HPV Today

Newsletter on Human Papillomavirus

www.hpvtoday.com

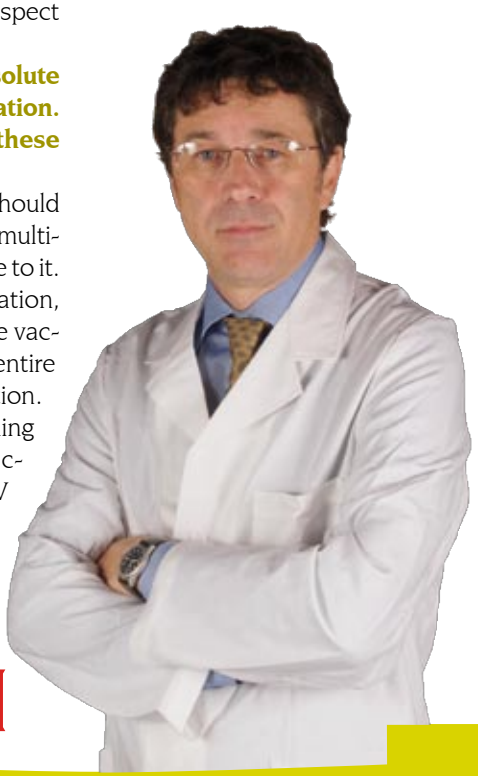
THE HPV VACCINE IN ITALY: HOW TO PUT RESEARCH DATA INTO PRACTICE. LET THE DEBATE BEGIN!

The HPV vaccine is an extraordinary tool for primary prevention and has been defined by Carolyn Runowicz, the president of the American Cancer Society, as "one of the most important advances in women's health in recent years". However, putting data into practice adds complexity to the subject and we will discuss this aspect with Luciano Mariani and Mario Sideri.

• HPV Today: research data have shown the absolute efficacy of the vaccination in the studied population. What do you think about the application of these results to the general population?

• Mariani: I personally believe that vaccination should preferentially occur through organized programs in multi-cohorts prior to sexual debut (pre-exposure) or close to it. This setting better suits a more precise standardization, a more rigorous application and monitoring of the vaccination and, indeed, leads to benefits for the entire community compared with individual vaccination. The major difficulty appears to be in determining the age-limits to recommend a mass vaccination as the clinical benefits of the HPV vaccine will probably be lower in sexually

(continues on page 3)



INTERVIEW WITH

M. SIDERI AND L. MARIANI

Nº 16 October 2008

EDITORIAL

HPV AND CANCER OF THE UTERINE CERVIX: A REVOLUTION IN CANCER PREVENTION

Prevention and early diagnosis are the most powerful weapons in the fight against cancer, particularly in the area of female malignancies, where mammographic screening has changed the epidemiology of this disease. In Italy, 35% of the breast tumours operated on today are non-palpable lesions, which are treated by means of super-conservative surgery, thereby respecting the integrity of the female body.

Again in the female sphere, cytology screening has enabled a remarkable reduction in incidence and mortality in cervical cancer, and it is no exaggeration to say that the discovery of the relationship between HPV and cervical cancer represents a real revolution in our approach to prevention. Thanks to the introduction of HPV-DNA detection tests, prevention has moved from a morphological diagnosis of a pre-cancerous state to the molecular identification of neoplastic risk. This is a tangible sign of the influence of molecular medicine on clinical practice, where it is changing our therapeutic approach, and therefore also the clinical classification of tumours themselves, in both tumour prevention and management.

The introduction of prophylactic vaccination is also an important milestone as, for the first time in the history of humanity, there is now a preventive vaccine against cancer. This turning point brings female children and adolescents into the area of oncology, and in cancer centres we now see very young women in the vaccine clinic alongside those who have been operated on and those undergoing chemotherapy. This is a concrete sign of the scientific progress that has been made in prevention and early diagnosis and, indeed, in our understanding of the natural history of this disease.

But is the medical community ready for such a revolution? Are doctors ready to play their key role in the field of prevention? One of the distinct features that HPV vaccination introduces is the interdisciplinary nature of cancer prevention and, in this sense, the revolution therefore affects several medical professionals. Substantial energy and commitment must therefore be invested in order to ensure that the latest knowledge and expertise is transferred to, and disseminated within, the framework of the healthcare system. A new era in oncology is underway: are you ready?

Umberto Veronesi
European Institute of Oncology, Milan, Italy.

Website: www.hpvtoday.com

Correspondence and collaborations:
E-mail: box@hpvtoday.com

Published by:
BYPASS Ediciones
C/ Bruselas, 7C
28813 Torres de la Alameda. Madrid. Spain.

Editorial staff:
Alejandro Santos, Cristina Rajo and Mar García

Legal deposit: M-35437-2001 ISSN: 1885-9291

Mario Sideri[1] and Luciano Mariani[2]
[1]Preventive Gynecology Unit - European Institute of Oncology, Milan, Italy. [2] National Cancer Institute, Ist. Regina Elena, Roma, Italy.

(from page 1)

active women of 23-26 years (because some will have already been exposed to the virus) and there is not yet a clear indication for a mass-vaccination program. It will also be important to consider the number of sexual partners in this subset of the "adult" population, as well as the past/recent history of HPV-related diseases.

•**Sideri**: With respect to a public intervention, I agree with Luciano that the real target of the vaccination should be cohorts who have not been exposed to the virus. However, I think there is also a case for individual vaccination of women older than twelve who might have already been exposed to the virus. The difficult question is whether to make a selection of patients and which criteria to adopt. For opportunistic vaccination, where the intervention is a personal option, it is most appropriate to find a method that directs the patient to the most appropriate choice for her risk level.

In this case, genotyping seems to yield more objective risk data than an evaluation of previous sexual activity and HPV-related diseases, which are surrogates of the real risk factor, namely the persistence of viral infection due to oncogenic genotypes.

•**Mariani**: Does this mean that for an individual vaccination you consider polymerase chain reaction (PCR) to be essential alongside the Papanicolaou smear?

•**Sideri**: It is not essential but is better than Pap smear alone as it identifies a high-risk woman. In this setting, searching for a positive test for HPV-16/18 type identifies a group of women at well-documented risk of developing cervical intraepithelial neoplasia (CIN) 2-3 and also a subgroup of women for whom the benefit of the vaccine is doubtful.

•**Mariani**: But don't you think this will disproportionately increase the already excessive costs of the vaccine alone? After all, when we talk about reduction of health expenses we cannot talk only about "public and institutional" health but must also consider "private and individual" health. A favorable cost-benefit ratio should be considered even in the case of "individual" vaccination.

•**Sideri**: What is the cost of a cancer prevented? If we consider public health it's the cost of all the vaccines administered divided by the number of tumors. But what is it if we consider private vaccination? It's one vaccination per prevented tumor if the tumor is yours. Otherwise you have wasted your money. It's like insurance: if nothing happens, you spent the money for nothing. The question is: what is the cancer risk for that individual woman? To answer this question you should answer some other questions first. What is the probability of a middle-class woman who regularly undergoes cervical screening developing cancer? How much does the vaccine lower this probability? What's the impact of a previous exposure to the virus? Using sexual activity to make a decision is not as accurate as HPV genotyping and indeed can be very subjective. If counseling is needed, I think it would be better to choose on the grounds of an objective finding –the persistence of an HPV 16/18 infection– that gives an objective risk of cancer development, which at least deserves accurate screening, and that has been shown to have a detrimental effect on the vaccination efficacy.

Mariani: We are in a transition period, with many uncertainties, that could last for quite a long time. Nevertheless, the chance to avoid the traumatic experience of a genital tumor leads to an emotional and ethical desire to spread the vaccine as widely as possible to all women.

