio de Janeiro, Brazil, for self-collection of specimens for Hybrid Capture II (HCII) compared to the conventional Pap smear (PAP), obtained by physicians. Method: we performed a randomized controlled clinical trial in which women were recruited through home visits and randomly allocated to self-collection for HCII (51%) or for PAP (49%).

**Results:** a hundred women participated. The compliance in patients who were allocated to CHII was significantly higher than among patients allocated to PAP (68.8% and 32.7% respectively; p < 0.001). Conclusion: our findings suggest the self-collection for CHII can be an opportunity to reach women who are resistant or have difficulties of access to cervical cancer prevention programs based on cytology.
Title: Pap Test, HPV Test and Cervicography as a Triage for Positive VIA Test: Another Option for Cervical Cancer Screening in Developing Countries Along with Simple Cost Effective Analysis

Introduction: It was expected that the use of triage examination such as HPV test, Pap test, and cervicography could help reduce the false positive rates of VIA (Visual Inspection with Acetic Acid application) prior to making any referral for colposcopic examinations. In developing countries that possessed health facilities with limited resources such as Indonesia, efforts must be made to ensure that patient referral was made only for high-risk cases. The aim of this study was to gather information on the effectiveness of examinations in the form of positive predictive value and cost effectiveness analysis of Pap test, HPV test, cervicography as a triage examination in positive VIA test.

Methods: During the period of January 2005 to January 2006, colposcopy clinic of Cipto Mangunkusumo General Hospital Jakarta admitted 130 females with positive VIA test referred from 8 Primary Health Centers in Jakarta. During that period, 14 midwives of those Health Centers performed examinations in 1,250 women in accordance with inclusion criteria, i.e., ages between 25 and 45 years. Pap test, HPV test with Hybride Capture 2 method, cervicography and colposcopy were performed in all cases. Biopsies were done if there were any lesion. Data of the examination results were analyzed using a computer-based diagnostic test with Stata 7.0. Analysis of cost effectiveness analysis was performed using Treeage® software.

Results: In this study, positive VIA test results were found in 130 women (10.4%) of 1,250 women undergoing examinations with ages ranging from 25 to 45 years. The results of histopathological examinations showed the positive results of precancerous lesion in 67 women (its percentage also described Positive Prediction Value of colposcopy+biopsy examinations in the cases with positive VIA tests, i.e., 51.5%). Prevalence rate of cervical precancerous lesions in the present study was 5.4%, with a 0.2% high grade lesion prevalence of approximately 2% of the overall positive IVA cases that were referred. The results of Positive Predictive Value which also described effectiveness of each examination as a triage in positive VIA tests were: Pap test 82% (CI 95% 75%; 88%), HPV test 58% (CI 95% 49%; 66%), cervicography 94% (CI 95% 90%; 98%), Pap+HPV test 73% (CI 95% 64%; 79%), Pap+cervicography test 86% (CI 95% 81%; 90%), HPV+cervicography 78% (CI 95% 72%; 84%), Pap+HPV+cervicography test 77% (CI 95% 72%; 82%).

Conclusion: Either triage examination with Pap test, HPV test and cervicography or a combination of any of them could enhance the effectiveness and cost effectiveness of VIA test in detecting cervical precancerous lesions.

Keywords: VIA test, Pap test, HPV test, cervicography, triage, cost effectiveness analysis
Peri-Natal Mortality and Other Severe Adverse Pregnancy Outcomes Associated with Treatment of Cervical Intraepithelial Neoplasia: A Meta-Analysis

Study Objective: To assess the relative risk (RR) of peri-natal mortality (PM), severe preterm delivery (PD) and low-birth weight (LBW) after treatment for CIN.

Methods: Eligible studies, published between 1960 and 2007, were retrieved through a literature search, if they provided data on severe pregnancy outcomes for women with and without prior treatment for CIN. Considered outcomes were: PM, severe PD (<32/34 weeks), extreme PD (<28/30 weeks), LBW <2000g, <1500g and <1000g. Excisional and ablative treatment procedures were analysed separately.

Results: A significantly increased risk of PM was observed for women treated by cold knife conisation (CKC) (RR=2.87; 95%CI:1.42-5.81). Moreover, CKC was associated with a significantly higher risk of severe PD (RR=2.78; 95%CI:1.72-4.51), extreme PD (RR=5.33; 95%CI:1.63-17.40) and LBW <2000g (RR=2.86; 95%CI:1.37-5.97). Laser conisation (LC), described in only one study was also followed by a significantly increased chance of LBW <2000g and <1500g. LLETZ was not associated with a significantly increased RR of serious adverse pregnancy outcome. Neither was ablative treatment using cryotherapy (CT) or laser. However ablation by radical diathermy (DT) was followed by a significantly higher frequency of PM, severe and extreme PD and LBW below 2000g or 1500g.

Conclusions: In contrast to CKC, serious adverse outcomes have not been demonstrated after LLETZ. However, even the milder sequelae after LLETZ such as PD may result in perinatal morbidity, increased socio-economic burden and parental anxiety. The risk of these should be balanced against the patients’ characteristics and the need of minimum residual rates. Other factors related to the severity and the extent of disease might affect the degree of tissue destruction and may account for differences in pregnancy outcomes.
Presentation Abstract

**Speaker** Ms Fiona BRUINSMA

**Session Title:** C03: Free Communications

**Session Date:** Monday 20 October

**Session Time:** 1115 - 1300

**Session Venue:** Upper NZI Room

**Presentation Time:** 1130 - 1145

**Presentation Theme:** Epidemiology

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**Title:** Risk of Preterm Birth Following a Cervical Lesion - Is the Effect of Treatment Mediated by Prior Birth Outcome?

Many women diagnosed with a cervical lesion may not yet have begun or completed their childbearing and therefore pregnancy outcome is a significant issue. This analysis examined the relationship between treatment status, prior pregnancy outcome and the risk of subsequent preterm birth.

The study used a retrospective record-linkage cohort design. The cohort comprised women referred to the Royal Women’s Hospital, Melbourne (1982-2000) who subsequently had a birth recorded on the population-based Victorian Perinatal Data Collection system (n=5,548).

The interaction between previous pregnancy outcome and treatment status was tested in a multivariable model. Having a previous preterm birth was associated with an increased odds of preterm birth, regardless of treatment status (untreated – adjusted OR 2.37, 95% CI 1.30-4.31; treated -aOR 2.03, 95% CI 0.99-4.13). Treatment was associated with an increased odds among women with no known prior birth (aOR 1.42, 95%CI 1.08-1.87) but not among women who had a previous term birth (aOR 0.71, 95% CI 0.48-1.04). An alternative way to look at the data is to conduct a stratified analysis. Stratifying on the basis of prior birth outcome, treatment was associated with an increased risk of preterm birth among women with no prior birth (aOR 1.40, 95% CI 1.06-1.84) but not among women with a previous term birth (aOR 0.78, 95% CI 0.49-1.23), or a prior preterm birth (aOR 0.79, 95% CI 0.31-2.01).

The findings suggest that the highest risk groups are treated women with no prior birth and women with a previous preterm delivery, regardless of treatment status.
Title: An Audit of Invasive Cervical Cancer Review Process

The NHS Cervical Screening Programme has launched a systematic screening-history review for all cervical cancers diagnosed and recommends that the individual results be shared with patients.

Whilst the process is described, no performance benchmarking standards are provided. As we have carried out such reviews for several years we audited our experience for the period April 2003 to March 2007 with a view to identifying appropriate standards.

Ninety-eight of the 99 cases of invasive cervical cancers diagnosed in the study period were reviewed. Previously derived internal standards concerning documentation and the communication of results with members of the screening team (responsible gynaecologist, the pathology department and the hospital coordinator) were met.

In thirty-seven (38%) cases it was not appropriate or possible to invite the patient for a review consultation. Of the sixty women invited to discuss the results of the review, only 24 (40%) chose to attend. Only 9 (38%) respondents were seen within six weeks following completion of the review.

This time consuming exercise is feasible but the principle challenge is to share the results in a timely fashion. Only a minority of patients appear to want to know how it is they developed cervical cancer despite being in a screening programme.
The Effect of Cigarette Smoking on the Frequency of Colposcopy Visits, Treatments and Re-referrals

Current research has confirmed that cigarette smoking is a risk factor for cervical cancer. The objective of this pilot study was to observe if women who smoked and were referred to the colposcopy department at Christchurch Women’s Hospital, required more follow up visits, treatments and re-referrals compared to non-smokers. New patients (n=494) who attended at the Christchurch Women’s Hospital colposcopy department in 2001 had their data observed for a six year period. The results identified that women who smoked were three times more likely to need a third follow up visit and twice as likely to need further treatments to remove abnormalities when compared to non-smokers. This pilot study also identified that 71% of Maori women attending the clinic were smokers compared to 44% of non-Maori women. The results are being used to highlight to health professionals that treatment has a greater chance of success if patients cease smoking. The results have also supported the maintenance and development of the smoking cessation clinic for colposcopy patients at Christchurch Women’s Hospital where the link to cervical abnormalities and smoking is explained and behaviour modification is offered.

We also found that Maori women were poor attenders for colposcopy when compared to non-Maori and these results identified a need for further research and development of strategies to improve attendance.
Presentation Abstract

Speaker  Ms Jacqueline LOUWERS

Session Title:  C03: Free Communications
Session Date:  Monday 20 October
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Presentation Theme:  Gynaecology

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Title: Efficacy of HPV Testing in Women Attending a University Gynaecological Outpatient Clinic

HrHPV testing in addition to cytology improves the efficacy of cervical screening. In this retrospective study the additive value of hrHPV testing to cytology was studied in a population of women visiting the outpatient clinic of a university hospital.

The hrHPV GP5+/6+-PCR test was performed on all women (n=1166) who underwent a cervical smear test in the gynaecological outpatient clinic of the VU University Medical Center in Amsterdam, between January 1st and July 1st 2007. Management and treatment was according to routine clinical practice. History and follow-up data were retrieved from the Dutch nationwide network and registry of histo- and cytopathology (PALGA), the hospital information system and via re-call of the patients. Here, we focus on the women with normal cytology and a positive hrHPV test.

Of the women included 1016 (87.1%) had normal cytology, of whom 153 (13.1%) were hrHPV positive. Up until now, cytological or histological follow-up data are available for 44 of these women. Fourteen of them had one or more abnormal test results in follow-up. The histological abnormalities comprised CIN 1 (three women), CIN 2-3 (three women) and CGIN 2 (Cervical Glandular Intraepithelial Neoplasia; two women). Follow-up data of the other hrHPV positive women are currently being gathered.

The data collected so far underline the clinical relevance of additive hrHPV assessment as this resulted in the detection of additional cases of high-grade cervical disease. This warrants a further cost-effectiveness study with regard to routine hrHPV screening of a hospital population.
The latent human papilloma virus infection gave no characteristic changes in Pap-smears. HPV transmission during pregnancy from mother to child may occur and may have influence on placental function. Aim. The main aim of the study was to find DNA HPV in cervical smears and placentas proceeding from pregnancies complicated by FGR.

Material and methods: Two groups of women with normal Pap-smears were compared. The study group consisted of 60 pregnant women in pregnancy complicated by FGR. The control group consisted of 20 pregnant women in pregnancy with normal fetal weight. The samples for DNA presence were taken from uterine cervix and from the central part of placenta after the delivery. The presence of HPV DNA and typing of HPV using the PCR method were done.

Results: In the study group, in cases of DNA presence high risk HPV (type 16, 18) was found in 9% of cervical smears and in 100% of those cases HPV DNA was present in placental fragments. In 70% it was 16 type, in 30% 18 type. In the control group low risk HPV (type 6, 11) was found in cervical smears and 50% of those cases HPV was present in placenta.

Conclusions: The latent infection of high risk HPV might be the reason for materno-foetal transmission of HPV. High rate of high risk HPV in FGH group suggests the correlation between HPV infection and FGR etiology.
Title: HPV Infections in Adolescent Population and High School Rock Concerts for Education of Adolescent Population

In period from 2000 to 2006 a survey was conducted on a sample of 380 adolescent and young girls in the Zagreb area and 190 girls in Jastrebarsko area. The purpose of the survey was to indicate the difference in HPV types among urban and rural adolescent and young women population. The following examinations and tests were carried out: gynaecological exam, Pap test, colposcopy, including taking of epidemiologic anamnesis.

HPV genotyping was carried out by application of polymerase chain reaction method. The hypothesis was that HPV infection risk is higher in urban than in rural areas. Conclusions based upon given results: With correct and timely application of cytology, colposcopy and targeted biopsy in adolescents with cytological picture of dysplasia, accuracy of the diagnosis is increased, unnecessary conisation in avoided, and the follow up period is reduced. Cytological tests should be performed at least once a year beginning from the first sexual intercourse regardless of age. The most important factor in prevention of CIN is recognizing high risk adolescents (case history). The most effective prevention of sexually transmitted diseases is a stable, harmonious relationship, with a faithful partner. A necessary condition prior to the onset of sexual intercourse is a physical and mental maturity of both partners. It is recommended that the partner who has a urinary or sexually transmitted infection should first recover and then together with the partner maintain normal sexual hygiene. For systematic prevention of sexually transmitted infections diseases in this moment it is necessary: introduce an effective sexual education in schools starting from primary school, develop interdisciplinary cooperation between social and medical sciences, including all experts. Still the best and most important education comes from a healthy family as the core of our society.

We want to do something for that young population so we organized High school rock concerts. In appropriate assembly rooms of some Grammar and Secondary School of Zagreb during weekend evenings (Fridays, Saturdays) educational lectures held, were given about sexually transmitted diseases, particularly HPV and after the lectures rock concerts were held by some young so-called "demo" group consisting of secondary school students of Zagreb. Lectures were short (each 20-30 min) accompanied with discussion. Lecture was given in the form of Power Point presentation.

By organizing concerts the interest of that population to attend would be greater. Rock concerts after the lecture in some kind of bait for that population to be present at the lecture. By offering free refreshing beverages and media support by radio listened mostly by the young as well as the musical web portal, it has been tried to make popular the whole project. Questions made after the lecture were those usual for that age. They asked about the way of contracting HPV, medical treatment of partners and use of contraceptives and also about vaccina. Booklets explaining in a popular way the sexually transmitted diseases, way of catching infection and protecting methods were distributed. We continued with this project also in the this school year.
The Future of Cytology in Cancer Prevention

Cervical cancer is one of the rare cancers where there is easy access to the organ and the screening test is simple and relatively cheap. In addition, the slow progress of the disease means that there is a long period of time to detect precancerous lesions before they become invasive. The Pap screening has been very successful. However, this test is also limited in terms of its sensitivity and its low reproducibility. Even in developed countries the coverage is never 100%. In developing countries, the coverage is very low because of a lack of resources and a lack of pathologists and cytologists.