•**Sideri**: The HPV vaccine is a great opportunity for primary prevention that we should take without hesitation. The vaccine is still protective in already exposed women, and testing for HPV identifies both women at increased cancer risk and women at lower risk who can maximize vaccine efficacy.

•**HPV Today: in summary, what would you recommend as public and private policy for HPV vaccines and cervical cancer prevention in Italy?**

•**Mariani**: I strongly recommend to move in two directions: the first concerns the national health system implementing organized HPV mass-vaccination strategies for young girls of 12 years of age, with a catch-up until age 16. In this setting the critical goal is to obtain high coverage to achieve the maximum benefit for the community and prior HPV testing or genotyping is clearly irrelevant. The second direction concerns young sexually active women (17 to 26 years) who will be largely followed in the private setting by gynecologists. The goal is to offer protection to individual women. Again, the consensus of most scientific societies is that no prior viral test is necessary in order to decide whether or not to vaccinate.

•**Sideri**: I fully agree in the recommendation that the maximum effort has to be put into implementing mass-vaccination programs among adolescents. In the private sector, however, when vaccination is offered to the individual young sexually active woman, screening with or without HPV testing should be routinely offered in addition to vaccination. This is particularly important for women older than 25 years of age, for whom routine cervical screening is recommended in Italy. In this context, HPV genotyping could be useful for identifying the occasional woman who is already positive for one of the HPV types included in the vaccine and who will gain a reduced protection from vaccination, but should derive the maximum benefit from an accurate follow-up of her HPV infection.]

THE HPV TEST AND PAP SMEAR AS OUTCOME PREDICTORS IN CONSERVATIVELY TREATED ADENOCARCINOMA *IN SITU* OF THE UTERINE CERVIX

Silvano Costa
Department of Obstetrics and Gynecology, S.Orsola-Malpighi University Hospital, Bologna, Italy.

The relative proportion and absolute incidence of invasive and preinvasive glandular lesions of the uterine cervix have been changing in Western countries over the past 50 years. Reports from the 1950's and 1960's indicated that adenocarcinomas (AdCa) accounted for only 5% of cervical cancer cases, while in the 1970's AdCa represented 20-25% of all cervical carcinomas.[1]

Extra-fascial/radical hysterectomy has been considered as the standard treatment for all glandular *in situ* lesions because of the possibility of persistent disease in excisional biopsy with negative borders due to multi-focal disease and because of concerns regarding occult invasive AdCa in the deep clefts of the endocervical glands.[2] In recent years, however, there has been a trend towards fertility-sparing surgery as, in the majority of cases, clinicians have to deal with young women who desire conservative therapy.

In a review of 14 studies comprising 157 adenocarcinoma *in situ* (AIS) patients with negative conization margins, 26% harboured residual AIS and an unsuspected invasive cancer was disclosed in 2% of cases, which implies hysterectomy as the definitive treatment.[3]

Adding to the complexity of management is the fact that others emphasize the risk of "unnecessary" hysterectomies if further radical treatment is indicated solely on the basis of the margin status.

The conservative alternative to hysterectomy is cone biopsy with close surveillance, which traditionally involves repeated cytology, colposcopy and, eventually, punch biopsy and endocervical curettage. Unfortunately, however, these methods have a substantial false-negative rate for glandular lesions either in the primary diagnosis or in the follow-up of treated patients.[4]

It has been reported that detection of HPV DNA may indicate a persistent high-grade squamous lesion missed by Papanicolaou test in the follow-up of cervical intraepithelial neoplasia (CIN) 3 treated patients.[5] The performance of cervical cytology and HPV testing Hybrid Capture® 2 (HC2®, Qiagen Gaithersburg, Inc., MD, USA, previously Digene Corporation) in the detection of histologically confirmed residual or recurrent AIS or invasive AdCa during the follow-up of women with conservatively treated AIS has been investigated recently in 42 patients who were carefully counseled regarding their risk of persistent disease.[6] **The results of this study showed that the predictive power of an HPV test for disease clearance/persistence is statistically significant whereas the predictive power of the Papanicolaou smear does not reach statistical significance at any of the follow-up visits.** Furthermore, the HPV test shows a better negative predictive value (NPV) while the PAP smear is more specific in detecting residual AIS, and the combination of PAP smear and HPV test gives a sensitivity (SE) of 90% in detecting persistent lesions at the first follow-up visit and 100% SE at the second. In addition, the NPV of 100% seems to be very useful in preventing unnecessary hysterectomies (Table 1).

	HPV test	Pap test	Pap test+HPV test
First follow-up visit			
Sensitivity	90%	60%	90%
Specificity	58%	69%	50%
PPV*	64%	55%	52%
NPV**	88%	73%	89%
Second follow-up visit			
Sensitivity	84%	66%	100%
Specificity	59%	73%	52%
PPV	42%	44%	40%
NPV	91%	87%	100%

* PPV = *Positive predictive value*; ** NPV = *Negative predictive value*.

Table 1.
Performance of the Pap test and HPV test in the follow-up of AIS patients treated conservatively.

These results suggest that a high risk-HPV (HR-HPV) test in conjunction with cytology offers a clear advantage over single cytology in monitoring those women who have been conservatively treated for glandular intraepithelial neoplasia. This is because the high sensitivity and NPV of this combination helps to ensure the early detection of those patients at increased risk of disease recurrence and progression, thereby preventing unnecessary radical treatment. A multi-centre trial based on a larger cohort is warranted to confirm these preliminary data.

References: 1. Bryson P *et al.* Is electrosurgical loop excision with negative margins sufficient treatment for cervical ACIS? Gynecol Oncol 2004;93:465-8. **2.** ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynaecologist. Management of abnormal cervical cytology and histology Obstet Gynecol 2005;106:645-63. **3.** Cohn DE *et al.* Invasive cervical adenocarcinoma immediately following a cone biopsy for adenocarcinoma *in situ* with negative margins. Gynecol Oncol 2005;98:158-60. **4.** Raab SS. Can glandular lesions be diagnosed in pap smear cytology? Diagn Cytopathol 2000;23:127-33. **5.** Costa S, et al. Factors predicting human papillomavirus clearance in cervical intraepithelial neoplasia lesions treated by conization. Gynecol Oncol 2003;90:358-65 **6.** Costa S *et al.* Human papillomavirus (HPV) test and Pap smear as predictors of outcome in conservatively treated adenocarcinoma *in situ* (AIS) of the uterine cervix. Gynecol Oncol 2007;106:170-6.

PEDIATRICIAN KNOWLEDGE AND ATTITUDES REGARDING HPV DISEASE AND ITS PREVENTION

Nicola Principi
Istituto di Pediatria, Università di Milano,
Fondazione IRCCS "Ospedale Maggiore Policlinico,
Mangiagalli e Regina Elena", Milano, Italy.

HPV vaccine has to be administered before the beginning of sexual activity in order to have the highest efficacy, therefore it is recommended in young females aged 11-12 years or even as young as 9 years. As a consequence, administration of HPV vaccine has to be dealt with by pediatricians, who can thus significantly influence patients' and parents' immunization decisions and play a key role in promoting vaccination.