The HPV 16/18 vaccine has been developed thanks to virus-like particles (VLPs) which are non-infectious but which provoke the production of neutralising antibodies. The duration of the protection seems to be very good so there may be no need to do a repeat injection. However, the current vaccines only provide protection against 70% of cervical cancers. Also, they do not protect women who are already infected by HPV 16 or 18. This implies vaccinating much earlier than the average age of the first sexual experience. If women are vaccinated between 10 and 15 years old, the time necessary to begin to see the impact on this vaccinated population on the incidence of cervical cancer will be at least 20 years. The time necessary to see the total impact of vaccination, with the entire generation of women having been vaccinated, will be closer to 30-50 years. It is therefore evident that there can be no question of ending screening when vaccination is introduced because there will be a time shift in the impact of a vaccination programme of at least 20 years. This impact will also greatly depend on vaccination coverage. The impact on cervical screening programme by cytology will be much earlier and depends of the catch up population concerned by the vaccination programme (16-25 years). The vaccination will decrease the percentage of abnormal smears with lowering the probability of high-grade lesions but not much low grade lesions or minor atypia. Then cytology will be more prone to loss of accuracy. Then, for the young vaccinated women, primary HPV testing with triage by cytology and prolonged screening interval would be probably the best scenario. Pap screening or primary HPV screening for older non vaccinated women remains a debate. HPV screening on self sampled material in women who have not routine Pap screening could become more important. Cervical cancer prevention can be obtained in the future with the synergy of prophylactic vaccination for the young and adapted cervical cancer screening for the older women. Organized programme will permit to control the coverage, adapt the test and the interval to the age and follow appropriately the positive cases.
Title: HPV as a Primary Screening Test

Many studies showed that testing for the DNA of high-risk HPV is more sensitive (an increase over 50%), but less specific than cytology in detecting high-grade cervical intraepithelial neoplasia (CIN). Using both hrHPV DNA testing and cytology as primary screening tests (i.e. testing all women for both and referring to colposcopy those positive to either) further increased sensitivity only marginally compared to HPV alone but strongly decreased specificity. Therefore HPV DNA testing should better be used alone as primary screening test. On the other hand cytology may be used in order to triage HPV positive women. This means testing for cytology only HPV-positive women. Those with abnormal cytology are immediately referred to colposcopy while those with normal cytology are advised to repeat (after 12-18 months) and referred to colposcopy only if HPV infection is persistent. Randomised trials showed that this strategy, in women over age 30-35, allowed earlier detection of persistent high-grade CIN and that HPV negative women are at low risk of high-grade CIN for many years and can have prolonged screening intervals. This strategy also allowed increased sensitivity compared to cytology with only a slight loss in specificity among women aged 25-34 years, where HPV infection is very frequent. On the other hand, in this age group, direct referral to colposcopy of all HPV positive women could lead to overdiagnosis of regressive CIN and should be avoided. Different molecular methods (typing, viral load, E6/E7 mRNA transcripts, p16 overexpression) are under study for improving the specificity of HPV testing.
Title: Visual Screening with Acetic Acid (VIA) and Lugol’s Iodine (VILI)

Naked eye visibility of most cervical neoplasia after application of 3-5% acetic acid (VIA) or Lugol’s iodine solution (VILI) and the need for affordable, simple screening tests have prompted their evaluation in the early detection and prevention of cervical cancer in low-resource settings. A positive VIA is characterized by well-defined acetowhite lesions while a positive VILI is based on the appearance of definite mustard-yellow lesions on the cervix. Immediate results following visual screening have opened up ‘screen and treat’ or ‘single visit’ approaches allowing diagnostic investigations and/or treatment in the same session as screening to ensure a high compliance to treatment of screen-positive women. A range of personnel including doctors, nurses, midwives, and paramedical health workers can be rapidly trained in providing visual tests. The sensitivity of VIA to detect CIN 2 and 3 lesions and invasive cervical cancer varied from 37% to 95% and the specificity varied from 49% to 97% The sensitivity of VILI varied between 44-92% and specificity between 75-85% in cross-sectional studies in developing countries. The wide range in accuracy of visual tests in different studies underscores the subjective nature of the test, the varying competency of test providers, and the varying quality of reference standards used. Recently a 35% reduction in cervical cancer mortality following a single round of VIA screening has been demonstrated in a randomized trial. Although maintaining provider competence and quality assurance is challenging for visual tests, they do provide an affordable alternative approach for the early detection of cervix cancer.
Title: Cytological Assessment and Natural History of AIN

Anal cancer though relatively rare in the general community, has a much higher incidence in homosexual and bisexual men, and in women who have cervical, vaginal and vulval HPV associated lesions. The incidence in women, particularly those infected with HIV, or otherwise immunosuppressed, is poorly documented. Highly active antiretroviral therapy (HAART) for the treatment of HIV/AIDS has had a substantial impact on the incidence and natural history of many AIDS associated conditions, but as it appears that HAART has no ameliorating influence on anal intra-epithelial neoplasia, it is likely that as survival improves the incidence of anal neoplastic disease will increase further.

Screening for anal intra-epithelial neoplasia by cytologic assessment of "liquid based" anal cellular samples has similarities to, and differences from cervical cytologic assessment. These will be discussed. The reported sensitivity and specificity of such tests varies widely depending upon the quality of the sample and the experience of the pathologist. Screening utilising a combination of cytology and HPV DNA testing improves the accuracy of detection of significant disease as correlated with anoscopic and histologic follow-up.

The long term prevention of anal HPV associated disease by universal HPV vaccination in immunologically competent individuals may not be mirrored in an immunosupressed population.
Title: Anoscopic Assessment of AIN and Anal Cancer

The use of High Resolution Anoscopy (HRA) has increased over the last 10 years, although there are still relatively few clinicians trained to perform this procedure. Those with skills in colposcopy of the lower genital tract may consider adding this skill to their practice, after an appropriate preceptorship with a clinician experienced with this procedure. The cervical transformation zone serves as a mode for the anal transition zone. Some of the same abnormal colposcopic findings seen on the cervix such as aceto-white epithelium, punctation and mosaic, are also seen in the anal canal. The case studies presented will demonstrate various grades of presenting anal cytology and the corresponding HRA view of the squamocolumnar junction, the anal canal, and the peri-anal region. The lesions will range from benign warts to anal cancer.
**Title: Treatment and Follow up of AIN**

High-grade anal intraepithelial neoplasia (HGAIN) has the potential to progress to anal cancer and treatment of HGAIN may reduce the likelihood of progression, analogous to the treatment of cervical intraepithelial neoplasia to reduce the incidence of cervical cancer.

There are several approaches to treatment of HGAIN. None have been evaluated in rigorous randomized controlled trials, but there is a growing literature on different treatment approaches in relatively small cohorts of patients. At the University of California San Francisco, patients are treated at the UCSF Anal Neoplasia Clinic, a clinic devoted to treatment of AIN. Treatment is based on the location, size and number of lesions.

Small peri-anal lesions may be treated with local ablative measures such as electrocautery, 85% trichloroacetic acid (TCA) (1) or liquid nitrogen. Success has been reported in some studies using imiquimod (2). Larger lesions may require surgical excision, and topical 5-fluorouracil cream may be used to reduce the size of the lesion to allow for local ablative measures.

Small intra-anal lesions may also be treated with TCA (1). Larger lesions may be successfully treated with infra-red coagulation (IRC), an office-based procedure that is relatively simple to perform and well tolerated by patients (3-5). Lesions that are too large for IRC may be surgically excised (6). Topical 5-fluorouracil cream may be useful to reduce the size of the lesion, and intra-anal imiquimod has been reported to clear high-grade lesions in some patients (2). Other experimental treatment approaches include photodynamic therapy and topical cidofovir.

Lesions that are too large for treatment such as those that are diffuse, may benefit from close surveillance, e.g., every 3-4 months. The rationale is to monitor for progression to cancer. If a cancer is detected early enough, it may be possible to excise the lesion locally and avoid the morbidity associated with chemoradiation therapy, the current standard of care for anal cancer.

In all cases, patients undergoing treatment for HGAIN must remain in close follow-up due to risk of lesion recurrence or development of metachronous lesions. At UCSF patients are followed every 3 months after their lesion is cleared. If they remain disease-free for one year, they are placed on an annual screening regimen, consisting of a combination of cytology and high resolution anoscopy-guided biopsy.

**References**

Title: Clinical Evaluation of Cytology with Borderline Nuclear Changes in Glandular Cells

The National Health Service Cancer Screening Programme (NHSCSP), UK recommends referral for colposcopic assessment after a single smear with borderline nuclear changes in glandular cells. The aim of this observational study was to review the outcome of this management approach.

Method: A retrospective study of 222 women screened with a smear reported as borderline nuclear changes in endocervical cells or glandular cells between January 1997 to December 2006 (10 years).

Result: 114 women had conservative management following colposcopy and 39 had treatment with LLETZ or Laser. The rest 69 had conservative management without colposcopy. This study showed that women with borderline nuclear changes in glandular cells 0.09% had invasive diseases, 13.06% had High grade pre-invasive disease. Those who were conservatively managed a high grade lesion developed in 6% cases during a follow-up of 1-6 years. In the small subgroup analysis (n=27), HPV-DNA testing showed a NPV of 100%. It is the largest study on borderline glandular cytology with long term follow up.

Conclusion: With a similar incidence of high grade CIN (10%) and no greater risk of invasive disease, our analysis strongly suggests that conventional BNA in glandular smears can safely be triaged in the same way as conventional BNA in squamous cells. We believe a larger prospective study will be able to give us better information on this small but clinically significant subgroup of abnormal cytology.
Title: High Risk HPV Testing in the Follow-Up of Women treated for High-grade Squamous Intraepithelial Lesions – A Pilot Study

Objectives: To evaluate the proportion of women who test positive for high-risk HPV at their first follow up visit after treatment for high grade cervical intra-epithelial neoplasia. To calculate the costs and feasibility of using cytology in combination with hr HPV testing compared with cytology plus colposcopy to manage initial follow up for CIN 2/3. To evaluate the preference of patients with regard to these alternatives.

Design: 100 women attending colposcopy for first follow up visit after treatment of histologically confirmed HSIL (CIN 2 and 3) were evaluated for the presence of high risk HPV using Hybrid Capture 2 test on cervical samples collected in Sure Path liquid media. Clinical, epidemiological and cost data were used to calculate the cost effectiveness of the alternative regime. Women were asked to complete a survey of their preference.

Results: 85% of women treated for CIN2/3 tested negative for high risk HPV at first follow-up visit carried out 3-18 months post treatment. 75% had both negative cytology and a negative HPV test. This would represent a significant proportion of women who could be offered an alternative to routine colposcopic follow-up. The implications in the allocation and use of colposcopy resources at both a local and a national level are significant.

Conclusions: Removing the need for colposcopic examination in the routine follow up is cost effective and likely preferable to the women involved. This may consequently improve compliance with recommended surveillance schedule. A larger study would be required to prove equivalent safety.
Title: Effective Follow-up Post-treatment of CIN: Evidence for Combined Cytology and High Risk HPV Testing to Effectively Reduce the Duration of Intensive Follow-up

Objective: To evaluate HPV testing in combination with cytology in the follow-up of treated women.

Methods: A prospective cohort study of 917 women was recruited from 3 major UK centres after treatment for cervical intraepithelial neoplasia (CIN). These women were recruited at 6 months follow-up and cytology and HPV testing using HC II was carried out at 6 and 12 months. If either result was positive, colposcopy and any necessary interventions were performed. At 24 and 36 months, cytology alone was performed.

Results: At recruitment, 700 women had had high grade CIN (CIN grades 2 or 3) and 217 CIN1. At 6 months, 14.6% were HR HPV+ve and 10.7% had non negative cytology. Of those with negative cytology, 9% were HPV positive. By 24 months of follow-up, 9 of 10 detected cases of residual/recurrent CIN3/CGIN occurred in HR HPV+ve women. One case of cancer was identified at 23 months in a woman treated for CGIN with clear resection margins, who had been cytology –ve/Hr HPV-ve at both 6 and 12 months. Follow-up date out to 36 months follow-up will be presented.

Conclusions: Combined cytology and HR HPV testing at 6 months following treatment for CIN can safely allow women who are double negative to return to three year recall.
**Presentation Abstract**

**Speaker** Ms Jacqueline LOUWERS

**Session Title:** C06: Free Communications

**Session Date:** Monday 20 October

**Session Time:** 1415 - 1600

**Session Venue:** Upper NZI Room

**Presentation Theme:** Gynaecology

**Presentation Time:** 1500 - 1515

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**Title: Colposcopic Criteria to Identify Cervical Lesions Containing hrHPV**

Since koilocytosis is considered a manifestation of human papillomavirus (HPV) infection and koilocytotic cells might react differently to acetic acid, we aimed to define criteria that allow distinguishing hrHPV positive cervical lesions by a specific colposcopic image.

We retrospectively included all women who underwent colposcopy between 1998 and 2006 in the VUmc, Amsterdam, the Netherlands of whom a colposcopic image and a GP5+/6+-PCR hrHPV test result was available. First, 132 women were studied as a pilot to formulate a scoring system based on transformation zone visibility, acetowhitenning, punctation, mosaicism, atypical vessels, demarcation, leukoplakia, satellite lesions, cysts, gland openings, number and size of lesions and iodine reaction. The remaining 384 colposcopic images were scored using this system.

hrHPV positive lesions (n=296) were on average larger than hrHPV negative lesions and showed a coarser and more irregular punctation pattern (p = 0.045 and p = 0.041, Mann-Whitney test). When stratified for histological grade, no significant differences were found anymore, mainly because the abnormal features were particularly associated with high-grade lesions that were almost exclusively found in hrHPV positive women. When the combined score of punctation, mosaic pattern and lesion size was 6 or more (scale: 0-9), the positive and negative predictive values for a high-grade, hrHPV positive lesion were 91% (95%CI 82-99) and 25% (95%CI 20-29%).

hrHPV positive, high-grade lesions can be detected by a simple scoring system. There are no colposcopic criteria for the detection of hrHPV infections that are not associated with a high-grade lesion.
Title: A Low Rate of CIN2+ Following Negative Colposcopy in Women Originally Referred with HPV Positive Low-grade Cytological Abnormalities

Results from a National Screening Programme Pilot of HPV triage for low-grade cytological abnormalities, demonstrated a reduction in the rate of repeat cytology of over 70%. HPV triage is currently being evaluated on a wider scale prior to consideration for national implementation. In this context, there is a need to determine the ongoing management of HPV positive triaged women, who are found to have negative colposcopy at referral.

From the original pilot study cohort, we identified 948 HPV positive women with first borderline or mild dyskaryosis (ASCUS/LSIL) who had had negative colposcopy following referral and then had at least one year of follow-up and/or further cytology with related colposcopy outcomes. Liquid based cytology was used ThinPrep or Surepath and Hybrid Capture 2 for HPV testing.

Of the 948 women, 569 originally had borderline and 379 had mild dyskaryotic cytology. The rate of CIN2+ in women aged 25-34 and 35-64 years was 1.2% and 2% respectively. The rate overall was 1.5%; 1.2% and 1.9% in women with borderline and mild dyskaryosis respectively.

The rate of CIN2+ overall of 1.5% across the age range for borderline/mild dyskaryosis, is similar to that expected in the screened population. The data suggest that in the quality assured setting of the NHS Cervical Screening Programme that triaged women with negative colposcopy could be considered for return to recall.
Title: HPV: Burden of the Disease in Cervical Cancer in the Extended Middle East and North Africa (EMENA): A Comprehensive Review

Introduction: Cervical cancer is less common in the EMENA. The purpose of this paper is to review the prevalence of HPV in cervical cancer in the EMENA.

Materials and methods: We performed an extensive literature search (English and French literature). Data extracted included information on the method of HPV detection and HPV type-specific data. Other data included age and histology when available.

Results: In North Africa (Algeria, Morocco and Egypt): The prevalence of HPV varied between from 61-98% with HPV 16 as the predominant type (50-73%) followed by HPV 18.
In the Middle East (Jordan, Lebanon, and Israel): The prevalence of HPV varied between from 45-78% with HPV 16 as the predominant type (31-67%) followed by HPV 18.
In the gulf countries (UAE): High risk HPV was present in 87% of specimen.
In Turkey, Iran and Pakistan: The prevalence of HPV varied between from 60 to 100% with HPV 16 as the predominant type in 27-95% of specimen followed by HPV 18.
The studies were varied with small number of patients and varied detection methods that are difficult to compare. Most were PCR. The average age was 30-70 years.

Conclusions: Although the studies on the prevalence of HPV in the EMENA region are not abundant, but there enough data to suggest that the prevalence of HPV in cervical cancer is around 60-90% with HPV 16 as the most predominant type.
Title: Difference Does Matter with HPV Vaccine Mass Immunisation Programs. Critical Issues for Mass Immunisation of HPV Vaccine in Mixed Culture Communities from the Australian Experience

Introduction: This study investigated the influence of culture on the attitudes and intentions of parents from three diverse cultural groups in Australia towards HPV vaccination among preadolescent children; General Practitioners [GPs] (family physicians) and Aboriginal Health Workers [AHWs]. It showed that cultural difference and geography does matter and how attitudes, social norms and experiences of both consent givers and health providers impact on vaccine uptake, education resources and infrastructure needs.

Methods: Participants (15 per group) for the qualitative semi-structured interviews were purposively selected according to ethnicity, gender, age and drawn from two specific categories: (i) Australian parents [male and female] of Anglo, Aboriginal and Chinese descendency (ii) practicing GPs; and AHWs. This sample is not representative of the wider cultural group. Recruitment was through hospital clinics; AHW networks; related cultural and medical associations.

Results: Challenges facing uptake of HPV vaccine were varied reflecting Australia’s cultural and geographic diversity and its influence on (i) HPV vaccine communication and education (ii) informed consent (iii) vaccine uptake. GPs and AHWs demonstrated a positive attitude but conceded it was difficult to explain to some parents why sexually naïve children will benefit from a vaccine for a sexually transmitted virus. Parents displayed diverse social and cultural values, attitudes and information needs toward the vaccine that influenced HPV education and communication interventions; and intentions to consent.

Discussion: There has been a low uptake of the third dose of the quadrivalent HPV vaccine in some regions of Australia. Culturally sensitive messages and planning will play a key role in HPV vaccine education, delivery and uptake. Successful implementation and uptake of the HPV vaccine in multicultural nations is complex and challenging. It requires a coordinated national effort and understanding of the role of culture and diversity as integral to successful HPV vaccine mass immunisation programs.
Presentation Abstract

**Speaker**  Dr Richard HILLMAN

**Session Title:**  C05a: Anal Intraepithelial Neoplasia CONTINUED  
**Session Date:**  Monday 20 October  
**Session Time:**  1630 - 1730  
**Session Venue:**  Lower NZI Room  
**Presentation Time:**  1650 - 1710  
**Presentation Theme:**  Epidemiology

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**Title:** Screening and Prevention Strategies for AIN  

To evaluate the usefulness of anal cytological screening, we conducted a retrospective case note review of 335 attendees at an anal dysplasia clinic in Sydney, Australia from July 2002 to May 2008. Clinically indicated anal swabs were taken and eluted in ThinprepTM bottles for Papanicolaou staining. High Resolution Anoscopy (HRA) was then performed and biopsies taken from identified abnormalities.

"Most recent" & "most serious" anal cytological results were then compared with the most severe histological result obtained at HRA. The "Most recent" analysis considered only pairs of cytology and histology results obtained within 3 months of each other. The "most serious" analysis paired each biopsy result with the highest grade Pap result ever recorded. "Most recent" comparisons thus explored the possible implications of a single anal cytology result, while "most serious" comparisons explored the possible implications of an anal cytology screening program.

Results are given in the Table below:

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<th>Pap Test</th>
<th>Most Recent</th>
<th>Most Serious</th>
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| Cytological negative result as an indicator of histological LSIL or below | 82.9%  
82.9% | 39.5%  
77.1% | 70.4%  
70.4% |
| Cytological HSIL result as indicator of histological HSIL | 27.4%  
46.2% | 70.0%  
83.3% |

These results show that a most recent negative Pap smear was a good indicator of the absence of high grade dysplasia (82.9% sensitivity). In addition, the "most serious" Pap was a useful indicator for the presence of high grade dysplasia.

In this particular setting, the sensitivities and specificities of anal cytological screening appear to be broadly comparable to those seen in cervical screening programs.

* presenting author
Vulvar Pain

Vestibulodynia, or localized vulvodynia, formerly named vulvar vestibulitis, is a common cause of dyspareunia. Until 1981, dyspareunia was considered a result of vaginismus. Since then it was discovered that dyspareunia can be caused by vestibulodynia, a physical condition characterized by hyperesthesia of the vestibule. In a population based study, 16% of women aged 18-64 reported histories of chronic vestibular burning, knifelike pain, or pain on contact that lasted three months or longer. This highly prevalent condition causes many women to abstain from intercourse. The etiology of localized vulvodynia has yet to be elucidated. Histopathologic evaluation of the vestibule in these women reveals chronic inflammatory infiltrate, a significant number of mast cells around the superficial minor vestibular glands, and an increase in the number of nerves in the vestibular stroma and epithelium.

The diagnosis of vulvar vestibulodynia is based on the 1987 Friedrich's clinical criteria: 1. severe pain upon vestibular touch or attempted vaginal entry; 2. tenderness to localized pressure within the vulvar vestibule, and 3. physical findings confined to vulvar erythema of varying degrees.

Currently, the most effective therapy for localized vulvodynia is surgical excision of the vulvar vestibule. Other treatments are rehabilitation of pelvic musculature using biofeedback techniques, topical oils or anesthetic creams, behavioral therapy, low dose tri-cyclic antidepressants, certain anti-convulsants, such as Gabapentin and Pregabalin, low oxalate diet, and local interferon injections.

Several treatments are used for vestibulodynia, with the most common being surgical excision of the vestibule (Vestibulectomy, Perineoplasty) and biofeedback pelvic muscle training.
**Presentation Abstract**

**Speaker**  Dr Andreas CLAD

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<td>1645 - 1700</td>
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<td>Gynaecology</td>
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**Title:** Imiquimod Treatment of Vulval Condyloma Removes both Vulval and Cervical Warts

Imiquimod, an immune modifier that stimulates Langerhans cells via the toll like receptor 7, is known to be effective in removing genital warts. The objective of this study was to evaluate whether Imiquimod had to be applied on all genital warts or whether distant warts that are not directly treated with Imiquimod would also go into remission. Thirteen women with multiple vulval warts and concomitant condyloma on the cervix uteri were treated with Imiquimod. Imiquimod was exclusively applied on the outer vulva 2-3 times weekly. All women showed complete remission of all vulval condyloma at the end of treatment. On average 40 sachets Imiquimod were applied. In all of these 13 women all cervical condyloma also disappeared during the treatment period although Imiquimod was not applied intravaginally. These data strongly suggest that Imiquimod also acts on “distant warts”.

Langerhans cells are stimulated to phagocytosis by Imiquimod and migrate to the regional lymphnodes where they activate specific cytotoxic T-cells. These activated T-cells attack HPV infected cells not only at the site where Imiquimod was applied, but also at other sites where epithelial cells were infected with the same HPV-type.
Title: Developing Optimum Follow-up Strategies After Treatment of CIN: A C-5 Group Follow-Up Scoring System (FUSS)

Introduction: To evaluate the accuracy of various markers alone or in combination to predict treatment failure (TF) following treatment of CIN.

Methods: In a prospective study, women treated by LLETZ were assessed at regular intervals with cytology and colposcopy. At the same assessments, samples were also collected for HPV testing and typing, viral load, p16 and microspectroscopy. Women with cytologic or colposcopic suggestion of residual disease who had repeat excision that confirmed CIN were TF. Those with normal cytology and colposcopy during the first 2 post-operative years or with negative histology at repeat excision were considered as treatment successes. Accuracy parameters for cytology, colposcopy and the new markers were assessed for each test alone or in combination together with histopathological information and age.

Results: 363 women completed 2 years of follow-up. Out of 33 who underwent a repeat LLETZ, twenty-six were histologically confirmed TF. At 6 months the sensitivity was highest in cases of positive HPV testing, followed in decreasing sequence by positive HPV typing, p16, high viral load, cytology and colposcopy. The simpler combination that provided almost 100% negative predictive value at 6 months was that of negative cytology and HPV testing with favourable histopathological variables and age less than 35.

Conclusion: HPV test, cytology and p16 staining give the highest prediction of TF. The combination of HPV testing, cytology, initial histology and age could allow the distinction of low risk cases that could return to routine screening. All the above parameters should be evaluated in a cost analysis and could be integrated in a TF prediction scoring system, allowing tailored post-treatment surveillance.
Presentation Abstract

Speaker  Dr Bjorn STRANDER

Session Title:  C08: Free Communications
Session Date:  Monday 20 October
Session Time:  1630 - 1745
Session Venue:  Upper NZI Room
Presentation Time:  1715 - 1730
Presentation Theme:  Gynaecology

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Title: Swede-Score - A New Colposcopic Scoring System

Aim: To construct a simple and easily understandable scoring system for colposcopic examination that can facilitate education of colposcopists and increase the accuracy of evaluation.

Materials and methods: 297 examinations were performed in women referred for colposcopy according to the current protocol for the Western Region of Sweden. Histology results were as follows: 30% benign, 25% Low grade lesions (LGL) 45% High grade lesions (HGL) including cancer. Five colposcopic variables were scored: aceto-whiteness, margins & surface, vessels, lesion size and iodine staining. Each variable could be assigned one of three ordered values. Exclusion criteria were post-menopausal, pregnant and puerperal women, and incomplete colposcopy. Multiple logistic regression was used to assess the ability of each single score to predict high-grade lesions in histology (cone or biopsy).

Results: All five studied variables independently predicted for High grade lesions. The analysis resulted in an “ideal” weighted scoring system which performed well with respect to sensitivity and specificity (area under the ROC-curve 0.90). However, the values generated involved decimal places which reduced the practical use of this system. Rounding off of each weight gave a more useful and simple scoring system with values of 0, 1 or 2 without any change in the area under the curve, 0.90. The possible total score was then 0 to 10. A score of ≥5 points identified all HGL and ≥8 points had a specificity of 90%. No patient with HGL in histology scored 0 with respect to aceto-whiteness or margins & surface.
Title: Cervical Screening Failures: An Analysis

Method: Detailed analysis of cervical cancer cases that develop despite the presence of a comprehensive national screening programme can yield information on the effectiveness or inadequacies of the programme.

Results: A review of 88 cervical cancers diagnosed in the triennium 2003-2006 was undertaken and cases categorised using the NHSCSP (2006) criteria.

Conclusion: The majority of the cancers (66%) were Stage 1B1 or less at presentation. There was a significant difference in age and stage of disease, Stage 1 cancers were diagnosed at a younger age, p=0.03. Seventy-five women (85%) had had at least one smear in the past. There was no association between the number of smears performed and the age of the patient, p=0.197. 12 patients (14%) had previously been referred for colposcopy. One screening programme problem was identified in 46 cases and multiple problems in 12 cases. The most common problem was patient compliance, identified as the principle-contributing factor in 40 cases (45%). Cytological undercall was found to be the major factor in 15 cases (17%). 95% of the screen detected cases were Stage 1 at diagnosis compared to 42% in women classified in the ‘never attended’ or ‘never invited’ categories. The greatest numbers of lapsed attendees were women aged between 30-39 years, 11 out of 26 cases.

Avoidable factors can be identified in the majority of cervical cancers that occur within an established screening programme.
Title: The Invasive Potential of Cervical Intraepithelial Neoplasia 3

In 1966 the Senior Medical Staff at the National Women's Hospital in Auckland agreed to a proposal by Dr Herbert Green to attempt to verify his premise that carcinoma in-situ of the cervix (now termed CIN3) was not a precursor of invasive carcinoma. From 1965 some women received no treatment of curative intent, often only a diagnostic punch or wedge biopsy, the purpose being to confirm the diagnosis and exclude invasive cancer. Women were followed with repeated clinical, cytological, and sometimes colposcopic examinations. Persistent abnormalities were often not considered an indication for treatment. The study was not a randomised trial, not all women with CIN3 were under Green's care and no records exist of which women were chosen for the study.

Alarmed by the number of women developing cancer, the hospital cytologist/colposcopist, Dr Bill McIndoe (and later his pathology colleague, Dr Jock McLean) expressed their concerns to the hospital authorities and a hospital "Working Party" investigated these concerns but failed to adequately resolve the issues or terminate the study.

Frustrated by the failure of the hospital authorities to address his concerns, McIndoe began presenting his interpretation of the natural history of CIN 3 (Green's study) at international conferences, the first being the 3rd World Congress of the IFCPC in Florida in 1978. I presented a further follow-up report at the 5th IFCPC World Congress in Japan in 1984 and the findings were published the same year. (1) In this study based solely on cytology follow-up (not on adequacy of treatment), cancer of the cervix or vaginal vault developed in 18% of women with positive follow-up cytology at 10 years and 36% at 20 years.

In 1987-8 a Committee of Inquiry, headed by Judge Sylvia Cartwright examined the issues arising from Dr Green's unethical experiment. (2)

This study has recently been updated. (3) The medical records, cytology and histopathology of 1,063 women with CIN3 diagnosed women 1955 and 1976 were reviewed. To take into account the CIN3 lesion may have been completely removed, we classified adequacy of treatment by type of procedure, presence of CIN3 at the margin, subsequent cytology and where appropriate, censored for subsequent adequate treatment.

In 143 women managed only by punch or wedge biopsy the cumulative incidence of invasive cancer of the cervix or vaginal vault was 31% (95% CI 22.7-42.3) at 30 years and 50.3% (CI 37.3-64.9) in the subset of 92 women who had persistent disease within 2 years. However, the cancer risk in 593 women whose initial treatment was adequate and where treatment of recurrent disease was conventional, the cancer risk was only 0.3% at 10 and 20 years and 0.7% at 30 years. Thus, untreated women had 50-100 times the risk of invasion compared with women treated by full excision. This study provides the most direct estimates yet available of the rate of progression from CIN3 to invasive cancer.

REFERENCES:
**Presentation Abstract**

**Speaker** Lois EVA

**Session Title:** C10: ISSVD Sponsored Session

**Session Date:** Tuesday 21 October

**Session Time:** 0835 - 1015

**Session Venue:** Lower NZI Room

**Presentation Theme:** No Theme Allocated

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### Terminology of Vulval Lesions

**VULVODYNIA**
- **Generalized**
  - Provoked (sexual, non sexual or both)
  - Unprovoked
  - Mixed
- **Localized (vestibulodynia, clitorodynia etc)**
  - Provoked
  - Unprovoked
  - Mixed

**VULVAL INTRAEPITHELIAL NEOPLASIA**
- **VIN, Usual type**
  - Warty type
  - Basaloid type
  - Mixed type
- **VIN, Differentiated type**
- **VIN NOS (unclassified)**

**VULVAL DERMATOSES**
- **Spongiotic pattern**
  - Atopic dermatitis
  - Allergic contact dermatitis
  - Irritant contact dermatitis
- **Acanthotic pattern (formerly, squamous cell hyperplasia)**
  - Psoriasis
  - Lichen simplex chronicus
- **Primary (idiopathic)**
  - Secondary (superimposed on lichen sclerosus, lichen planus, or other vulvar disease)
- **Lichenoid pattern**
  - Lichen sclerosus
  - Lichen planus
- **Dermal homogenization/sclerosis pattern**
  - Lichen sclerosus
- **Vesiculobullous pattern**
  - Pemphigoid, cicatricial type
  - Linear IgA disease
- **Acantholytic pattern**
  - Hailey-Hailey disease
  - Darier's disease
  - Papular genitocrural acantholysis
- **Granulomatous pattern**
  - Crohn's disease
  - Melkersson-Rosenthal syndrome
- **Vasculopathic pattern**
  - Aphthous ulcers
  - Behcet's disease
  - Plasma cell vulvitis

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* presenting author
Lichen Sclerosus, Lichen Planus and Lichen Simplex

Lichen sclerosus is an autoimmune skin disorder most common in females and affecting the vulval skin more often than non-genital skin. It has a characteristic morphology consisting of white patches and plaques which may be localised or generalised on the vulva. Atrophy of medial vulval skin can occur with burying of the clitoris and loss of labia minora. Itch is a common symptom but some patients have no symptoms. In most cases there is a good response to treatment with a potent topical steroid. In about 4% of patients a squamous cell carcinoma of the vulva develops within lichen sclerosus.