Several studies have indicated that pediatricians are currently not sufficiently well trained to carry out this task. Their knowledge of HPV and related pathologies is very poor because HPV is a sexually transmitted infection and sexual activity usually only begins at about 14 years in young girls from Western countries, which means that pediatricians are therefore not often involved in the management of diseases that usually occur in adulthood.[1,2]

Significant findings demonstrating the poor knowledge of pediatricians regarding HPV infection and its prevention have recently been obtained from a group of 311 Italian pediatricians (140 primary care pediatricians, 122 hospital

(*continues on page 6*)

Question	Primary care pediatricians (n=140)	Hospital pediatricians (n=122)	Pediatric residents (n=49)
Do you speak about questions related to sexuality with your patients' parents?			
Never	17 (12.1)	11 (9.0)	9 (18.4)
Only if they raise the subject	60 (42.9)	52 (42.6)	17 (34.6)
Only if they have specific problems	39 (27.9)	42 (34.5)	19 (38.8)
Always	24 (17.1)	17 (13.9)	4 (8.2)
Do you think your patients' parents are interested in HPV prevention?			
I don't know	69 (49.3)	57 (46.7)	18 (36.7)
No	6 (4.3)	14 (11.5)	6 (12.2)
Yes, all	12 (8.6)	8 (6.6)	2 (4.2)
Yes, not all but more than 50%	23 (16.4)	19 (15.6)	9 (18.4)
Yes, but fewer than 50%	30 (21.4)	24 (19.6)	14 (28.5)
Why do you think your patients' parents would accept HPV vaccination?			
To prevent a sexually transmitted disease	30 (21.4)	25 (20.5)	10 (20.4)
To prevent a potentially carcinogenic infection	94 (67.2)	91 (74.6)	36 (73.5)
For both reasons	16 (11.4)	6 (4.9)	3 (6.1)
Why do you think your patients' parents would refuse HPV vaccination?			
Little fear of disease	39 (27.9)	24 (19.7)	1 (2.0)
Fear of adverse events	39 (27.9)	24 (19.7)	1 (2.0)
Refusal of a vaccination against a sexually transmitted disease	18 (12.9)	18 (14.8)	16 (32.65)
Fear of increasing patients' sexual activity	53 (37.8)	49 (40.1)	16 (32.7)

Table 1.
Attitudes of physicians towards discussing questions related to sexuality with their patients' parents, as well as their beliefs as to whether their patients' parents would accept or refuse HPV *vaccination, and why.*

(*from page* 5)
pediatricians and 49 pediatric residents) to whom an anonymous questionnaire was sent.[3] Analysis of the data collected in this study shows that a great number of pediatricians do not have correct information regarding this virus, its role in causing diseases, and the possibility of vaccinating against it (Table 1). The data regarding the best moment for HPV vaccine administration are particularly interesting because a considerable number of pediatricians indicate an age beyond the period when sexual activity usually begins that is significantly higher than that recommended. The most important information derived from this survey, however, concerns the behavior of pediatricians when faced with the problems related to a sexually transmitted disease (Table 1). **Many Italian pediatricians acknowledge that they do not usually discuss questions of sexuality with older children, adolescents and their parents, unless they ask for explanations of these topics.** Indeed, many of them honestly admit to have problems in discussing HPV diseases and HPV vaccine administration and indicate that they cannot predict the interest of adolescents and their parents in HPV prevention. Moreover, taking into account that HPV-related problems are completely new for children and adolescents as well as for their parents, a sizeable number of pediatricians predict that some children and adolescents may refuse the HPV vaccine because of their limited awareness of HPV-related disease, whereas parents may worry that a vaccine against a sexually transmitted disease could promote risky sexual behavior.

The inadequate knowledge of pediatricians regarding HPV-related problems could therefore represent a barrier to widespread vaccination. **If an adequate degree of acceptability of HPV vaccine by young patients and their parents is to be ensured, it is vital that pediatricians become involved in programs of continuous medical education regarding HPV-related problems before plans for the use of HPV vaccines are implemented.**

References: 1. Kahn JA *et al.* Pediatricians' intention to administer human papillomavirus vaccine: the role of practice characteristics, knowledge, and attitudes. J Adolesc Health 2005;37:502-10. **2.** Daley MF *et al.* A national survey of pediatric knowledge and attitudes regarding human papillomavirus vaccination. Pediatrics 2006;118:2280-9. **3.** Esposito S *et al.* Pediatrician knowledge and attitudes regarding human papillomavirus disease and its prevention. Vaccine 2007;25:6437-46.

Carlo Signorelli
Istituto di Igiene
University of Parma,
Italy.

The Directing Board of the Italian Agency for Drugs Administration (AIFA) established commercialization and reimbursement rules for anti-HPV vaccines on March 3rd 2007 for Gardasil® (Merck & Co., Inc., Whitehouse Station, NJ, USA) and on November 21st of the same year for Cervarix™ (GlaxoSmith-Kline Biologicals, Rixensart, Belgium) (Table 1). The statement sets out the indications for the prevention of severe dysplasia of the uterine cervix (cervical intraepithelial neoplasia, CIN, 2/3) and of uterine cervical carcinoma induced by HPV genotypes 16 and 18 for both vaccines, and for Gardasil® alone for high degree dysplasia of the vulva (vulvar intraepithelial neoplasia, VIN2/3) and diseases of the external genitalia induced by genotypes 6 and 11 (i.e. *Condyloma acuminatum*). **These indications are based on the recognized efficacy of Gardasil® and Cervarix™ in adult women between 15/16 and 25/26 years, and on the demonstration of immunogenicity in 9-15-year-old children and adolescents (Gardasil®) and 10-25-year-old girls and women (Cervarix™)**. Protective efficacy has not been evaluated in males.

The two vaccines are classified in Italy as H-RR class: this designation identifies the vaccines as being dispensed by the National Health Service (NHS) at no cost for a well-delimited cluster of the general population — currently 12-year-old females. This cohort was selected because the strongest immune responses are observed in prepubertal children.[1] Both vaccines are, however, available for other cohorts as a full-price drug and are dispensed on presentation of a medical prescription.

The twelve-year-old female cohort was selected because: 1) first sexual intercourse is rare at this age;[4] 2) the fact that education is compulsory at this stage makes the cohort easily enlistable; 3) the setting up of communications

ANTI-HPV VACCINATION PROGRAM MANAGEMENT IN ITALY

September 2006	Date of issue of Marketing Authorization valid throughout the European Union for Gardasil® (EMEA)
March 2007	AIFA establishes commercialization and reimbursement rules for Gardasil®
November 2007	AIFA establishes commercialization and reimbursement rules for Cervarix®

Table 1.
Milestones in the introduction of anti-HPV vaccination in Italy.

with families is well established; and 4) vaccination procedures and the follow-up of vaccinated girls are easier.
Starting 2008, the NHS has been offering the first dose of HPV vaccine to approximately 280,000 girls, with two boosters in the following six months. The annual charge to the Italian NHS is estimated at €75 million. The Ministry of Health has also emphasized that screening procedures will remain the mainstay of prevention.
The various regional governments currently have different approaches to HPV vaccination (Figure 1). Two regions (Basilicata and Valle d'Aosta) have already started their campaign, and eleven regions have set a starting date: eight regions plan to start in January 2008 and three regions between February and June 2008. The remaining six regions have not yet set a date (Table 2). All thirteen regions that have planned the beginning of their immunization campaigns will provide free administration to 12-year-old females.
Mass vaccination for HPV, even in the relatively restricted cohort of 12-year-old females, is a major challenge for the Italian NHS and many questions still remain unsolved, especially how to promote the vaccination campaign, whether the vaccine should be offered to other cohorts in addition to 12-year-old girls, which priorities need be identified, and whether the Italian NHS is ready to face this challenge.
A consistent answer appears difficult, however, mainly because of the inhomogeneous state of Italian Public Health due to historical and still unsolved differences between northern and southern regions. These were recently enhanced by the so-called "Devolution", the transferal of health competencies to regional governments. Moreover, the screening programs run differently in different Italian regions.

ITALIAN REGIONS	MONTH/YEAR
Basilicata	07/2007
Valle d'Aosta	10/2007
Calabria	01/2008
Lazio	01/2008
Liguria	01/2008
Piemonte	01/2008
Puglia	01/2008
Sicilia	01/2008
Toscana	01/2008
Veneto	01/2008
Sardegna	02/2008
Emilia Romagna	03/2008
Friuli Venezia Giulia	06/2008
Abruzzo	Not yet decided
Campania	Not yet decided
Marche	Not yet decided
Molise	Not yet decided
Lombardia	Not yet decided
P. A. Trento	Not yet decided

Table 2.

Figure 1.

Figure 1 and Table 2
Anticipated date of initiation of the HPV vaccination campaign in the different Italian Regions (Instituto Superiore di Sanità (ISS), 24/10/2007).

References: 1. Frazer IH. HPV vaccines. Int J Gyn Obst 2006;94:S81-S88. **2.** Istituto Superiore di Sanità. Centro Nazionale di Epidemiologia Sorveglianza e Promozione della Salute. Rilevamento sull'introduzione della vaccinazione anti-HPV nelle Regioni italiane: Risultati preliminari (24/10/2007). **3.** Signorelli C. HPV Human Papillomavirus. Infezione – Tumore della cervice uterine – Vaccinazione. Roma: Società Editrice Universo, 2007. **4.** Signorelli C, Colzani E. Age at first intercourse and HPV immunization. J Prev Med Hyg 2007;48:37-38.

NEW TECHNOLOGIES FOR CERVICAL CA
THE ITALIAN NTCC STUDY

The New Technologies for Cervical Cancer (NTCC) screening study is a randomised controlled trial conducted in nine organised cervical screening programmes (Turin, Padua, Verona, Trento, Bologna, Imola, Ravenna, Florence and Viterbo) from six Italian regions. These programmes routinely invite women aged 25 to 64 years for a Papanicolaou test every three years.

Women aged 25-60 years attending for a new routine cervical screening episode were eligible, with exclusion of pregnant and hysterectomized women and those treated for cervical intraepithelial neoplasia (CIN) within the last five years. They were randomly assigned to a conventional or to an experimental arm. Women assigned to the conventional arm had conventional cytology and were usually referred to colposcopy if cytology result was of atypical squamous cells of undetermined significance (ASCUS) or more severe. The experimental arm followed two phases. During phase 1, women were tested for both HPV DNA (by Hybrid Capture® 2, HC2®, Qiagen Gaithersburg, Inc., MD, USA, previously Digene Corporation), only the probe for high- and medium-risk types) and liquid-based cytology (ThinPrep®, Cytyc Corp., Boxborough, MA, USA). HC2® results were expressed in RLU (Relative Light Units, the ratio of the specimen's light emission to the average of three concurrently tested 1 pg/ml HPV DNA controls), which is related to viral load. Management in this phase varied according to age: women in the age range 35 to 60 were always referred to colposcopy if either HPV was positive (≥1 RLU) or cytology was ASCUS or more severe, whereas those in the age range 25 to 34 were referred to colposcopy only when cytology was ASCUS or more severe. HPV-positive but cytologically normal women in this latter age group were invited for repeat cytology and HC2® after one year and referred to colposcopy if either test was positive at repeat. This approach was used in order to increase specificity, given the high prevalence of HPV infection in this age range. During phase 2, women were tested with stand-alone HC2® and women that tested HPV positive were referred to colposcopy independently of age. Overall, 94,370 eligible women were enrolled: 45,174 during phase 1 and 49,196 during phase 2.

A quality-assurance system for HPV testing, based on the circulation of "clinical" samples between participating laboratories, was set up. This showed the high reproducibility between centres[1] and could represent the baseline in case of routine implementation of HPV testing. As with most randomised trials in this field, NTCC was designed to study longitudinally the occurrence of new lesions in groups of women tested and managed (and, if needed, treated) differently on the basis of test results. Comparing the disease occurrence at the subsequent screening round allows

Age 35–60 Criteria for referral	Endpoint CIN2+				Endpoint CIN3+			
	Detection rate per 1000	Relative sensitivity (95% CI)	PPV (%)	Relative PPV (95% CI)	Detection rate per 1000	Relative sensitivity (95% CI)	PPV (%)	Relative PPV (95% CI)
EXPERIMENTAL ARM Liquid-based cytology **≥ASCUS or** HPV **≥1 RLU**	4.49	**1.47 (1.03–2.09)**	4.5	**0.40 (0.23–0.66)**	2.33	1.25 (0.78–2.01)	2.3	**0.34 (0.21–0.54)**
HPV ≥ **1 RLU**	4.37	**1.43 (1.00–2.04)**	6.6	**0.58 (0.33–0.98)**	2.27	1.22 (0.76–1.96)	3.5	**0.50 (0.32–0.79)**
HPV ≥ **2 RLU**	4.25	1.41 (0.98–2.01)	8.5	0.75 (0.45–1.27)	2.21	1.19 (0.74–1.92)	4.4	0.63 (0.40–1.00)
CONVENTIONAL ARM Conventional Cytology ≥ASCUS	3.06	1.00	11.4	1.00	1.86	1.00	6.9	1.00

Age 25–34	Endpoint CIN2+				Endpoint CIN3+			
	Detection rate per 1000	Relative sensitivity (95% CI)	PPV (%)	Relative PPV (95% CI)	Detection rate per 1000	Relative sensitivity (95% CI)	PPV (%)	Relative PPV (95% CI)
EXPERIMENTAL ARM Liquid-based cytology **≥ASCUS.** In addition, if HPV **≥1 RLU** and cytology normal repeat both tests after 1 year and refer if **either** is positive	9.16	**1.61 (1.05–2.48)**	8.5	**0.55 (0.37–0.82)**	2.67	0.70 (0.37–1.34)	2.5	**0.24 (0.13–0.45)**
HPV ≥ **1 RLU;** if cytology normal repeat both tests after 1 year and refer if **either** is positive	9.00	**1.58 (1.03–2.44)**	12.1	0.78 (0.52–1.16)	2.50	0.66 (0.34–1.27)	3.4	**0.33 (0.17–0.61)**
HPV ≥ **2 RLU;** if cytology normal repeat both tests after 1 year and refer if **both** are positive	8.83	**1.55 (1.01–2.40)**	15.8	1.02 (0.69–1.52)	2.50	0.66 (0.34–1.27)	4.5	**0.43 (0.23–0.82)**
CONVENTIONAL ARM Conventional Cytology ≥ASCUS	5.68	1.00	15.5	1.00	3.79	1.00	10.3	1.00

Table 1.
Relative sensitivity and PPV *for* CIN2+ *and* CIN3+ *of different screening strategies versus conventional cytology* ≥ASCUS. NTCC *study phase 1*[2,4]. *Bold: Result statistically significant* $p<0.05$. ASCUS: *atypical squamous cells of undetermined significance;* CI: *confidence interval;* CIN: *cervical intraepithelial neoplasia;* PPV: *positive predictive value;*RLU: *relative light unit.*

GRAPH

ANCER SCREENING:

Guglielmo Ronco
(On behalf of the NTCC study group).
Unit of Cancer Epidemiology, Center for Cancer Prevention (CPO), Turin, Italy.

the rate of regression of excess lesions detected by HPV testing to be estimated and whether longer screening intervals are safe to be evaluated. Follow-up is still to be concluded.