Lichen planus is another autoimmune skin disorder, which sometimes affects the vulva. It occurs less frequently on the vulva than lichen sclerosus. The vagina is often involved. Two main types are seen: Erosive vulvovaginitis and papular lichen planus. In the former there is painful erosion and inflammation of the vulval skin and vaginal mucosa. The second type has a similar appearance to lichen planus elsewhere on the skin with purplish papules and plaques with characteristic Wickham’s striae (white lines forming a lacey pattern). The two may co-exist and often there will be lichen planus on the non-genital skin and other mucosal surfaces. Treatment is with topical steroids both on the skin and in the vagina. Systemic therapy may be required and some cases are refractory to treatment. There is an increased incidence of squamous cell carcinoma.

Lichen simplex is a response to prolonged itching and scratching developing on normal skin, and results in thickened white plaques of skin with excoriations, and is indistinguishable from chronic dermatitis or lichenification which develops secondarily in a number of dermatoses, including atopic dermatitis, contact dermatitis either irritant or allergic and seborrhoeic dermatitis. Treatment aims to stop the “itch-scratch-itch” cycle by avoidance of irritants such as soap for washing, and use of topical steroid preparations.
Presentation Abstract

**Speaker**  Dr Mary RUBIN

<table>
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<tr>
<th>Session Title:</th>
<th>C11: Nurse Colposcopists</th>
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<tr>
<td>Session Date:</td>
<td>Tuesday 21 October</td>
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<td>Session Time:</td>
<td>0835 - 1015</td>
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**Authors**  Mary Rubin *

**Title:** Pioneering the Art and Science of Colposcopy

This presentation will focus on my personal journey of integrating the art and science of colposcopy into my scope of practice as an advanced practice clinician. It will go on to demonstrate the learning experiences that were most useful and those that created barriers to learning. I will discuss the development of an organized basic colposcopy program that was user friendly for advanced practice clinicians and physicians and using that model for multiple programs in the US. Methods for learning the basic concepts of the normal and abnormal were perfected and the Rubin and Barbo Assessment Tool was developed. Several quality colposcopy education programs are now available to meet the needs of advanced practice clinicians and more tools are available to assist in that learning process.
Title: The Role of the BSCCP in Training Nurse Colposcopists

The British Society for Colposcopy and Cervical Pathology (BSCCP) has a well established training programme for both doctors and nurses. The aim of the training programme is to develop a competent colposcopy practitioner. The practitioner will be able to assess, diagnose, treat and review patients referred to a recognized colposcopy clinic in accordance with protocols. Since the introduction of the training programme it has become necessary for anyone practicing colposcopy to be trained to the appropriate standard. Colposcopy is an exciting and rewarding area for Nurses working within the Gynaecological field to specialise in. There are now over 100 trained Nurse Colposcopists and many more Colposcopy Nurses who are registered as members of the BSCCP, so the network in this area is growing all the time.

Colposcopy is dependant on trained manpower and is a technique that can be performed after an appropriate interval of training and education. Nurses can achieve the same level of skills and competencies as medical personnel and the addition of a nurse colposcopist greatly enhances the efficiency of the service and healthcare provision.

The BSCCP as a Society actively encourages networking and open communication for its Nurse members and provides meeting facilities at the Annual Scientific Conference in liaison with the BSCCP Nurse Representative.
Title: The Benefits of the Nurse Colposcopist Role in New Zealand

Background
The nurse colposcopist role was developed at National Women's Hospital by Professor Ron Jones, Dr Paul Patten and Georgina McPherson in the year 2000. The role was established in New Zealand to reduce waiting times, improve access to women and offer a choice in provider to women.

Benefits of the role
During the evolution of the nurse colposcopist role ongoing evaluation has been undertaken to demonstrate the benefits the role. The data presented is from the period of January to July 2007 when the nurse colposcopist was employed as a Nurse Practitioner (NP) and was able to work independently.

Colposcopy, histology and cytology correlation audit was undertaken of all new patients. The NP achieved a correct correlation of 85% (212/249).

Waiting times decreased for high grade and low grade referrals once the NP role was established. There was an increase in waiting times in April for low grade referrals because of the laboratory strike. However the NP was able to run alternative clinic options which enabled the service to manage high grade referrals.

There was an increase of first specialist appointment productivity. The flexibility of the NP role led to less clinics being cancelled and additional clinics being offered. This resulted in additional revenue for the service. The NPs non attendance statistics were consistently lower than the medical staff.

A patient satisfaction survey of the NP service demonstrated high levels of satisfaction from women in regards to the care they received, waiting times to be seen and communication of results.

The nurse colposcopist role can provide clinically effective care which is cost effective in New Zealand. The benefits to the women include improved waiting times, choice of provider and improved access to colposcopy services.
Title: ASCCP Survey of Advanced Practice Clinicians

Advanced Practice Clinicians (APCs) are the nurse practitioners, certified nurse midwives and physician assistants who are members of the American Society of Colposcopy and Cervical Pathology. This group represents an increasing number of colposcopists within the Society and in the educational course offerings. A review of American nursing education and the roles of APCs will be discussed. The results of a survey of APC members of ASCCP will also be presented.
Title: The Role of the Nurse Colposcopist in Ireland

History:
The need for Nurse Colposcopists was identified in 1999 due to the limited number of doctors who had specialised in this area and the increasing number of patients being referred for colposcopy. There are now 13 accredited Nurse Colposcopists practising in Ireland.

Role:
Nurse Colposcopists in Ireland have four main roles: Autonomy in Clinical Practice, Expert Practice, Professional and Clinical Leadership and Research. The Nurse Colposcopist can assess, diagnose, review and discharge patients referred to a recognised colposcopy clinic in accordance with medical and nursing protocols. Most Irish nurse colposcopists also perform LLETZ. They provide a permanent link for patients, doctors and staff, continuity of care and co-ordination of the colposcopy service by a colposcopist and act as a patient advocate.

Clinical Performance of all colposcopists is monitored against national guidelines every 3 months with the Irish Cervical Screening Programme.

Training:
The British Society for Colposcopy and Cervical Pathology (BSCCP) has laid out training requirements in conjunction with the Royal College of Obstetricians and Gynaecologists in London.
Vulval intraepithelial neoplasia (VIN) is a rare condition with an increasing incidence from which an invasive carcinoma can develop. It affects mainly young women and causes many severe and long-lasting symptoms such as pruritis, vulvodynia and psychosexual dysfunction. Over 80% of women present with multifocal vulvar disease, and often neoplastic changes can be found in the entire lower genital tract. Clinically, it is important to distinguish unifocal from multifocal lesions, since unifocal VIN tends to progress to invasive carcinoma ten times more often than multifocal VIN does. VIN is caused by HPV or can develop on the background of lichen sclerosus. VIN is divided in VIN usual type (warty, basaloid and mixed) and VIN, differentiated type. The two types differ in morphology, biology and clinical features. The natural history is still unclear. Untreated patients who hardly ever progress to an invasive vulvar carcinoma have been published, whereas others have seen progression in nearly all untreated patients. Importantly, invasion may occur many years after VIN is diagnosed. Therapy for high grade VIN comprises surgical removal of all visible lesions to relieve symptoms and prevent the development of invasive disease by means of cold knife surgery or CO2 laser vaporization. At the same time, treatment should be directed towards preservation of the normal anatomy and function of the vulva. However, there are limitations to surgery. The percentage of lesions with positive surgical margins ranges from 24-68%. Recurrences are common, because persistent infection with HPV is not affected by surgical treatment. Progression is not influenced by radical excision, and surgery can mutilate the vulva, thereby causing psychosexual distress. New treatment modalities are photodynamic therapy and immunomodulation with imiquimod, an immune response modifier with antiviral and antitumor properties, that is effective in the treatment of multifocal VIN. In a placebo controlled trial, 35% of patients treated with imiquimod had a complete response. Histological and clinical regression were strongly related to clearance of the underlying causative HPV infection. Imiquimod is generally well tolerated, far less invasive than surgery, relieves itching and pain, does not adversely influence health-related quality of life, body image or sexuality, and is a convenient, self-administered treatment.
Title: High Sustained Efficacy of a Quadrivalent HPV-6/11/16/18 Vaccine Against Vulvar and Vaginal Intraepithelial Neoplasia (VIN1-3 and VaIN1-3)

A quadrivalent HPV6/11/16/18 vaccine (Gardasil/Silgard, Merck) has been licensed in over 100 countries for the prevention of cervical cancer/pre-cancerous lesions and genital warts, as well as vulvovaginal pre-cancerous lesions. Based on the high efficacy observed in FUTURE I-II, the independent Data and Safety Monitoring Board of these studies recommended vaccination of women in the placebo group earlier than planned. We present end-of-study vaccine efficacy data against VIN1-3 and VaIN1-3.

18,150 women (16-26 yrs) were enrolled in 1 of 3 Phase IIb/III trials. Subjects were randomized (1:1) to quadrivalent vaccine or placebo, administered on Day 1, Months 2, and 6. Genital specimens were obtained at Day 1 and at 6-12 month intervals through 48 months, with algorithm-based referral to colposcopy. Biopsies were HPV-typed and pathologic endpoints determined by a blinded pathology panel. Analyses were per-protocol (subjects received 3 doses, had no major protocol violations, and were negative to the relevant HPV-type Day 1 through Month 7). In the per-protocol population, 100% efficacy was observed for all endpoints.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Placebo</th>
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<td>n=7,900</td>
<td>n=7,902</td>
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<table>
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<tr>
<th>Efficacy (%)</th>
<th>Confidence Interval</th>
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<tr>
<td>Cases Rate†</td>
<td>Cases Rate†</td>
</tr>
<tr>
<td>VIN1 0</td>
<td>0.0 16 0.1 10074-100</td>
</tr>
<tr>
<td>VIN2/3 0</td>
<td>0.0 13 0.1 10067-100</td>
</tr>
<tr>
<td>VaIN1 0</td>
<td>0.0 12 0.1 10064-100</td>
</tr>
<tr>
<td>VaIN2/3 0</td>
<td>0.0 10 &lt;0.1 10055-100</td>
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†Rate = n/Subject years at risk*100

Precursors of HPV-related vulvovaginal cancers are often not recognized, and are increasing in incidence. Prophylactic HPV vaccination is expected to greatly reduce the morbidity, mortality, and health care costs associated with these diseases.
Title: Perceived Uncertainty Coping Strategies, and Adaptation in Women with Human Papillomavirus (HPV) on Papanicolaou Smear

The overall purpose of this study was to explore, identify and describe the perception of uncertainty over time in a college age group of women experiencing the unexpected event of an abnormal Pap smear. More specifically, the relationship of uncertainty to other concepts such as knowledge, coping strategies, and adaptation as guided by the King Interacting Systems Framework (1981) and the Mishel Uncertainty in Illness Model (1988a) were explored for important linkages through path analysis and correlations.

The sample consisted of female patients from the Student Health Service at a large urban university setting in the mid-Atlantic region of the United States. The subjects included 88 nonpregnant women who had human papillomavirus on Papanicolaou smear, had indications for colposcopy, had an ability to communicate in English, and were without history of cancer.

The relationship between uncertainty and coping strategies was supported in the emotion-focused path as predicted, but not in the problem-focused path. This held true even when the emotion-focused and problem-focused subscales were examined. Evidence of adaptation to uncertainty through emotion-focused coping was found in the significant relationship between emotion-focused coping and body attitude. Similarly, there was a significant relationship between emotion-focused coping and moods in the path analysis and in correlations with the subcategories of positive and negative moods. The problem-focused indirect path from uncertainty to adaptation did not show any significant relationship. Likewise, uncertainty also had no significant direct effect on body attitude or promptness of follow-up, but did have a direct impact on moods. The direct path from previous knowledge to uncertainty was not supported.

This study represents an attempt to test and extend the Model of Uncertainty in Illness by exploring the direct and indirect pathways among knowledge, uncertainty, coping strategies and adaptation in a group of young women experiencing an abnormal Pap smear. Additional studies must be done to further clarify these relationships and to extend the model to deal more effectively with uncertainty over time.
Title: Bringing in the Outpatient: How can we Improve Attendance at Colposcopy Clinics?

Background
The Colposcopy Clinic in AMNCH, Tallaght, Dublin 24 saw 695 new patients and 1628 follow-up patients in 2007. However, administrative staff processed 4178 appointments. Default and cancellations accounted for the extra slots. Colposcopy clinic non-attendance has always been problematic. The health implications for the colposcopy patient who does not attend are profound. The anxiety, experienced by women requiring colposcopic assessment and possible treatment, is well recognised. Socio economic factors, family and work commitments have also been reported as causes for default from clinic visits. Impact on clinic planning and administration of precious appointment space makes this an important issue for clinic managers and practitioners.

Review of default rates
The literature was checked to review past and current rates of non-attendance to Colposcopy Clinics. Interventions used to encourage turnout were examined. Local research to improve attendance was added to the pool of knowledge.

Recommendations
- Improve co-operation between primary and secondary care
- Tailor appointment intervention to local custom and needs
- Create local DNA policies
- Provide information that uses plain language, is accurate and reflects local practice and intervention
- Provide text reminders of appointments
- Allow patients to self choose appointment date

Conclusion
Several studies have reported default rates from colposcopy clinics but few have looked at women's opinion, attitude or reason for default. Most women eventually attend for first appointment but this may take up to 12 months. Follow-up appointments are more difficult and close co-operation with primary care is paramount. There remains a small group of women who default despite all efforts to persuade them to attend. Further research is needed to identify the requirements of these women and to enlighten them as to the benefits of colposcopy compared to the risk of non-attendance.
Title: Cultural and Social Implications of Introducing HPV Testing and Vaccination

With the implementation of HPV screening and prevention strategies, there have been concerns raised by both patients and providers. These issues pose challenges to widespread implementation of cervical cancer prevention approaches. The acceptance of HPV testing and vaccination is impacted by cultural, social and political influences in both developed and developing countries. These challenges will be discussed with suggestions for intervention.
Modification from the European Perspective

There are two approaches of using colposcopy: a) triage colposcopy, when women are referred to colposcopy if the screening test is abnormal (abnormal cytology or clinically suspicious cervix); routine colposcopy as part of routine gynaecological examinations. In the latter context colposcopy also serves as a screening tool, particularly of the cervical carcinoma.

Colposcopic terminology has traditionally based on triage colposcopy and the question arises whether this terminology is fully adequate for routine colposcopy as well. The term "unsatisfactory colposcopy is of particular interest.

In the latest edition of the International Terminology of Colposcopy published by IFCPC, the term "Unsatisfactory colposcopy" is used and defined as: "An unsatisfactory colposcopy examination occurs when the squamocolumnar junction cannot be visualised. It may also occur if associated trauma, inflammation, or atrophy preclude a full colposcopic assessment, or when the cervix is not visible".

One may wonder what the term "unsatisfactory colposcopy" means. Does it mean that when the squamocolumnar junction cannot be visualised the colposcopy examination has no information? What about examining colposcopically the exocervix alone? Has it any clinical impact?

Using colposcopy and cytology for screening the possible findings when the squamocolumnar junction cannot be visualised, and their clinical implications are the following:

1. In the presence of abnormal colposcopy of the ectocervix: a) if cytology is normal, CIN cannot be ruled out, further evaluation is required; b) if cytology is ASCUS or LSIL, CIN is very likely and it is located on the exocervix.

2. In the presence colposcopically normal ectocervix: a) if cytology is negative, it is very unlikely that the patient has CIN or cancer, the false negative rate is next to zero; b) if cytology is abnormal the lesion is located in the endocervical canal.

With this in mind, the term "unsatisfactory colposcopy" may be restricted when "associated trauma, inflammation, or atrophy preclude a full colposcopic assessment, or when the cervix is not visible".