We can, however, summarise the main results at recruitment for phase 1 as they have been published. These results allow the cross-sectional accuracy of different screening methods to be studied. In the age group 35-60, for example, HPV alone at a cut-off of 1 RLU increased the sensitivity for histologically confirmed CIN2 or more but decreased the PPV with respect to conventional cytology. Increasing the cut-off to 2 RLU substantially improved the PPV while the relative sensitivity remained practically unchanged. Adding liquid-based cytology to HPV testing increased the sensitivity only marginally but strongly reduced the PPV (see Table 1).[2] We also computed the resources employed to detect a CIN2+ for this age group with different strategies.[3]

In the age group 25-34, despite 14% of women being HPV positive, the PPV of a strategy based on HPV testing alone as a primary test, with triaging by cytology of those found to be positive (and direct referral to colposcopy of ASCUS+ women only but test repeat after one year for the remaining), was only slightly lower than conventional cytology. With this strategy, HPV testing showed an approximate 50% increase in sensitivity, similar to that observed in older women with direct referral to colposcopy of all HPV-positive women. With the same strategy, but increasing the cut-off to 2 RLU and with stricter referral criteria at test repeat (colposcopy only if both HPV and cytology were positive), the sensitivity was found to be virtually unchanged; the PPV was similar to that of conventional cytology. This approach is plausibly the best even at older ages, as shown also by the HPV in Addition to Routine Testing (HART) trial.[4]

Adding liquid-based cytology to HPV testing for all women and referring to colposcopy those positive to either test increased the relative sensitivity only marginally but strongly decreased the PPV for this age group as well (see Table 1).[5]

When considering both age groups together, liquid-based cytology allowed the proportion of unsatisfactory slides to be reduced with respect to conventional cytology (relative frequency: 0.62; 95% (confidence interval, CI,: 0.56-0.69).

However, the sensitivity for CIN2+ was only slightly and non-significantly increased (relative sensitivity: 1.17; 95% CI: 0.87-1.56) while there was a remarkable loss in PPV (relative PPV: 0.58; 95% CI: 0.44-0.77).[6]

We also used data from phase 1 to estimate the sensitivity and specificity of HPV testing for triaging women with ASCUS or LSIL with increasing age. The specificity of HPV testing was very low (32%; 95%CI: 25-39) in women aged 25-34 with LSIL. However, the specificity of HPV testing was 61% (95%CI: 55-67) among women aged 35-60 with LSIL.

This value is similar to that observed for women aged 25-34 with ASCUS (57%; 95%CI: 50–63) and seems acceptable for a triage test as it would result in more than halving the number of colposcopies.

CONCLUSIONS AND RECOMMENDATIONS

If cytology is used as a screening test and HPV for triage:

- **HPV testing can be applied for women with ASCUS, irrespective of their age, and for women aged 35 or more with LSIL.[7]**

If HPV testing is used as the primary screening test:

- **HPV testing should be the only screening test, without systematically adding cytology for all women.**
- **If HC2® is used, the best cut-off is at 2 RLU (2 pg/ml of viral DNA).**
- **Using HPV as a screening test and cytology for "triage" of HPV-positive women leads to a gain in sensitivity with only a small loss in specificity, compared to conventional cytology, even among women aged 25-34, where infection is very frequent.**

References: 1. Carozzi F *et al.* Reproducibility of HPV DNA testing by Hybrid Capture 2 in a screening setting: Intralaboratory and interlaboratory quality control in seven laboratories participating in the same Clinical Trial. Am J Clin Pathol 2005;124:1-6. **2.**Ronco G *et al.* Human Papillomavirus testing and liquid-based cytology: results at recruitment from the New Technologies for Cervical Cancer randomized controlled trial. J Natl Cancer Inst 2006;98:765-74. **3.** Giorgi Rossi P *et al.* The impact of new technologies in cervical cancer screening: results of the recruitment phase of a large randomised controlled trial from a public health perspective. Int J Cancer 2007;121:2729-34. **4.** Cuzick J *et al.* Management of women who test positive for high-risk types of human papillomavirus: the HART study. Lancet 2003;362:1871-76. **5.** Ronco G *et al.* Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment for a randomised controlled trial. Lancet Oncol 2006;7:547-55. **6.** Ronco G *et al.* Accuracy of liquid-based versus conventional cytology: overall results of the new technologies for cervical cancer screening randomised controlled trial. BMJ 2007;335:28-31. **7.** Ronco G *et al.* HPV triage for Low grade (L-SIL) cytology is appropriate for women over 35 in mass cervical cancer screening using liquid based cytology. Eur J Cancer 2007;43:476-80.

EVALUATION OF HPV E6/E7 MRNA, AND VIRAL LOAD IN PREDICTING C

The identification of high-risk HPV infection as a necessary cause of cervical cancer opened up the prospect of improving the efficiency of cervical cancer screening programmes and early diagnosis of its precursors through the detection of HR-HPV DNA as a diagnostic test with higher sensitivity than cytology. However, as only a small proportion of infected women develop invasive cervical cancer, HPV gives a low positive predictive value (PPV) for high-grade cervical intrapithelial neoplasia (CIN) and carcinomas and, even when HPV testing is used for triaging prior to colposcopy for those patients with minor cytological abnormalities, its PPV is sub-optimal and a substantial proportion of patients are still referred unnecessarily for colposcopy.

Molecular markers may further improve the selection of HPV-positive subjects with three principal objectives: 1) to identify women with current CIN2+ lesions; 2) to identify transient infections; and 3) to identify women without current CIN2+ lesions but at higher risk of developing precancer in the next three years

Several strategies towards this objective (Table 1) have been investigated in the last few years and we are currently extending our research interests to the identification of viral parameters that allow the stratification of high-risk HPV (HR-HPV)-positive women at risk of high-grade CIN disease. p16INK4A immunostaining (Figure 1) has been proposed as a putative surrogate biomarker of dysplasia and as a tool for triaging women with low-grade or borderline cytology, particularly when triage by HPV is inefficient. Several studies[1,2] have reported a differential expression of p16 in high- and low-grade squamous intraepithelial lesions (HSIL, LSIL) and normal cervical epithelial cells. p16INK4A has been shown to be associated with HPV-infected HSIL but its positive predictive value (PPV) and sensitivity for relevant outcomes (CIN2+) have yet to be determined. In a previous report[3] we assessed the accuracy of p16 and HR-HPV testing for identifying HSIL in 283 cervical samples (ThinPrep®, Cytyc Corp., Boxborough, USA) on a consecutive series of women referred to colposcopy for abnormal cytology (>ASCUS): p16 sensitivity for

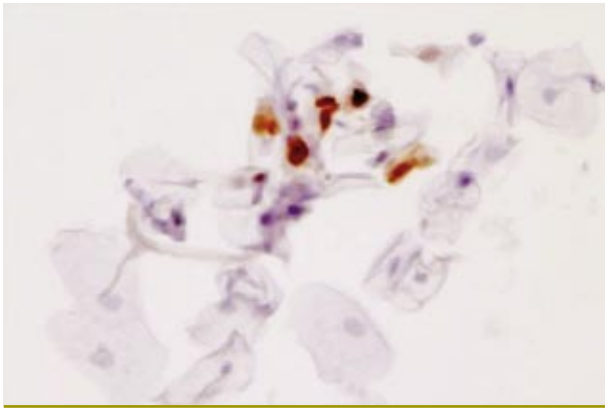


Figure 1. *p16INK4A immunostaining.*

CIN2+ was 88%. Patients with cytological abnormalities but without CIN2+ lesions were then followed-up for 36 months to evaluate the immunohistochemical expression of p16INK4A as a marker of progression. We observed a significant p16 overexpression in the group that progressed from LSIL to HSIL when compared with the group that did not progress. Moreover, p16 could be useful for triaging HPV-positive women when an HPV test is used as a primary screening test.

We also conducted a pilot study to evaluate and compare HPV genotyping, E6/E7 mRNA expression (HPV types -16, -18, -31, -33 and -45) and HPV-16 viral load in 93 HR-HPV positive women aged 25-64 years, who were referred for colposcopy if Pap reports were ≥ASCUS or for surveillance after loop excision for ≥CIN2. The primary endpoint of the study was to detect histologically confirmed CIN2+ lesions.

There was a significant association with detection of HPV-16, -18, -31, -33 -45 and final outcome in comparison with the other HR types. Sensitivity for CIN2+ was 78.9%, specificity 42.5% and PPV 56.6%. Khan *et al.* [4] have reported an increased of risk of developing CIN3 for up to 10 years for HPV-16 and -18 compared to other oncogenic types. In our series the positivity rate of m-RNA PreTect™ HPV-Proofer (Norchip AS, Klokkarstua, Hurum, Norway), as determined from the cytology results, was: 25% among negative, 38.1% among ASCUS, 46.7% among LSIL and 70.4% among HSIL. The positivity of mRNA expression according to the histological results was statistically significant (p=0.028). No CIN2+

P16 EXPRESSION IN CIN2-3 LESIONS

Francesca Carozzi, Cristina Sani, Gianluigi Venturini, Simonetta Bisanzi, Massimo Confortini, Carmen Visioli

CSPO- Instituto Scientifico della Regione Toscana, Firenze, Italy.

	Description	Hypothesis of application	Disadvantages
Genotyping	Evaluating HPV type in the sample	Management of type-specific HR-HPV-positive women Evaluation of HR-HPV persistence. Differentiation of the risk for CIN2+	Test performance and reproducibility. Absence of validated methods
Viral load	Measure of the severity of a viral infection and replicative activity	To distinguish the HR-HPV infections that are clinically relevant	Difficulty in determining a clinically relevant cut-off Test performance and reproducibility Absence of validated methods
Physical status	Evaluation of the integration status of HPV genome into the host chromosome	Characterization of the CIN lesions at major risk of progression to CIN3 or invasive carcinoma.	Capability of identifying a small number of integrated forms
p16	Evaluation of $p16^{INK4a}$ protein overexpression	Increase the PPV of the HR HPV test for CIN2+	Interpretation pattern Cut-off optimization
E6/E7 m-Rna expression	Evaluation of the expression of the viral E6/E7 oncogenes	To identify the lesions at major risk of progression	Qualitative *versus* quantitative expression
Ipermethylation	Evaluation of pattern of HPV genes' methylation	Methylation of HPV DNA could be a host defence mechanism for suppressing the transcription of foreign DNA or a strategy that the virus uses to mantain a long-term infection	Preliminary studies have confirmed the impression of high specificity whitout achieving the required sensitivity

Table 1. *Proposed biomarkers of risk of neoplastic progression.* CIN: *cervical intraepithelial neoplasia*; HR: *high risk*; PPV: *positive predictive value.*

lesions were found in mRNA negatives during follow-up (24 months). The correlation coefficient between HPV-16 copy numbers measured by real-time polymerase chain reaction (PCR) and by Hybrid Capture® 2 (HC2®, Qiagen Gaithersburg, Inc., MD, USA, previously Digene Corporation) reached a value of 0.66, which is similar to the value found in other reports. Nevertheless, our preliminary results show that E6/E7 mRNA expression is correlated with E6 HPV DNA load (by real-time PCR) but not with a semi-quantitative viral load (by HC2®).

The association between viral load and cervical disease therefore probably depends on the HPV type, the physical state of the virus and the heterogeneity of the cervical lesion

It is interesting that E6/E7 mRNA expression is positive in 90.6% (29-32) of cases where the load is equal to, or greater than, 500 HPV-16 copies/ng DNA.

The current complexity of these relationships suggests that viral load has a limited value when it comes to discriminating women with and without lesions. In conclusion, markers for HPV transforming activation are an important area of reasearch but their clinical value and application still need further clarification.

References: 1. Klaes R *et al.* Overexpression of p16(INK4A) as a specific marker for dysplastic and neoplastic epithelial cells of the cervix uteri. Int J Cancer 2001;92:276-84. **2.** Sano T *et al.* Overexpression of p16 and p14ARF is associated with human papillomavirus infection in cervical squamous cell carcinoma and dysplasia. Pathol Int 2002 May-Jun;52(5-6):375-83. **3.** Carozzi FM *et al.* Role of P16(INK4a) expression in identifying CIN2 or more severe lesions among HPV-positive patients referred for colposcopy after abnormal cytology. Cancer Cyt 2006 Apr 25;108(2):119-23. **4.** Khan MJ *et al.* The Elevated 10-Year Risk of Cervical Precancer and Cancer in Women With Human Papillomavirus (HPV) Type 16 or 18 and the Possible Utility of Type-Specific HPV Testing in Clinical Practice, J Nat Cancer Inst 2005;97(14):1072-9.

Agostino Faravelli
for Patologi Oltre Frontiera.

PAP SMEAR DIAGNOSIS VIA SATELLITE FOR AFRICA WITH 'PATOLOGI OLTRE FRONTIERA'

Patologi Oltre Frontiera (POF –Pathologists Without Borders) was founded in 2000 by a small group of pathologists. POF is an Italian non-governmental organization (NGO) whose mission is to strengthen or build laboratories for anatomical pathology in developing countries where this service is completely absent or is reliant on a very small number of pathologists (i.e., ten in the whole of Tanzania, nine in Madagascar and only one in Zambia).

POF's first project was the "restoration" of a laboratory in Mwanza, Tanzania, which had been abandoned by the British after the declaration of independence in 1971. Since then, several projects have been completed in Cuba, Zambia, Kosovo, Palestine and Egypt, while others are currently underway in Madagascar, Congo, Mozambique, Uganda and Benin. The common denominator of all these projects is the use of telepathology as a fundamental support service.

On the basis of this urgent necessity, a pilot project was set up in 2005 in Chirundu, a small village at the southern tip of Zambia, where there is a small but efficient rural hospital run by Italians –the Mtendere Mission Hospital. A pathology laboratory was built and two local technicians were trained over only fourteen months thanks to a few volunteers who travelled to Chirundu. After this period, the two technicians were able to prepare and read Pap smears and separate the negatives from the possibly positives. In addition, they learnt to prepare inclusions and histological sections from both biopsies and surgical specimen. Digitalized photographs from suspicious or positive Pap smears are prepared and sent over the Internet, using dedicated software, to a group of nearly 60 expert reviewers. Around 20 of them usually see the images and give their opinion, although only one, nominated in turn, is responsible for the final diagnosis and its communication to the local technicians.

As for the histological samples, all the slides are scanned (a 20x objective is used for histological sections, and a 40x one for non-cervical cytological smears) and the files are transferred to a server. An organised group of volunteer pathologists can then log-on from anywhere in the world through a broadband satellite connection and see the scanned slides; this produces a histological diagnosis within four days. Alongside this, a dense information network manages the personal details of the patients and the diagnosis is transferred from Europe to Africa, authorised by a digital signature. The technicians print and hand over the reports to the surgeon every morning. All the histological and cytological slides, including the negative Pap tests, are sent to Italy every six months to undergo quality control.

The most important activity undertaken by POF is the prevention of cervical cancer, which represents the primary cause of cancer death for women in south-western Africa, a region that has the highest incidence in the world

Encouraged by this positive experience, the volunteers of POF are planning a Master in Cytology and Histology for ten cytotechnologists at the University of Lusaka, the capital of Zambia, who will then work in the surrounding territory. POF is also trying to facilitate the training of specialist African pathologists to work in the new laboratories created to render the diagnosis procedures self-supporting. In this case e-learning could contribute to the teaching process.

For more information visit: www.patologioltrefrontiera.it/

POINT OF VIEW

THE COMPLEX STORY OF HIV-POSITIVE WOMEN AND CERVICAL CANCER SCREENING

Flavia B. Lillo
San Raffaele Scientific Institute, IRCCS, Milano, Italy.