If the cervix but not the whole transformation zone can be colposcopically assessed, i.e. the squamocolumnar junction cannot be visualised, the following terms may be more appropriate:

The squamocolumnar junction not visible, colposcopically normal ectocervix (abbreviation NVSCJ-NE - Not Visible Squamocolumnar junction - Normal Ectocervix)

The squamocolumnar junction not visible, colposcopically abnormal ectocervix (abbreviation NVSCJ-AE - Not Visible Squamocolumnar junction - Abnormal Ectocervix)

Unsatisfactory colposcopy: the cervix is not visible or cannot be assessed due to associated trauma, inflammation, or atrophy
Title: Is There Really a State of Iodine Negativity - What is the CTZ (Congenital Transformation Zone)

Histogenesis:
Müllerian epithelial cells are stem cell for endocervical reserve cells and endocervical columnar cells. They have the capacity to transform into both endocervical columnar and squamous-type epithelium in the endocervix during early cervical development. During embryogenesis transitional-squamous epithelium replaces the glandular epithelium of müllerian type. In normal circumstances this process becomes complete, so that squamous epithelium covers the whole vagina and the ectocervix by the time of birth. Remaining müllerian epithelium, which is then known as adenosis in the vagina and ectropion on the ectocervix, most probably undergoes gradual replacement by squamous epithelium in later intrauterin life and perhaps also for some time after birth. The product of this late squamous change is seen as the CTZ (1).

Colposcopy:
The CTZ is relatively common (4%), and the colposcopist should be thoroughly be familiar with its appearance. The epithelium is nonglycogenated and is faintly acetowhite; usually the degree of acetowhiteness is very minor and may be difficult to see. It can be recognized clearly following the application of Schiller's iodine. It does nor require treatment (2).

Histology:
Colposcopically inconspicuous iodine-yellow areas are usually caused by benign metaplastic epithelium. The risk of neoplasia is low = 2%. In treated cases one can find LG-SIL in 4% (3).

References:
Title: Europe

This is a report of the work of the European Federation for Colposcopy (EFC).

EFC was formed in 1999. The objectives of EFC were the training and accreditation of colposcopists in Europe. Currently there are 33 member countries. The first task of EFC was to have agreed standards for training, and using the Delphi technique, member countries agreed on 51 Minimum Standards for Training. The next step was to agree guidelines for the management of 10 standard colposcopic problems - using the Delphi technique, a consensus was reached.

The next objective was to see if a programme of Accreditation could be introduced - this is proving more difficult because each country has its own overall clinical training programme and problems, but already, 9 countries have some form of programme of Accreditation. The British Society for Colposcopy and Cervical Pathology (BSCCP) also has a programme of Re-accreditation every 3 years.

To help meet its objectives, EFC has a programme of training courses, run in conjunction with National Societies, and in the last 12 months, course have been held in Croatia, Athens, Belgrade, Prague, Moscow, Montenegro, Georgia and Birmingham. In the next 12 months it is planned to have courses in Romania, Armenia, Nice and Birmingham, and hopefully some other countries.

The course in Georgia was a combined course with IFCPC, and it is hoped that other combined courses can be held in the future.

EFC has Triennial meetings. 2007 was in Belgrade. 2010 will be in Berlin, and 2013 in Prague.

The European Commission commissioned a group to produce "EUROPEAN GUIDELINES for QUALITY ASSURANCE in CERVICAL CANCER SCREENING". EFC provided the clinical input to this very valuable report, a report which gives guidelines which are applicable to any country in the world.

The work of EFC and the European Guideline can be accessed through the EFC website www.efc.cx
Title: Liquid Compared with Conventional Cervical Cytology: A Systematic Review and Meta-analysis

OBJECTIVE:
To compare test performance characteristics of conventional Pap smears and liquid-based cervical cytology samples.

DATA SOURCES:
Eligible studies, published between 1991 and 2007 were retrieved through Pubmed/EmBase searching, completed by consultation of other sources.

METHODS OF STUDY SELECTION:
Studies were selected if a conventional and a liquid-based sample were prepared from the same woman or when one or the other type of sample was taken from separate but similar cohorts. The current systematic review is restricted to studies where all subjects where submitted to gold standard verification, based on colposcopy and histology of colposcopy-targeted biopsies allowing computation of absolute and relative test validity for cervical intraepithelial neoplasia grade-II or worse. Randomized trials were selected as well, if all test positive cases were verified with the same gold standard, allowing computation of the relative sensitivity. Impact of study characteristics on accuracy was assessed by sub-group meta-analyses, meta-regression and summary ROC (receiver operating characteristic) curve regression.

TABULATION, INTEGRATION, AND RESULTS:
The relative sensitivity, pooled from 8 studies, with complete gold standard verification, and from one randomized clinical trial, did not differ significantly from unity. Also the specificity, considering high-grade and low-grade squamous intraepithelial lesions as cut-off, was similar in conventional and liquid cytology. However, a lower pooled specificity was found for liquid-based cytology when presence of atypical squamous cells of undetermined significance was the cut-off (ratio=0.91; 95% CI: 0.84-0.98). Differences in study characteristics did not explain inter-study heterogeneity.

CONCLUSIONS:
There is no evidence available indicating that liquid-based cytology improves detection of cervical intraepithelial neoplasia grade-II or worse.
Psammoma Bodies in Routine Cervical Smear, a Time for Vigilance

Introduction: Psammoma bodies are discrete laminated forms of calcifications found in various benign and malignant conditions, and are observed rarely in cervicovaginal smears. They are seen at an incidence of 1 in 30,000 and are twice as common in genital tract malignancy when compared to benign conditions.

Malignancies reported with psammoma bodies in cervicovaginal smears (PBCS) include serous carcinomas of the uterus, fallopian tubes, ovaries, and neuroendocrine carcinomas of the cervix.

Various benign conditions are associated with psammoma bodies, including oral contraceptive pills, benign papillary structures of the ovary, intrauterine devices, endosalpingiosis, tuberculous endometritis.

Case report: We report the case of a 56-year-old patient with an incidental finding of psammoma bodies on a routine cervical smear. Colposcopic examination revealed a healthy cervix and vagina. Serum CA 125 and a pelvic ultrasound were normal. A diagnostic laparoscopy revealed unexpected findings of small volume but extensive peritoneal metastatic disease. Representative biopsies confirmed the presence of serous adenocarcinoma.

Discussion: Unexpected finding of psammoma bodies in routine cervical smears pose diagnostic difficulties. Psammoma bodies associated with malignancy tend to occur in the postmenopausal women with a median age of 60 years and a range of 21–76 years in the literature. In the female genital tract, they are most commonly described in association with serous carcinomas of the ovary and less commonly with uterine serous or clear-cell carcinomas. The increased association of PBCS with pelvic malignancy in postmenopausal women warrants thorough investigation to exclude or confirm its presence even in asymptomatic women.
Title: FTIR Microspectroscopy: An Objective and Potentially Automated Discriminator of Exfoliative Cervical Cytology

Introduction: Infrared (IR) absorbance of cellular biomolecules generates a vibrational spectrum, which can be exploited as a “biochemical fingerprint” of a particular cell type.

Study Objectives: Biomolecules absorb in the mid-IR (2-20 μm) and Fourier-transform infrared (FTIR) microspectroscopy applied to discriminate different cell types is evaluated.

Methods: Exfoliative cervical cytology collected into LBC was examined. This consisted of cervical cytology free of atypia (i.e., normal; n=60), specimens categorised as containing low-grade changes (i.e., CIN1 or LSIL; n=60) and a further cohort designated as high-grade (i.e., CIN2/3 or HSIL; n=60). IR spectral analysis was coupled with principal component analysis (PCA), with or without subsequent linear discriminant analysis (LDA), to determine if normal versus low-grade versus high-grade exfoliative cytology could be segregated.

Results: With increasing severity of atypia, decreases in spectral absorbance intensity were observable throughout the 1500 cm⁻¹ to 1100 cm⁻¹ spectral region; these absorbance regions were associated with proteins (1460 cm⁻¹), glycoproteins (1380 cm⁻¹), amide III (1260 cm⁻¹), νasPO2 (1225 cm⁻¹) and carbohydrates (1155 cm⁻¹). In contrast, νsPO2 (1080 cm⁻¹) appeared to have an elevated intensity in high-grade cytology. Inter-category variance was associated with protein and DNA conformational changes whereas glycogen status strongly influenced intra-category.

Conclusions: The computational segregation of IR spectra generated using FTIR microspectroscopy has the potential to be an objective and automated approach to discriminate between normal and different grades of cervical cytology.
Title: Safety and Preliminary Efficacy Data of a Novel Casein Kinase 2 (CK2) Peptide Inhibitor Administered Intralesionally at Four Dose Levels in Patients with Microinvasive and Pre-Invasive Stage Cervical Cancer

Introduction: CIGB-300 is a novel cyclic peptide that impairs casein kinase 2 phosphorylation after intracellular delivery. It behaves as pro-apoptotic both on HPV-positive and -negative tumor cell lines. Local CIGB-300 injections could exhibit clinical benefit in patients with cervical malignancies.

Study Objectives: To investigate the safety and tolerability of CIGB-300 in patients with microinvasive and pre-invasive stage cervical cancer.

Patients and Methods: Thirty-one women with colposcopical and histological diagnosis of microinvasive and pre-invasive stage cervical cancers were enrolled in clinical trial fase I. CIGB-300 was administered sequentially in a four-dose at 14, 70, 245 and 490 mg for 5 consecutive daily intralesional injections to groups. Local and systemic toxicities were monitored daily. Fifteen days after the end of treatment, were evaluate the clinical benefit of CIGB-300 with colposcopy and histology to conization by loop electrosurgical excision procedure The HPV status was also analyzed by PCR on the biopsy materials.

Results: At the lowest dose level only grade 1 adverse events occurred, while at the second and third levels, grade 2 events were also observed. Only one grade 3 event (vasovagal episode) occurred at the fourth dose level. The most frequent local events were pain, bleeding, hematoma and erythema at the injection site. The systemic adverse events were rash, facial edema and itching. A significant reduction of the initial lesion area was demonstrable by morphometric colposcopy. 19.3% of the patients exhibited a full histological regression. The presence of HPV was to undetectable levels in 50 % of the patients.

Conclusion: CIGB 300 was found to be a safe product in the doses studied and the results of the evaluation of the therapeutic effect have been favorable.
Title: Detection of High-Risk HPV mRNA in Liquid Based Cytology (LBC) Specimens with the APTIMA® HPV Assay

The objective of this study was to evaluate the ability to detect high-risk HPV (hrHPV) mRNA and DNA in disease positive (CIN3+) LBC specimens. Almost 600 clinical specimens were collected from patients with abnormal cytology. Samples were stored in LBC vials at room temperature for up to 3 years and a subset (n=379) was tested for hrHPV mRNA in the APTIMA HPV (AHPV, Gen-Probe Incorporated) Assay, a qualitative nucleic acid test designed to detect the E6/E7 mRNA of 14 hrHPV types in LBC specimens. Detection of hrHPV DNA was determined with the Hybrid Capture 2 HPV DNA Test (HC2, Qiagen Incorporated) for a subset of the specimens. AHPV results for all 379 samples were compared to cytology and histology results. In addition, a comparison to HC2 results was performed for the subset of 192 samples. The AHPV assay yielded a positive result in 100 out of 103 CIN 3 and all 16 cervical carcinoma and carcinoma in situ specimens (sensitivity 97.5% for CIN 3+). The HC2 test yielded a positive result in 65 out of 66 CIN 3 and 5 out of 7 cervical carcinoma specimens (sensitivity 95.9% for CIN 3+). The AHPV assay had a significantly lower positivity in histologic normal specimens (13.5%), compared to the HC2 assay (34.9%). These results indicate that the AHPV Assay is able to detect high-risk HPV mRNA in retrospective LBC specimens stored at room temperature for up to three years with strong correlation to disease. The AHPV assay had higher specificity and slightly higher sensitivity than the HC2 assay.
**Folate Status, Hypomethylation and Gene Specific Methylation in Cervical Intraepithelia Neoplasia and Cervical Cancer**

Gene specific hypermethylation (GSM) is a frequent epigenetic event in human cancers and is associated with tumour suppressor gene silencing, resulting in the development of cancer. Folate is directly involved in DNA methylation via one carbon metabolism through which it may influence gene stability and expression.

To investigate whether, in progressing from normal cervix to invasive cervical cancer, there is evidence for changes in either folate status, hypomethylation or gene specific methylation (GSM). Fifty women from normal, CIN 1, CIN2, CIN3 and invasive cervical cancer groups were recruited to a cross sectional study. Cervical smears were collected from each participant and DNA isolated from the cervical cells. Gene specific methylation was performed using methyl sensitive polymerase chain reaction. Red cell folate (RCF) was measured to determine folate status. Levels of global DNA methylation were detected using the SAM acceptor assay.

RCF was significantly higher in the normal group when compared to the other groups (p=0.004). Hypomethylation was significantly higher in the cancer group when compared to CIN1 (p=0.003). A definite trend towards increased methylation from normal to high grade CIN and cancer was seen in death associated protein kinase (DAPK), e-cadherin, and hypermethylated in cancer (HIC) genes. GSM was increased in low grade CIN in the retinoic acid receptor (RARb) and glutathione S-transferase P1 (GSTP1).

There is a potential role for DNA methylation as a marker in the early diagnosis of cervical cancer. In contrast to genetic changes, epigenetic changes can be readily reversed thus providing exciting therapeutic opportunities.
The Correlation Between Both the Positive Results of the DNA HPV HR Test and HPV Genotyping Test and the Presence of CIN Among Women with Pap Smears Demonstrating Cases of ASC-US and LSIL

The diagnostic algorithm for women with ASC-US include performing the DNA HPV HR molecular test, colposcopy or the repetition of pap smear. The newest modifications of the diagnostic algorithm in case of LSIL cytological diagnosis are based on an attempt of performing the molecular test, which reveals the presence of DNA HPV HR and/or genotyping HPV, especially the type 16. 67 women with ASC-US and 48 women with LSIL were included in the research. Among 67 examined women with ASC-US, 31 had positive test demonstrating presence of any from 15 types of HPV HR had, and in this group, the histology examination confirmed presence of CIN 1 in 12 cases. There was no such case among 36 patients with ASC-US, DNA HPV HR negative in which the presence of CIN was confirmed. In the group of 29 women with LSIL the result of the test demonstrating the presence of any of 15 HPV HR was positive. DNA HPV 16 was recognised among 5/9 of examined women with LSIL, without CIN.

Conclusions: The negative result of DNA HPV HR test precisely recognized women with pathological pap smear: ASC-US and LSIL, without CIN, HPV type16 DNA genotyping among women with LSIL did not increase the sensitivity DNA HPV HR tests in the assessment of risk of the presence of CIN.
Title: Does the Degree of Cervical Dysplasia Affect Women's Attitudes Towards the HPV Vaccine?

The Human Papilloma Virus (HPV) immunisation programme is to be introduced into England in 2008. Underpinning the success of the programme will be parental acceptance of the vaccine. The aim of this study was to assess knowledge and gauge acceptance of the vaccine amongst women attending a colposcopy clinic; in particular, whether knowledge and acceptance of the vaccine is affected by the degree of cervical dysplasia of the patient (low grade or high grade disease). 100 patients attended the colposcopy clinic in 2008. Patients were interviewed by the consulting clinician and demographics and details of the vaccine were collected. The results of the study showed a mean age of attendees of 38.4 years (range 23-70 yrs). Overall, only 28% of patients had heard about the HPV vaccine; however 70% were aware of a 'cervical cancer vaccine'. There was no statistical difference between knowledge of the HPV vaccine and the 'cervical cancer vaccine' amongst women with low and high grade disease (P = 0.846 and P = 0.892 respectively). 90% of the patients would recommend the vaccine to a close member of their family or a friend. The degree of cervical dysplasia did not affect parental acceptance of the vaccine (P = 0.445). In conclusion, the findings of this study suggest that the HPV vaccine is viewed largely positively by women; however, knowledge of the HPV vaccine amongst patients attending colposcopy clinic is inadequate. The degree of cervical dysplasia did not affect knowledge or acceptance of the vaccine amongst these women.
Title: Updates on Prophylactic HPV Vaccination

Introduction
HPV infection is very common, with approximately 6.2 million new cases of genital HPV reported each year. HPV infection has the highest incidence of all sexually transmitted infections and is most prevalent in young, sexually active individuals. It is estimated that a woman's life time risk of acquiring one or more genital HPV infection is at least 75%. There are approximately 40 - 60 types of HPV specifically infecting the genital area and these are classified into 2 groups: high-risk (HR) or oncogenic types and low-risk (LR) types. HR types, the most common of which are 16 and 18, are the causative agent worldwide of 50% of cervical precancerous lesions (cervical intraepithelial neoplasia (CIN) 2/3) and 70% of cervical squamous cell carcinomas (SCC) and adenocarcinomas (ASC). HR types are also implicated in 60% to 90% of other anogenital cancers (such as vulvar, vaginal, anal, and penile cancers), 20% to 75% of oropharyngeal cancers, and 25% of low-grade cervical lesions. HPV-18 is the second most common cause of cervical cancer and a more frequent cause of ASC than HPV-16. The incidence of ASC is increasing and its precursor lesion, adenocarcinoma in situ (AIS), is difficult to detect by routine Papanicolaou cytology screening.

The two most common LR HPVs, HPV genotypes 6 and 11, cause approximately 90% of genital warts or condylomata acuminate, and 10% of low-grade cervical lesions. They also cause recurrent respiratory papillomatosis (RRP), a rare but potentially fatal childhood disease caused by vertical transmission from mother to infant, or as adult-onset RRP which presents later in life.

HPV prophylactic vaccines
With the development of HPV viral like particles (VLP), the first generation of prophylactic vaccines were possible. Phase 2 and subsequently phase 3 clinical vaccine trials of prophylactic bivalent HPV 16/18 and quadrivalent HPV-6/11/16/18 vaccines have demonstrated these vaccines as generally safe, well tolerated, highly immunogenic and effective in preventing vaccine-related HPV infection and/or disease.

Efficacy and Safety of the Bivalent and Quadrivalent HPV Vaccines
Large-scale, phase 3, randomized, double-blind, placebo-controlled trials recently published for both vaccines show efficacy, immunogenicity, and safety in women 15 to 26 years of age, for an average of 5 years. (1-3)The number of adverse events (AEs) was similar between either of the vaccines and placebo groups in all 3 trial published to date. For both vaccines, vaccine recipients were significantly more likely than placebo recipients to have injection site reactions, with pain at the site of injection as the most common AE.

Efficacy of the quadrivalent vaccine in mid-adult women aged 24 to 45 years has been recently assessed and shown 91% (95% CI, 74-98) effectiveness in reducing the combined incidence of HPV 6/11/16/18-associated persistent infection (defined as the detection of the same HPV genotype 2 or more times over a median follow-up time of approximately 6 to 12 months), CIN, or genital warts. (4)

Emerging research indicates that both vaccines show cross-protection against several nonvaccine oncogenic HPV infections.

Prophylactic HPV vaccines as a public health tool
In June 2006, the quadrivalent HPV vaccine was approved by the US Food and Drug Administration (FDA), by the Therapeutic Goods Administration (TGA) Australia and thereafter many countries in Asia, for the prevention of HPV 6/11/16/18-associated cervical cancer, AIS, and CIN I-3, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN) grades 2/3, and genital warts in women. A bivalent vaccine that protects against HPV 16 and 18 is currently under review by the FDA and was licensed in Australia by the TGA in May 2007, in Europe and some Asian countries thereafter in 2007.

In Australia the quadrivalent HPV vaccine has been registered for all girls aged 11 to 12 years, as an ongoing school-based government funded programme with a catch up for those (for 2 years only) 13 to 26 years. Sexually active women may also benefit from HPV vaccination, as longitudinal studies show very few have been exposed to all vaccine HPV types. In some countries, vaccination for girls and boys aged 9 to 12 years has been endorsed based on immunobridging data.

Conclusion and challenges
Both the quadrivalent and bivalent HPV vaccines have both been shown to be safe and effective in clinical trials. Their established efficacy and safety support widespread vaccination to reduce the morbidity and mortality associated with HPV infection and related disease. Challenges however include an appropriate delivery system of vaccines at affordable prices to those countries where burden of disease is greatest, education of the lay and
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medical communities about HPV, and with ongoing comprehensive surveillance systems to measure the impact on disease, cross protection and potential genotype replacement.

References:


Making The Choice: Protecting Women Against Diseases Caused By HPV Types 6, 11, 16 And 18

Large-scale phase 3 randomized, double-blind, placebo-controlled clinical vaccine trials of prophylactic quadrivalent HPV-6/11/16/18 vaccines show these vaccines are highly immunogenic, efficacious in preventing vaccine-related HPV infection and/or disease and generally safe and well tolerated in women 15 to 26 years of age, and for an average of 5-6 years.

With cervical cancer being the second commonest cancer of women worldwide, there is an opportunity to impact disease burden with comprehensive rollout of this effective public health to all of prophylactic vaccination. Challenges however include an appropriate delivery system of vaccines at affordable prices to those countries where burden of disease is greatest, education of the lay and medical communities about HPV.

23,348 women from 5 Phase III randomized clinical trials to receive either quadrivalent HPV vaccine or placebo, had pregnancy tests performed immediately prior to each injection, and those testing positive were not vaccinated. Subjects who became pregnant after enrollment were discontinued from further vaccination until resolution of pregnancy, and all pregnancies were followed for outcomes. Pregnancy outcomes reported here include those documented at pregnancy resolution or during the neonatal period (ie, the first 6 weeks of life). Overall 15.5% of the population became pregnant. Overall, the administration of quadrivalent HPV vaccine to women who became pregnant during the Phase III clinical trials did not appear to impact pregnancy outcomes.
Title: Immunology of HPV: Natural Infection and Vaccines

HPVs are successful pathogens inducing chronic infections that are exclusively local and intra-epithelial and rarely result in the death of the host or systemic sequelae. They achieve this enviable lifestyle by a combination of passive and active immune avoidance. The viral infectious cycle is confined to the epithelial compartment, there is no viraemia or blood born spread and virus particles are shed from mucosal surfaces far from vascular and lymphoid channels. This together with down regulation of anti viral cytokine responses allows long periods of uninterrupted virus replication in the epithelium during which the host is ignorant of virus presence. This is a high risk strategy for the host in infections with the high risk HPVs since failure to elicit a local cell mediated response can result in the development of high grade precancers and invasive cancers of the cervix and other ano-genital sites.

Prophylactic HPV L1 VLP vaccines circumvent the viral epithelial evasion strategies since they are delivered by intra-muscular injection. The stromal dendritic cells of the muscle that encounter the highly immunogenic repeat structure of the VLP then migrate with their cargo to the lymph node initiating an immune cascade that results in a robust T cell dependent B cell response generating high levels of L1 specific serum neutralizing antibody and crucially strong immune memory.
Title: National HPV Immunization Program: The Australian Experience

The National Human Papilloma Virus (HPV) Vaccination Program is funded by the Australian Government and started in 2007, and under the program the HPV quadrivalent vaccine, Gardasil, will be provided free to girls and women aged 12 to 26 years. There are 3 aspects to the program: an ongoing vaccination program for all 12 year old girls and a 2 year catch up program for school girls aged 13-18 and a general practitioner based program for women aged 19 to 26 years. The school-based program started in April 2007 and the community-based program will start in July of that year and will run till June 2009. This program is expected to have a significant impact on the incidence of HPV infection and markedly reduce the clinical burden of HPV-related disease in Australia. Boys and men are not included in the Program at this stage because there is not yet enough clinical effectiveness data available in males, despite the public health grounds for including them.

The implementation of a vaccination program with Gardasil for 12 to 26 year women has been shown to be cost-effective in Australia. It is estimated that the vaccination program will reduce the lifetime risk of cervical cancer by 48%, compared to the current screening system. This estimate is based on data from the National Cervical Screening Program in Australia, 100% vaccine effectiveness, lifetime duration of efficacy and 80% coverage. The vaccine should also substantially reduce the incidence of cervical precursor lesions and the related interventions and range of other HPV related diseases.

Logistics around the school based program have involved teams of trained nurses visiting schools on an organised rotational basis. The school-based program has been administered over the course of a single school year to reduce the potential for missed doses. Preliminary information regarding the program suggests that high coverage rates in the order of 80 to 85% have been achieved in the school vaccination program with high levels of compliance with second and third doses. Approximately 65% of eligible women aged between 18 and 26 years have been vaccinated in the community based program.

A National HPV Vaccination Program Register is being developed by the Australian Government to collect data about the Program. Personal details identifying the patient will be kept confidential and information will not be sought about the patient's sexual history. Personal information collected will be used to evaluate the impact of the HPV Vaccination Program on cervical cancer rates, to issue reminders if the course is incomplete, to issue confirmation the course is complete and to contact vaccine recipients should booster doses become required.

The National HPV Vaccination Program presents an additional prevention strategy against cervical cancer and other HPV-related diseases and will complement the existing successful National Cervical Screening Program.
Title: Ablative Therapy in the Management of Cervical Intra-epithelial Neoplasia

Despite the widespread adoption of Loop Excision of the Transformation zone in colposcopy practice, ablative treatment potentially still has a role in treating cervical intraepithelial neoplasia. In low resource settings, when clinical settings might not facilitate loop excision, low cost and low morbidity ablative treatment might be the only therapeutic option to provide treatment in rural or impoverished communities. In modern colposcopy practice, particularly persistent low grade disease in an entirely visible transformation zone can be treated with ablative treatment, if the colposcopists theoretically wants to minimise long term damage to the cervix. Ablative treatment also has a role in treating disease extending from the ectocervix to the vagina. This presentation will discuss the advantages and disadvantages of ablative therapies in modern colposcopy practice.
Title: Excision of the Transformation Zone

The treatment of CIN is to remove the transformation zone. This may be achieved by excision or ablation using a variety of modalities. According to the available evidence and with the exception of cryocautery all the available methods have equivalent success/failure rates. But excision has other clinically important advantages that make it superior to ablative techniques. However the available evidence, though poor, suggests that all excisional techniques are associated with an increase in the risk of preterm labour (PTL). This does not translate to an increase in serious pregnancy related perinatal morbidity but needs to be explored and understood.

The contributory reasons for this increase in PTL occurs needs further research. At this time there is good evidence that the type (1, 2 or 3), size and thickness of the excised transformation zone are independent risk factors for subsequent PTL. They are also related to the risk of incomplete excision, which is an important predictive parameter of excisional treatment. The size, thickness and type of TZ are important known variables that should inform colposcopists and their patients when approaching treatment where it is indicated. The evidence to support these arguments will be presented.
Title: Comparisons of Treatment Methods

In the era of evidence based medicine, the choice of treatment modality should be selected by its clinical utility and the supporting evidence to justify its use. We have identified all the gold standard evidence from randomised or controlled trials comparing different treatment and management. We have performed systematic reviews of surgical treatment, management of low grade disease, obstetric outcomes after treatment of CIN etc. Colposcopists should make their choice of treatment based on robust clinical principles and this should be supported by no-biased interpretation of the evidence. In this presentation, we review the evidence from Randomised Controlled Trials or Controlled Studies and illustrate the evidence base for clinical decision making. An example, is the comparison of laser ablation compared with loop excision with disease persistence as an outcome as illustrated in the forest plot below. Where the evidence base is weak, we will highlight areas of possible future research that the IFPC might want to adopt in this field.
Micro-invasive Cervical Cancer

There appears to be a rising incidence of micro invasive carcinoma, with FIGO Stage 1A accounting for about 25% of all cases of invasive cervical cancer. Increased ascertainment from the use of excision may be responsible in part but there appears to be a true rise matching that of pre-invasive disease.

Women with micro invasive cervical carcinoma are usually asymptomatic and screen detected with only 12% of women presenting with symptoms. Colposcopic findings may suggest micro invasion in a third of cases with a further 14% thought to be frankly invasive colposcopically. Colposcopic features are widely debated and not specific thus the accuracy of colposcopy in diagnosis is limited. Features include markedly atypical and prominent vessels, which can be coarse with a ‘corkscrew or comma’ appearance or have an irregular calibre with branching and a wide intercapillary distance.

The survival rate of Stage 1A cervical cancer is excellent. FIGO quotes Stage1A1 having a 99% survival rate. Radical treatment with high mortality has been replaced with conservative methods, often loop excision. Conservation of fertility is an important issue and the majority of women are treated conservatively, although a third require further excision to ensure adequacy of treatment. There is still a place for simple hysterectomy when fertility is no longer an issue and this can provide reassurance.

Women managed conservatively need to be carefully followed up for recurrence of cervical intraepithelial and invasive disease. There is no standard approach or guidelines regarding the follow-up of conservatively managed Stage 1A disease. Follow-up can involve cytology and colposcopy; there is no clear evidence that colposcopy has an advantage over cytology alone. High risk HPV testing may distinguish those at high risk of recurrence or assist in tailoring further treatment to retain fertility. Most women with micro invasion are diagnosed, treated and followed up in the colposcopy clinic with satisfactory information and support.
Follow-up After High Grade Cervical Treatment

The women treated for CIN2-3 remain at a substantially increased risk of recurrences, which persists longer than 10 years. The women treated for CIN2-3 are more likely to develop invasive cancer and the risk is two to five times greater than that of the general population. The main objective of the follow-up of patients treated for high-grade CIN is in one hand, to detect and treat the recurrences and on the other hand, to determine a subpopulation presenting a high risk of recurrence which should be followed-up more intensively. At present, frequent follow-up every year with cytology and colposcopic evaluation of the cervix is the preferred strategy recommended in France by Authorities. But both, cytology and colposcopy don't have a very good sensitivity in this situation. HPV test is more sensitive compared to cytology or colposcopy in detecting CIN treatment failures. It would be more prudent to use a strategy involving both cytology and HPV test. The good sensitivity and the negative predictive value of combined cytology and HPV testing in detecting a residual disease or recurrence are around 100%. Women presenting negative results of both tests, could, then be considered at a low risk of recurrence and their surveillance should be the same as that of the screening of the general population and then re-checked every five year. In case of positivity a more intensive follow-up should be organized where colposcopy is the main tool.
Title: Therapeutic Vaccines

Therapeutic vaccines aim to develop a strong cellular immune response to HPV antigens that are expressed in transformed cells. Several therapeutic vaccines that target E6 and/or E7 proteins have been developed. A majority of clinical trials examining therapeutic vaccination have shown limited efficacy due to examining patients with more advanced-stage cancer who tend to have decreased immune function. Current trend clinical trials with therapeutic agents examine patients with pre-invasive lesions.

Vaccine platforms used to target HPV proteins in human clinical trials include: peptide-based therapies, viral vector-based therapies, DNA-based therapies, dendritic cell-based therapies.

Conclusion: Non-surgical treatment of CIN will happen but it will take time and effort, or require a combination of therapies to achieve a satisfactory clearance rate. We need to develop better strategies to treat this HPV-related lesion.
Title: Quality Assurance in Colposcopy

The United Kingdom National Health Service (UK-NHS) has been a leader in ensuring quality assurance in colposcopy. It has developed key indicators for hospital-based colposcopy clinics. Results in each clinic have to be submitted on a regular basis. In Australia, the ASCCP and RANZCOG have produced recommendations for standards in colposcopy and treatment but to-date colposcopy clinics do not have to submit key indicators for verification of standards. Other countries are considering implementing or have implemented systems to ensure colposcopy standards are maintained.