HPV-related pathologies are a relevant clinical issue in the management of human immunodeficiency virus (HIV)-positive patients (both male and female) because of their higher frequency and greater tendency to evolve into lesions of the anogenital and oropharyngeal regions than in the non-HIV-positive population.[1] As these cancers are preventable, the optimization of screening strategies becomes critical in the management of HIV patients as their life expectancy has improved greatly recently due to effective anti-HIV therapy.

The Agency for Health Care Policy and Research recommends that HIV-positive women undergo a Pap smear twice during the first year after diagnosis of HIV infection and, if the results are normal, annually thereafter. Women with low-grade cytological abnormalities should repeat the Pap smear at a shorter time interval than HIV negatives and, if the lesion persists or higher-grade lesions are diagnosed, should undergo colposcopy, directed biopsy and therapy. These guidelines to prevent cervical disease have not been modified for women on highly active antiretroviral therapy (HAART).

In our studies, HIV-positive women undergo colposcopy at least once a year and biopsies of atypical areas are taken independently of the Pap test result.

We have observed that the level of agreement between cytology and histology in HIV-positive women may be sub-optimal and a histological cervical intraepithelial neoplasia (CIN) 2/3 lesion may be missed by cytology in as many as 25% of cases. The presence of confounding factors, such as concomitant infections, chronic inflammation or dystrophic phenomena of the cervical epithelium, may account for the majority of discrepancies

In this context, although the benefit of introducing high risk (HR)-HPV detection for oncological prevention is debatable due to the high prevalence of HPV, it should still be considered. A recent study by Goldie *et al.*[2] has demonstrated that adding HPV testing to the two Paps obtained in the first year after HIV diagnosis, and modifying subsequent cytology screening intervals based on the results (six-month intervals for HPV positives), appears to improve the quality adjusted life year (QALY) index and provide the best incremental cost-effectiveness ratio.

Furthermore, collection of data on the circulation of HPV types in relation to the patients' immune status should be encouraged in the incoming era of HPV vaccination. Surveillance for oncogenic infections and monitoring of possible modifications of the epidemiological scenario is necessary to evaluate the realistic impact of vaccine programs in selected high-risk populations especially considering that HPV-16, although highly prevalent, is significantly less represented in high squamous intraepithelial lesions (HSIL) (31.9%) than in non-HIV subjects (odds ratio, OR: 0.6; 95% confidence interval, CI: 0.4-0.7).[3] This information may be relevant in geographical areas with a high prevalence of both HIV infection and cervical carcinoma (i.e., developing countries).

We have demonstrated that total HPV load is significantly higher in patients with HSIL than in HPV-positive controls without lesion in HIV-positive women. This would appear to provide an added value to the clinical interpretation and prevention of HPV-related diseases as higher HPV loads are detected in more than 75% of HSILs, even in cases of discordant cytohistological diagnosis.

In summary, we believe that the optimal screening procedure for cervical pathology in HIV-positive women should be multi-parametric and should include both morphological and virological markers.

As each result may contribute to the identification of women who need a higher level of surveillance (i.e., colposcopy, biopsy and eventual treatment), a kind of flowchart sequence of testing could be designed (i.e., a baseline screening including total HR-HPV load plus Pap test). The time intervals between visits could then be modified according to both results, possibly after having defined clinically relevant cut-off levels for HPV load.

References: 1. Stebbing J, Dancey G, Bower, M. A tale of three Hs: HPV, HIV & HAART. Future Oncol 2006;2:1-9. **2.** Goldie SJ *et al.* Cost effectiveness of human papillomavirus testing to augment cervical cancer screening in women infected with the human immunodeficiency virus. Am J Med 2001;111:140-9. **3.** Castle PE *et al.* Age-related changes of the cervix influence human papillomavirus type distribution. Cancer Res 2006;66:1218-24.

SPONTANEOUS POST-CERVICO-VAGINAL CO

Massimo Origoni *(center)*
Luigi Caputo *(right)*
Francesca Occhi *(left)*

Department of Obstetrics & Gynecology, Vita-Salute San Raffaele University, Milano, Italy.

The prevalence of HPV infection in pregnancy is similar to that observed in non-pregnant women,[1] although its implications are more relevant because of both maternal and neonatal concerns.[2] This has led to an intense debate about its most suitable management: destructive treatment or observation and vaginal delivery or caesarean section.[3] The most reasonable approach, however, seems to be to act on a case-by-case basis according to clinical patterns and patients' consent.

We present here a case involving the spread of cervical and vaginal condylomatosis during pregnancy in a 35-year-old woman. A progressive increase of the size and extension of the HPV clinical lesions was observed, starting from an isolated vaginal site (fornix) to a massive cervical and diffuse vaginal condylomatosis, between the first and third trimesters. The patient was initially screened cytologically and for HPV-DNA, with the results indicating a low-grade squamous intraepithelial lesion (LSIL) by Pap smear and HPV-16/18 DNA positivity. Colposcopy performed at 10 weeks of gestation revealed isolated cervical and vaginal condylomata with no colposcopic patterns of atypical transformation zone (AnTZ). Clinical observation was adopted and the patient was advised to undergo periodical cervico-vaginal examinations. The colposcopic findings

Figure 1

Colposcopy at 10 weeks.

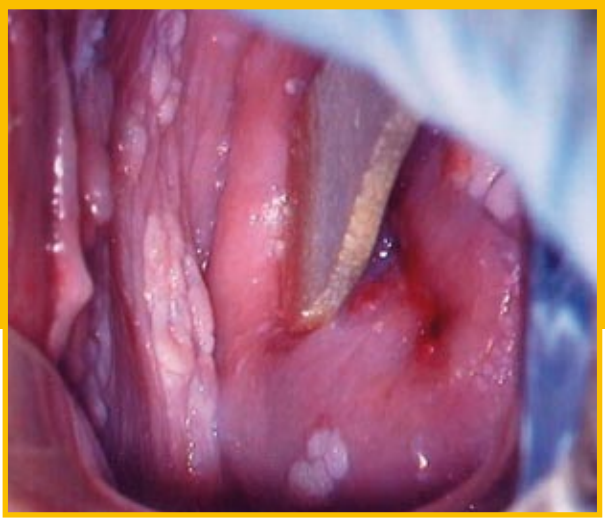
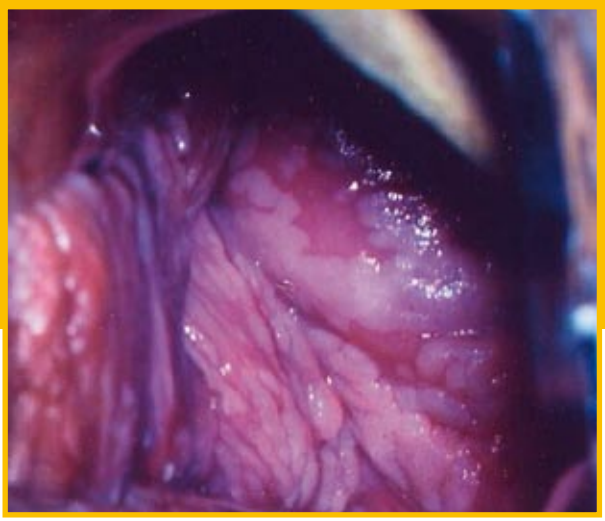


Figure 2

Colposcopy at 24 weeks.



CAESAREAN REGRESSION OF MASSIVE NDYLOMATOSIS IN PREGNANCY

at 10, 24 and 34 weeks are illustrated in Figures 1-3; three repeated Pap smears, performed after the same number of weeks, were consistent with the initial LSIL finding. The decision to perform a caesarean section at 38 weeks was taken jointly with the patient on the basis of the pre-term cervico-vaginal diffusion of the condition (Figure 3). An almost complete disappearance of the condylomatosis was observed at first 1 month post-partum follow-up (Figure 4).