The colposcopy clinic at Royal Women's Hospital in Melbourne has implemented a prospective database since 2000, which allows retrieval of key indicators as indicated in the UK. Annual reports of these indicators will be presented. Some of the key indicators have not been met despite attempts to improve quality. This may be due to setting to higher benchmarks by UK and not necessarily reflect the average colposcopist. However, it should not deter us from trying to achieve levels set as best practice. Colposcopy standards analysed have consistently shown that there are variations in the positive predictive values (PPV) within the individual colposcopist over time. Young gynaecologists joining our colposcopy clinics have much lower PPV's suggesting that colposcopy training during the Fellowship training program may be inadequate.

Colposcopy prediction alone have been shown to have its limitation and sensitivity can be increased by the number of biopsies taken at colposcopy. However, using histology of biopsy as gold standard for correlation can also be misleading esp. with CIN 2 results.

Colposcopy workshops and courses are available for ongoing training in many regions. We are now able to assist colposcopists to measure their performance using web-based colposcopy programs. It is pleasing when colposcopy performances post workshop are shown to improve utilising pre-and post-colposcopy tests. We hope that there may be an opportunity through this international society to implement a system that can set suitable benchmarks against which colposcopists can match their performance.

Beyond colposcopy, audits of treatment and obstetric outcomes are the next challenge for us.

References:
3) Gage JC et al Obst & Gynae 2006;108:264-272
4) Web-based colposcopy program. www.oncosystems.com * Disclaimer - this software is partly owned by the speaker, Jeffrey Tan.
Title: Quality Assurance in Cytology - The French Experience

The Pap screening has been very successful. However, this test is also limited in terms of its sensitivity and its low reproducibility. These pitfalls led to recommendations of quality assurance, which are single with cytology. These recommendations have been provided through the Clinical Laboratory Improvement Amendments (CLIA) and European guidelines for quality assurance in cervical cancer screening. They concern sampling, personnel and organisation, material requirements, handling and analysis of cervical samples, and recording of results. Internal quality control can be based on screening detection and reporting rates and on rescreening of slides. The reading of 10% of the smears taken randomly has been proposed by CLIA but the rapid review or preview of negative slides appear more effective to detect potential false negatives before the reports are issued. The review of a risk population (patients with prior history of abnormal smears, HIV positive, having a sexually transmitted disease) is considered as well more effective than 10% of the smears taken randomly to detect false-negative. The other methods generally recommended to detect false negative in a retrospective way are the rereading of previous negative smears when abnormalities appear on a smear or a biopsy under colposcopy. To detect the false positive results, correlating the results with a biopsy made under colposcopy remains a model, which is not applicable in routine because the women having a normal smear do not have, most of the time, histological follow-up. However, this can be performed with the abnormal smears where complementary explorations are requested and the cyto-histological correlation is possible. External quality can be performed by comparison of abnormal reporting rates and positive predictive value.

Communication with other laboratories, smear takers, health authorities (cancer registry responsible for the screening program), patients are also tools of quality management. Accreditation of a cytology laboratory remains voluntary in the majority of cases.
Title: Anal Intraepithelial Neoplasia

Although it is rare, the incidence of anal cancer is increasing among both men and women in the general population. Among HIV-negative men who have sex with men (MSM), the incidence of anal cancer may be as high as 37-fold higher than the general population and among HIV-positive MSM, the risk may be double that of HIV-negative MSM (1). Among HIV-positive women, the incidence of cervical cancer is more than 5-fold higher than the general population and anal cancer is nearly 7-fold higher (2). Likewise the incidence of other HPV-associated cancers including penile, vulva/vagina, and possibly oral cancer is elevated in the setting of HIV infection (2). Multiple studies show higher prevalence of anogenital HPV infection among HIV-positive individuals than HIV-negative controls, larger number of HPV types, more HPV persistence; and higher prevalence and incidence of high-grade dysplasia at virtually all anogenital sites (3,4).

Anal HPV infection is surprisingly common among both men and women spanning a wide age range and spectrum of sexual risk factors. Approximately 25% of men with no history of sex with men (MSM) have anal HPV infection, suggesting the possibility of routes of HPV transmission such as spread from the penis or from sexual partners via fingers or other objects (5). MSM are at even higher risk of anal HPV infection and receptive anal intercourse likely plays an important role in this population. Among sexually active HIV-negative MSM aged 18-60 years, about 60% have anal HPV infection with the prevalence remaining constant through this age range (6). Nearly all HIV-positive MSM have anal HPV infection (7).

Anal HPV infection is also common in women. About 27% of healthy Hawaiian women have anal HPV infection (8,9). HIV-positive women have a higher prevalence of anal HPV, with 68% being positive (10). In all of these women, anal HPV infection is as common as, or more common than cervical HPV infection. Data suggest that anal intercourse, spread of HPV from the cervix/vagina/vulva or spread from sexual partners via fingers/toys may play a role in spread of HPV to the anal canal in women.

Although not all men and women with anal HPV infection have anal intraepithelial neoplasia (AIN), the prevalence of AIN tends to mirror that of anal HPV infection in those populations where both were studied. At highest risk of AIN are HIV-positive MSM, followed, respectively, by HIV-negative MSM. HIV-positive women, HIV-negative women, and men with no history of sex with men. Not surprisingly, this also mirrors the incidence of anal cancer in these populations.

References
Vaginal intraepithelial neoplasia (VAIN) is a rare condition, approximately 200 times less common than CIN, which can present a significant management challenge. This presentation will address the clinical and colposcopic features, the natural history and the management of VAIN.

We have previously reported a series of 132 cases of VAIN 1. The majority of patients (73.3%) had high-grade VAIN (2/3) but early invasive carcinoma of the vagina was found in the course of management of the VAIN in 9 (6.9%) patients. Seventy-two (55%) had undergone a prior hysterectomy; 22 for preinvasive disease (CIN), 33 for invasive gynaecological cancer, 13 for benign reasons and in 4 the reason for the hysterectomy and/or the Pap smear history was not known. Twenty-one (16%) had received prior pelvic radiotherapy. VAIN was noted to involve either the vaginal vault (in the post-hysterectomy group) or the upper vagina (in the no hysterectomy group) in more than 80% cases.

A variety of treatment modalities were used with varying degrees of success. Excisional treatments such as upper vaginectomy (vault excision), local excision, hysterectomy or cone biopsy with excision of contiguous vaginal cuff had an overall cure rate of 72.1% (62/86). The state of the surgical margins did not correlate with the risk of residual disease. CO2 laser ablation was curative in 75.8% (25/33) cases and was significantly better than electro-coagulation diathermy which was curative in only 28.6% (4/14), p=.003. 5-fluorouracil cream was curative in 50% (6/12) cases. Radiotherapy was effective in eradicating VAIN in two cases where it was used as the primary treatment modality. An observational approach was initially adopted in 8 patients with low-grade VAIN which regressed in all cases.

Progression of high-grade VAIN to invasive cancer occurred in 8 cases - after no treatment (2), after treatment failure (5) and as a late recurrence (1). These data provide evidence that high-grade VAIN is a precursor to invasive vaginal cancer and that every attempt should be made to eradicate it.
Title: Information Systems for Colposcopy - A Health Systems Approach

The Oncology and Dysplasia Unit at the Royal Women's Hospital provides a multi-disciplinary approach to gynaecological cancer care, assessment and management of pre-cancerous abnormality of cervix detected through the cervical screening program and also incorporates the Hydatidiform Mole registry. The Unit are referred over 200 new Gynaecological cancer cases and 1,500 new Dysplasia cases each year.

History: We have a dysplasia database in a rudimentary form since 1970. It was difficult to monitor as the data was entered retrospectively and retrieving for analysis was hampered by the limitation of the database. A pilot Colposcopy program was developed in 1998 using the Access database software and following its initial success, a software developer was recruited to write the “On-Dysplay” software, that has been continuously updated to its current version. All the data from 1970 to 1997 were converted to an Access database that allows us to look back for cross-reference. All the data from 1998 are incorporated in the current database.

Outcome: We have been able to utilise the databases for administrative activities, monitoring of patients’ appointments and more importantly, produce clinical reports and publications that have improved patient care.

Overview of the operational functionality of “On-Dysplay”

"On-Dysplay" is used for patients referred for colposcopy, usually for abnormal pap smears or post-coital bleeding. It registers patients attending the Dysplasia clinic. It collects data prospectively at the time the patient sees the doctor. Results of the colposcopy examination and referral pap smears are entered on the day. Other tests results eg. Histo-pathology are entered when they are available, usually a week later and the doctor then decides on the plan of management for the patient. Letters are generated for the referring doctor and patient. Any planned operation will be sent to the Theatre booking and the database is available in the operating theatre for entry at the time of surgery.

Lessons learned from RWH

a) Leadership and commitment for data collection is vital for improving patient care. There needs to be a Clinician in this Leadership team;
b) Clinician needs a good working relationship with IT developer and helping the developer to understand the clinical condition and its management. This will improve efficiency of software development;
c) Financial support is not always forthcoming in-house;
d) IT Department need to be involved in the smooth running of the database in a network environment;
e) Data Manager is essential to the successful implementation and maintenance of the database;
f) Prospective data entry is preferable but requires structured training and commitment by all involved.

Benefits and improvements to patient care

a) Administrative improvement
We have been able to ensure our patients require prompt care and monitor the defaulters and contact them early for reviews. Information is available for clerical and clinical staff to advise patients and respond to queries promptly.

b) Quality of Care
We have been able to produce key clinical indicators to assess our Quality of care1,2.

(Table 1) The United Kingdom National Health Service required key indicators from hospital-based colposcopy clinics to be submitted on a regular basis3. We are able to compare our standards with them. This includes regular reports of Colposcopy standards that provide an indication of the quality of our Gynaecology trainees (reflection of our training program) and our Specialists (Continuing Professional Development).

c) Research and Publications
We have been able to combine research and clinical information in the database. This has improved our productivity with peer-reviewed publications.
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(see list below) It is also challenging established clinical practice with evidence that are recognised and published internationally. This has also stimulated us into further research and help the Unit to maintain its 'tertiary' standing.

Conclusion:
We have been able to achieve much with limited resources and fulfil our goals of Improving patient care through knowledge of our Quality of Care and Clinical Standards. We hope that Hospital Administrations and Departments of Health would be able to assist Hospitals that are striving to provide high standard of care through innovative projects like ours with their limited or on-going support.

Table 1

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<thead>
<tr>
<th>Dysplasia Clinic Indicators</th>
<th>NHS standard</th>
<th>RWH 2005</th>
<th>RWH 2006</th>
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<tbody>
<tr>
<td>Proportion of results and management plans communicated to women within 14 days of attending clinic</td>
<td>At least 90%</td>
<td>75%</td>
<td>80%</td>
</tr>
<tr>
<td>Proportion of women not attending follow up appointments</td>
<td>Less than 15%</td>
<td>21%</td>
<td>22%</td>
</tr>
<tr>
<td>Colposcopists accuracy of predicting high grade lesions or worse</td>
<td>65%</td>
<td>53%</td>
<td>58%</td>
</tr>
<tr>
<td>Proportion of treated women having a follow up smear within 6-8 months following treatment</td>
<td>At least 85%</td>
<td>81%</td>
<td>81%</td>
</tr>
</tbody>
</table>

References:
1) Quality of Care Report 2005 Royal Women’s Hospital.
2) Quality of Care Report 2006 Royal Women’s Hospital.

Publications from the Oncology & Dysplasia Unit relating to Dysplasia
**Title: The Management of Glandular Disease**

The main principle of management is excision of the area at risk as a single specimen by whatever means is appropriate to the patient and the operator. This must include the TZ with a length of canal as appropriate and the underlying glandular epithelium remembering the multifocal potential. It will depend on the patient's age, the transformation zone and whatever colposcopic features are evident.

Diagnostic excision is recommended before hysterectomy because of the high rate of occult invasive disease. Cold knife cone is the accepted standard of management but laser cone will give equivalent excision in experienced hands. Loop excision may be used in selected patients remembering the limitations of this technique.

While hysterectomy remains standard management for many women, conservative management is required in many Western countries because of the later age of first pregnancy with many women presenting with AIS now not having commenced their families. Long term follow up of these patients is mandatory and patients must be aware of the rare but definite risk of both preinvasive and invasive disease.

Coexistent adenocarcinoma should be managed in consultation with a gynaecological oncologist. Many patients with invasive disease can still be managed conservatively.
Title: Immunology of HPV Vaccines and Vaccination

HPV infection in the genital tract is common in young sexually active individuals, the majority of whom clear the infection without overt clinical disease. However most of those who develop benign lesions eventually mount an effective cell mediated immune response and the lesions regress. Regression of ano-genital warts is accompanied histologically by a CD4+ T cell dominated Th1 response, animal models support this and provide evidence that the response is modulated by CD4+ T cell dependent mechanisms. Failure to develop effective CMI to clear or control infection results in persistent infection and, in the case of the oncogenic HPVs, an increased probability of progression to CIN3 and invasive carcinoma. The central importance of the CD4+ T cell population in the control of HPV infection is shown by the increased prevalence of HPV infections and HGSIL in individuals immunosuppressed as a consequence of HIV infection. The prolonged duration of infection associated with HPV seems to be associated with effective evasion of innate immunity as reflected in the absence of inflammation during virus replication, assembly and release, and down regulation of interferon secretion and response thus delaying the activation of adaptive immunity. Serum neutralising antibody to the major capsid protein L1 usually develops after the induction of successful cell mediated immunity and these antibody and cell mediated responses are protective against subsequent viral challenge in natural infections in animals. Prophylactic vaccines consisting of HPV L1 VLPs generate high anti L1 serum neutralizing antibody concentrations and in clinical trials have shown greater than 95% efficacy against both benign and neoplastic genital HPV associated disease. These vaccines are delivered intramuscularly and therefore circumvent the immune evasion strategies of the virus.
Title: Natural History of Genital Warts: Analysis of the Placebo Arm of 2 Randomized Phase 3 Trials of a Quadrivalent HPV 6, 11, 16, 18 Vaccine

Objectives: The placebo arms of two Phase 3 efficacy studies of an HPV-6/11/16/18 vaccine were used to define the natural history of genital warts (GWs). The studies were designed to be of 4 years duration. As a result of the high vaccine efficacy, the independent Data and Safety Monitoring Board recommended vaccination of women in the placebo group earlier than planned. The end-of-study data reported here includes approximately 3.6 years of follow-up (max follow-up = 4.9 years).

Methods: Women (n=8,800) were comprehensively examined in the anogenital region for the presence of GWs which were biopsied for histopathological diagnosis (read by a blinded panel of up to 4 histopathologists) and tested for 14 HPV genotypes (6/11/16/18/31/33/35/39/45/51/52/56/58/59) using a PCR-based assay. Risk factors for GWs were assessed.

Results: Overall, 520 distinct lesions were diagnosed as GWs. HPV DNA was detected in 90.8%, and of those DNA positive, 94.7% harbored HPV6 and/or HPV11. Overall 3.4% of women became a case of HPV6- or HPV11-related GWs (incidence rate of 0.87/100 person-years-at-risk). We found high-risk (HR) HPV in 31% of all lesions, with HPV52 and HPV16 the most common in HPV6-related GWs, and HPV16 and HPV56 the most common in HPV11-related GWs. There was little difference in the time to development of HPV6 (6.0 months) and HPV11 (4.9 months) GWs. Risk factors for HPV6/11-related GWs included respective HPV infection at baseline, higher number of lifetime and new sexual partners, and baseline DNA positivity to an HR type. Seropositivity at baseline did not predict risk of development of a HPV6 or HPV11-related GW: 5 women who presumably had cleared an HPV6 infection in the past (i.e. seropositive and HPV DNA negative), went on to develop an HPV6-related GW.

Conclusions: We confirm the major role played by HPV6 and HPV11 in GWs, plus associated risk factors. Our data indicate that prophylactic vaccination with an HPV vaccine that includes HPV6 and 11 will be highly effective in preventing the majority of GW cases and will also eliminate HR types which are commonly observed as co-infections and which cause the majority of HPV-associated cervical and other anogenital cancers.
Title: Cancer Prevention in the Third World Without a Colposcope

Colposcopy services in many developing countries are either inadequate or do not exist. While there is a need to invest in such services, it is also important to look into alternative approaches to control the high-burden of cervical cancer. There is a vast potential to reduce cervix cancer morbidity and mortality by HPV vaccination. Currently bivalent (HPV 16, 18) and quadrivalent (HPV 6, 11, 16, 18) HPV vaccines have been developed and evaluated. The results from these studies indicate, with remarkable consistency, that a regimen of three intramuscular injections of HPV vaccine offers HPV-naïve women a very high-level of protection (~99%) from infections and CIN associated with the HPV types included in the vaccine; the vaccines were safe and well tolerated with relatively few side effects. While HPV vaccination holds great promise, there are still several challenges that need to be resolved before it can be widely implemented in high-risk developing countries. The second option involves ‘screen and treat’ or ‘single visit approaches (SVA) in which the screen-positive women with no clinical evidence of invasive cancer and satisfying the criteria for ablative therapy, are immediately treated with cryotherapy, without confirmatory investigations such as colposcopy or histology. In a randomized controlled trial in South Africa, SVA using VIA or HPV testing resulted in 46% and 74% reduction in the prevalence of high-grade lesions respectively. The safety, acceptability, and feasibility of such approaches have also been demonstrated in rural Thailand, Ghana and Guatemala and a large program is on-going in Thailand.
Title: Dynamic Spectral Imaging Colposcopy - Design of a Validation Study

We have designed a validation study in which the Dynamic Spectral Imaging System (DySIS) is compared with conventional colposcopy, without interfering with either of the two methods. DySIS is a novel imaging technique, based on in-vivo quantitative assessment and mapping of acetowhitening effect of the cervix. The study objective is to evaluate the performance of DySIS in reducing the inter and intra observer disagreement.

The study is designed as an open, prospective, comparative clinical trial. Patients referred to one of the two participating Dutch colposcopy clinics are asked to participate. After obtaining informed consent, the patients are examined by DySIS. During the three minute image acquisition time, DySIS is used as a regular videocolposcope. The colposcopist locates and grades the lesion based on conventional colposcopic criteria. Hereafter DySIS displays a pseudo-colour map with different colours representing different acetowhitening characteristics. Biopsies are taken from the colposcopist's and DySIS' most suspicious location. Always one “at random” biopsy is taken.

So far, 67 women have been included in this pilot study. During this phase, adjustments were made to DySIS to improve the ergonomics and to optimize the image quality. The colposcopists had a short learning curve to get used with the device. The patient compliance was very good; no patients ended the study prematurely and they were in general positive about DySIS.

The preliminary results from the pilot phase are encouraging. Evaluation of DySIS is currently underway in the context of the main phase of the study, which has been recently launched.
Introduction: Adverse obstetric outcomes are associated with excisional treatments for cervical intraepithelial neoplasia (CIN), the exact etiology of which is not known. It has been suggested that the risk of preterm delivery is proportional to the increase in the height of tissue removed from the cervix during conization. Traditionally volume measurements have not been reported. We have compared two excisional treatments, Laser cone biopsy and Lletz, in terms of the volume of tissue removed. Also we have determined the relation between the height and the total volume of the cone specimen.

Methods: We performed a retrospective study of 1022 women who had an excisional treatment (Laser cone or Lletz) between 1st January 2002 and 31st December 2007 in our colposcopy unit. The outcomes in the two procedures were compared using the Mann-Whitney Test.

Results: 343 women had Laser cone biopsy whilst 679 women had a Lletz biopsy. There was no difference in the mean age in the two groups. Although, there is a proportional increase in the volume of the cone as the height of the cone increases, a significant number of values are skewed suggesting that the diameter of the base of the cone contributes significantly to the total volume. Laser cone biopsy (mean vol 1.19 + 0.91 cm3) accounts for a larger volume of tissue excised as compared to Lletz (mean vol 0.49 + 0.41 cm3) (p<0.0001). This relationship is not altered when the two procedures are stratified for grade of lesion i.e. excision for low grade CIN (mean vol Laser 0.92 + 0.60 cm3, mean vol Lletz 0.40 + 0.31 cm3) (p<0.0001) or high grade CIN (mean vol Laser 1.26 + 0.96 cm3, mean vol Lletz 0.53 + 0.45 cm3) (p<0.0001).

Conclusion: The total volume of the cone specimen may be as important a parameter as height of cone. The amount of cervical tissue removed during Laser conization is significantly more as compared to Lletz.
Title: Does the Computerized Planimetry of Uterine Cervix Affect the Effectiveness of the Lletz/Leep Procedure in Treating Cervical Intraepithelial Neoplasia (CIN)?

Objectives: The purpose of the work was to evaluate whether computerized planimetry assessment of uterine cervix performed before the surgery among patients with CIN increases the effectiveness of LLETZ/LEEP procedure as a treatment method of CIN.

Material and Methods: 110 women with CIN, who had the LLETZ/LEEP procedure performed. The patients were divided into 2 groups. The first group consisted of 55 patients who had before the surgery the computerized planimetry assessment of CIN (location, shape, width, extends into cervical canal) had and on this grounds the size and shape of wire loop electrode and the treatment technique (one pass, multiple passes or "top heat" method) were chosen. The second group included 55 women who were treated using direct visual cervix assessment instead of the computerized planimetry before performing the LLETZ/LEEP procedure. The effectiveness of the surgery was evaluated on the basis of the margin status.

Results: Positive margin (incomplete excision) was observed among 14 (25.5%) women from group II. No positive margin was observed in group I. Positive margin was found among 10 patients with HGSIL and among 4 women with LGSIL. The statistical analysis revealed the statistical positive correlation between not making the planimetry and positive margin's appearance among women with CIN.

Conclusions: Computerized planimetry assessment of CIN made before the surgery increases the effectiveness of the LLETZ/LEEP procedure and decreases the rate of positive margin's appearance. Positive margin is observed more often among patients with HGSIL than among patients with LGSIL.
Results of Conserving Surgical Treatment of Cervical Cancer Stage IA and IB1

There are two reasons for looking at conserving and effective surgical mode of treatment of cervical cancer: procreation possibilities preservation and the decrease of perioperative complication percentage and quality of life aspects, especially in stages of the cancer of low risk metastases in lymph nodes and in which the risk of cancer spread is relatively low, namely FIGO IA1, IA2 and IB1.

The colposcopic-histological results were the basis for therapeutic qualification. According to own observation and literature data the percentage of regional lymph nodes metastases is 0-18%. We assumed that the diameter of lesion in colposcopy should not exceed 1,5-2 cm.

Material and methods: Conisation (n=97 [IA1-60], [IA2-(37)]) without unfavorable colposcopic-histological prognostic factors. Trachelectomy and laparoscopic lymphadenectomy n= 11 IA2 (8), in which the chance of lymph node metastases are more possible and 3 IB1.

Results: Concordance of histological evaluation of colposcopically directed punch biopsy vs surgical specimen was 93.3% for CAIA1, 91.1% for CAIA2 and 100% for CAIB1. Results of conisation treatment after 5 years follow-up were no recurrence in 42 (93.3%) of CAIA1, 19 (86.4%) of CAIA2 and 6 recurrence of CIN (5) and CaCx (1). Results of trachelectomy and laparoscopic trachelectomy (all cases below 5 years follow-up) were: no recurrence in 6 cases of CAIA2 and in 2 of CAIB1, while 1 CIN3 recurrence of trechelectomized CAIA2 case. There were 32 pregnancies (37.6%) and 28 deliveries (32.9%) among 85 conisation cases and 1 successful pregnancy after trachelectomy.
**Title:** Stage IA Squamous Cell Carcinoma of the Cervix: A Study of 365 Cases with Long-Term Follow-Up

**Objective:** To evaluate the long-term outcome of patients with microinvasive cervical squamous cell carcinoma (MIC) (International Federation of Gynecology and Obstetrics stages IA(1) and IA(2)).

**Methods:** A total of 365 patients (median age 38 years; range, 2-85) had MIC in conization specimens between 1967 and 2008. Of the 333 stage IA1 lesions, 181 had clear margins and 136 had positive margins (16 reports and specimens unavailable). Of the 32 stage IA2 lesions, 10 had clear margins and 13 had positive margins (9 reports and specimens unavailable). 166 patients with stage IA1 lesions (136 clear margins, 30 positive margins) were followed expectantly. Simple hysterectomies were done in 45 women with stage IA1 lesions and clear margins, 98 patients with stage IA1 lesions and positive margins, and 7 patients stage IA2 lesions. 18 patients with stage IA2 lesions underwent radical hysterectomy.

**Results:** None of the 24 patients who underwent lymphadenectomy had positive nodes. Mean follow-up was 9.9 (0-30.8) years. There were a total of 5 recurrences: 1 patient with stage IA1 lesions treated with conisation alone; 3 patients with stage IA1 lesions and simple hysterectomy; and 1 patient with stage IA2 disease.

**Conclusion:** These results suggest that most stage IA cervical carcinomas can be treated like CIN. Exact histology is essential. Radical surgery appears unnecessary.
Title: Loop Cone or Coin Treatment in CIN 1 - An Age Tailored Treatment

Introduction: CIN 1 treatment is controversial and can be classified as destructive or excisional. Directed biopsy in CIN 1 cases can give a false negative result for CIN 3 in 30% of the women. The ideal treatment should be able to make a correct diagnosis without causing damage.

Method: Our aim was to examine the pathological results in women treated by LLETZ because of CIN1, to find if there are any differences for CIN 2-3 diagnosis according to the patients’ age. We examined retrospectively our results for the years 2001-2003. From 2004-2007 young women up to 35 years old with CIN 1 on cervix biopsy after persistent lesion for 12 months were treated by LOOP Coin and older women were treated by the LOOP cone. We documented the final pathological results, the volume of the cone, and the height of the conus and recorded the complications.

Results: 464 women underwent LOOP Cone excision due to CIN 1. In 2 women Carcinoma was diagnosed, in 19.2% the final diagnosis was CIN 2-3, in 44.4% CIN 1 was found and normal histology was found in 35.8% of the patients. In young women age 18-24 the average volume of the conus was 1.47 cubic cm. and the height was 0.59 cm. and it gradually grows in women 45-54 years to an average of 2.79 cubic cm. and height of 1.05 cm.

Conclusion: Tailored treatment by a thin LOOP Coin in young patients diagnosed with CIN 1 had a diagnostic advantage of correct diagnosis of CIN 2-3 in 19.2% of the patients, with a minimal potential risk for future complications.
Title: Trial of Management of Borderline and Other Low-grade Abnormal Smears (TOMBOLA)

Outline: Annually in the UK around 250,000 cervical smears show low-grade abnormalities. Alternative management policies following borderline or mildly dyskaryotic smear are cytological surveillance or colposcopy. TOMBOLA is a randomised controlled trial which addresses clinical, psychosocial and economic outcomes of these two different management options.

Methods: A prospective randomised controlled trial of 4439 women aged 20-59, from 3 different centres in the UK with a low-grade smear with randomisation to cytological surveillance (six-monthly smears in primary care) or hospital-based colposcopy. All women were tested for HPV at recruitments and invited for an exit colposcopy visit and HPV test 3 years afterwards irrespective of intervening events.

Results: Cumulative incidence of CIN2 or more severe disease (CIN2+) in the colposcopy arm was 7.9% per year, higher than in cytological surveillance (5.8%; OR=1.43, 95% CI 1.23-1.67). This difference was less marked for CIN3+ (OR=1.27, 1.04-1.55), suggesting spontaneous regression of some CIN2, and that initial colposcopy can lead to over-treatment. There was little difference in psychosocial outcomes between arms. In comparison of biopsy and recall versus immediate LLETZ, there was no difference in cumulative incidence of CIN2+ or psychosocial outcomes. Immediate treatment was associated with more adverse events such as increased bleeding. There was no compelling economic reason to favour any one management method. A single test for HPV following a low grade smear does not appear to be effective in triage.

Conclusion: Women with low grade smears can be effectively managed by conservative cytological follow-up in primary care.
Title: How Effective is Cold Coagulation as a Treatment for High-grade CIN?

Introduction: Adverse obstetric outcomes are associated with excisional treatments as compared to destructive treatments for cervical intraepithelial neoplasia (CIN). Some have suggested a return to destructive treatments for CIN, particularly in young women, especially for low grade CIN.

Study Objective: We have compared the success rates following cold coagulation for low-grade CIN and high-grade CIN.

Methods: We performed a retrospective cross-sectional study of 172 women who had cold coagulation performed between 1st January 2000 and 31st December 2005 in our colposcopy unit. The outcomes were measured in terms of cytology results at 6 and 12 months following the treatment.

Success rates, odds ratio and relative risk of having an abnormal smear in the two cohorts (low-grade CIN v high-grade CIN) were calculated.

Results: Eighty-nine women with low-grade CIN and 83 women with high-grade CIN confirmed by colposcopically directed biopsy were included in the study. There was no difference in the mean age in the two groups. The overall success rate at 6 months was 94.7% (98.8% for low-grade CIN and 90.3% for high-grade CIN). The overall success rate at 12 months was 97.09% (100% for low-grade CIN and 93.9% for high-grade CIN). None of the women developed microinvasive/invasive cancer or CIN 3 at 12 months post-treatment. In our cohort, women with high-grade CIN were more likely to have an abnormal smear post-treatment as compared to women with low-grade CIN at 6 months (RR 8.57 Odds ratio 0.1 95%CI 0.01-0.8 P=0.03) as well as at 12 months (RR 11.78 Odds ratio 0.07 95%CI 0.004-1.46 P=0.08).

Conclusion: Cold coagulation in the presence of a satisfactory colposcopy is as effective a treatment for high-grade CIN as for low-grade CIN.
Presentation Abstract

Speaker  Dr Jean GONDRY

Session Title:  C25: Free Communications
Session Date:  Thursday 23 October
Session Time:  0830 - 1045
Session Venue:  Lower NZI Room
Presentation Time:  1030 - 1045
Presentation Theme:  Pathology

Authors  Affiliates
Professor Jean Gondry * 1  1.University Hospital of Amiens
Miss Muriel Hirsch
Mr Jean Charles Boulanger

Title: Cervical Stenosis and Conization

Objectives: To evaluate the incidence of cervical stenosis (CS) after conization and to identify the associated risk factors.

Methods: This is a retrospective study including 603 patients who underwent conization between 1999 and 2007.
The different parameters used for the study were:
-age of the patient
-menopausal status
-number of pregnancies
-height of removed tissue
-diameter of the endocervical canal at the top of conization
-and the size of the external os, three months after conization

We have defined cervical stenosis as an external os diameter ≤2 mm

Results:

- Influence of patient age:
The percentage of CS in women <45 years old was 9.5% versus 47.5% for women >45 years old.

- Influence of menopausal status:
The percentage of CS in pre-menopausal women was 10.85% versus 57.14% for post-menopausal women.

- Influence of number of pregnancies:
The average size of the external os in patients who were never pregnant was 5.87 mm, 5.36 mm in women who had few pregnancies, and 7 mm in women who had numerous pregnancies.

- Influence of the height of the cervical cone:
The average height of the cervical cone was 14.3 mm.
In patients with CS, it was 16.48 mm versus 13.98 mm in the non-CS patients.

- Influence of the endocervical canal diameter at the top of excision:
The average endocervical canal diameter for the overall patient group was 5.54 mm.
In patients with CS, the average was 4.08 mm versus 5.72 mm in the non-CS patients.

Conclusion: In our study, the main risk factors for cervical stenosis are: age > 45, menopausal status, cone height > 16 mm, and a narrow endocervical canal diameter.