Despite previous reports[1] that ongoing pregnancy does not correlate with increasing incidence of HPV infection, other papers[4,6] have reported progressive condylomata growth; this is consistent with our experience. It is therefore still unclear whether the maternal immune profile during pregnancy represents a negative or protective condition relative to HPV infection. Recent reports[7] have also found that transitory HPV viral load increases during pregnancy.

As for neonatal infection, vaginal delivery is a risk factor for exposure to HPV, particularly in pregnant women with high viral load close to delivery, although the real risks are still to be assessed. The prevalence of neonatal infection is almost 20%,[1,2] although newborns' oropharyngeal samples are usually clear of virus within 5 weeks after delivery;[5] this suggests viral contamination during passage through the birth canal rather than real infection.

Our experience, and the case presented here, suggests that genital condylomatosis, despite the high frequency of progressive worsening throughout pregnancy, is well managed with expectant clinical observation and that spontaneous post-partum regression is highly likely.

REFERENCES: 1. Alberico S *et al.* Maternal-fetal transmission of human papillomavirus. Minerva Ginecol 1996;48(5):199-204. **2.** Puranen M *et al.* Vertical transmission of human papillomavirus from infected mothers to their newborn babies and persistence of the virus in childhood. Am J Obstet Gynecol 1996;174(2):694-9. **3.** Tseng C-J *et al.* Perinatal transmission of human papillomavirus in infants: relationship between infection rate and mode of delivery. Obstet Gynecol 1998;91:92-6. **4.** Nahhas WA *et al.* "Abnormal" Papanicolaou smears and colposcopy in pregnancy: ante- and post-partum findings. Int J Cancer 1993;3(4):239-44. **5.** Tenti P *et al.* Perinatal transmission of human papillomavirus from gravidas with latent infections. Obstet Gyncol 1999;93:475-9. **6.** Fife KH,*et al.* Cervical humen papillomavirus deoxyribonucleic acid persists throughout pregnancy and decreases in the postpartum period. Am J Obstet Gynecol 1999;180(5):1110-14. **7.** Zoundi-Ouango O *et al.* Uterine cervical lesions during pregnancy: diagnosis and management. J Gynecol Obstet Biol Reprod 2006;35(3):227-36.

Figure 3

Colposcopy at 34 weeks.

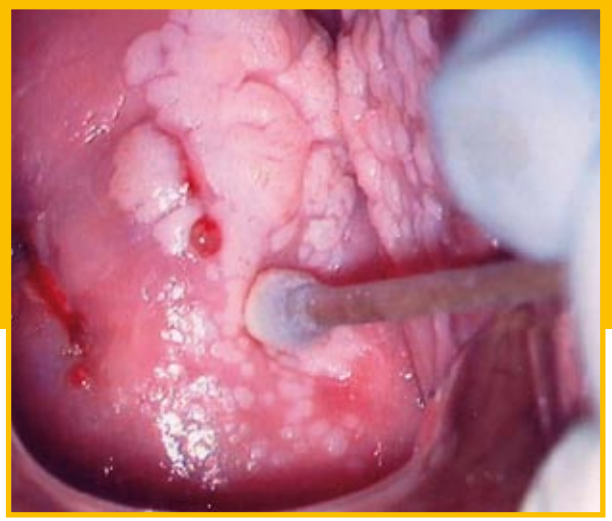
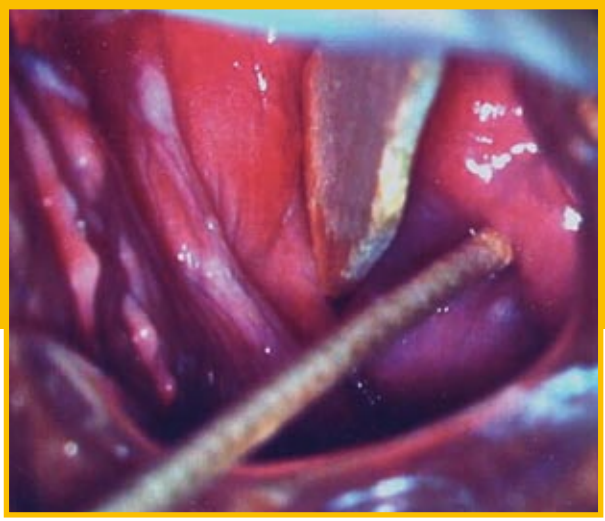


Figure 4

Colposcopy 1 month after delivery.



INTERNATIONAL AGENDA

Foshan, China

1st - 5th December 2008

BIT's Annual World Vaccine Congress

Venue: Fontainebleau Hotel
E-mail: sean@vaccinecon.com
Web: www.bitlifesciences.com/wcv2008

Boston, MA, USA

7th - 9th December 2008

Vaccine 2nd Global Congress

Venue: AAA Four Diamond Westin Boston Waterfront hotel
E-mail: mc_fcem@yahoo.co.uk
Web: www.vaccinecongress.com/index.htm

Las Vegas, Nevada, USA

11th - 14th December 2008

Advanced Colposcopy and Lower Genital Tract Dermatology

Venue: Bally's Las Vegas
E-mail: amason@asccp.org
Web: www.asccp.org

Nice, France

30th - 31st January 2009

6th European Congress: Perspectives in Gynecologic Oncology

Venue: The Palais de la Méditerranée
E-mail: meetings@imedex.com
Web: www.imedex.com/appweb/announcements/a049-01.asp

San Antonio, Texas, USA

5th - 8th February 2009

The 40th Annual Meeting on Women's Cancer

Venue: Henry B. Gonzalez Convention Center
E-mail: jenna.cummins@sgo.org
Web: www.sgo.org/content.aspx?id=58

Maracaibo, Venezuela

10th - 13th March 2009

XXV Congreso Nacional de Obstetricia y Ginecologia

Venue: Centro de Convenciones Maruma
E-mail: sgubib@chasque.net
Web:www.flasog.org/home/todasactividades.asp

San Diego, Ca, USA

11th - 14th March 2009

2009 APGO/CREOG Annual Meeting

Venue: Manchester Grand Hyatt
E-mail: bfetsko@apgo.org
Web: www. apgo.org

Melbourne, Australia

18th - 20th March 2009

Preventing Cervical Cancer: Integrating screening and vaccination

Venue: Sofitel Melbourne
E-mail: egray@conferencesolutions.com.au
Web: www.pcc2009.org.au/

Glasgow, Scotland

18th - 21st March 2009

2009 SGI Annual Scientific Meeting

E-mail: sgiava@aol.com
Web: www.sgionline.org

Washington, USA

20th - 23rd April 2009

World Vaccine Conference 2009

Venue: Westfields Marriott
E-mail: gina.geldenhuys@terrapinn.com
Web: www.terrapinn.com/2009/wvc_DC/index.stm

Chicago, Illinois, USA

2nd - 6th May 2009

ACOG 2009

E-mail: acm@acog.org
Web: www.acog.org

Malmö, Sweden

8th - 14th May 2009

25th International Papillomavirus Conference and Clinical Workshop

Venue: Malmö Exhibition & Convention Center
E-mail: hpv2009@destinationoresund.com
Web: www.hpv2009.org

Published with unrestricted educational grants from:

Gold sponsors

QIAGEN

gsk GlaxoSmithKline

MSD Vaccines

sanofi pasteur MSD vaccines for life

Silver sponsors

Roche

Opportunities for sponsorship, request for printed copies, meeting advertising and correspondence: **box@hpvtoday.com**