Cervical Cancer Screening: redefining the legacy of Papanicolaou

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“What I can do – I will
Though it be little as a Daffodil
That I cannot- must be
Unknown to possibility”.
Emily Dickinson. Poems. 1862

Cervico-vaginal cytology (Pap test), since the works of Georges Papanicolaou, has achieved an important reduction of mortality due to cervical cancer, especially in countries where screening programs with this test achieved high levels of participation; however, even reached this decrease in the incidence of the disease, has raised the need to improve the sensitivity of the test through additional diagnostic methods. In geographic areas with low incidence of cervical cancer, it is necessary to make repeated cytology and/or other types of examination to increase the sensitivity in this type of population. Since persistent human papillomavirus (HPV) infection is a necessary but not sufficient cause, to give rise to cancer of the cervix, efforts have concentrated on the development of diagnostic methods based on the detection of the virus, particularly the high risk or carcinogenic genotypes. However, in an ideal screening system, the best thing to do is performing a single test to determine which patients are at risk and which are not of developing cervical neoplasia and be subjected to additional tests.

April 24, 2014, the Food and Drug Administration (FDA) approved "the first DNA test for the human papilloma virus (HPV) for women aged 25 years and older that can be used on its own to help a healthcare professional to assess the need that a woman undergo additional tests for the
detection of cervical cancer\textsuperscript{1}. The Cobas \textsuperscript{®} test detects the presence in the cytological sample of 14 high-risk types of HPV (with separated results for VPH16 and VPH18), so that, on the basis of the results obtained, if there is presence of HPV 16 or 18, the patient should be referred to colposcopy, but if some of the other 12 types of high-risk HPV are present, the patient will have a Pap test to determine the need to be referred for colposcopic assessment. In the case of a negative test, the patient should be return to regular monitoring, with an interval decided by the attending physician according to the risk and conditions of the patient. The FDA decision is based on a study of ATHENA (Addressing THE need for Advance HPV diagnostic)\textsuperscript{2} posted in 2011 and a reanalysis\textsuperscript{3} in 2013 that evaluates the liquid-based cytology in comparison with the genotyping test for HPV as tools for screening for cervical cancer in the U.S..

In this study, they assessed about 40,000 patients which underwent liquid-base cytology and the Cobas\textsuperscript{®} HPV genotyping test. Patients with ASCUS cytology or more and/or test positive for HPV underwent colposcopy; there were also included patients with negative cytology and genotyping randomly selected for colposcopy, as a control group. Of the patients who presented cervical intraepithelial neoplasia 3 (CIN 3), 92% had positive HPV and only 52% had alterations in cytology; Similarly, patients with CIN 2, 82% had positive HPV test and 48% altered cytology. HPV testing was more sensitive but less specific than liquid-base cytology for CIN3 or more (sensitivity: 93% vs. 53.3%; Specificity: 56.9% vs. 73%, p < 0.0001). In March 2013, is published a follow-up of patients over age 30 for 3 years\textsuperscript{3}. 10 different strategies of screening combining cytology, HPV detection and genotyping of HPV 16 and 18 were evaluated in this extension. The strategies on the basis of sensitivity were analyzed compared to number of colposcopies needed to diagnose a case of CIN 3, whereas the colposcopies as a measure of the procedure that want to be avoided, since the unnecessary reference to the realization of the colposcopy is considered overvalued or overtreatment, which causes discomfort to the patient. Strategies that obtained a better relationship between sensitivity and number of colposcopies were HPV detection with cytology preparation following a positive result and genotyping of HPV 16 and 18.

There are several aspects that stand out from this new algorithm approved by the FDA. First, use high-risk HPV detection for selecting or screening patients who require further assessment is a valid argument, since only the patients with HPV carcinogenic present on the cervix, are susceptible to developing cervical neoplastic lesions, almost all possibly grouped into 14 genotypes involved in this test. A single test to select the group of patients truly at risk. The advantage of the realization of the HPV test is that it allows results without variation among laboratories, in particular commercial tests that are standardized, because they are automated procedures. The interobserver variation of Pap test is very high when compared with these tests of molecular biology, also the different categories of the cytological classification can lead to different results that would involve different behaviors depending on the case; HPV testing has binary options: positive or negative for high-risk HPV, positive or negative for HPV16 and/or 18. Another advantage of this test is that allows the patient taking her own specimen, that would facilitate the evaluation of large populations with a minimum of professional staff present. According to the ATHENA research only 8.4% of the evaluated patients presented test positive for HPV, which
decreases the number of Pap smears that must be carried out by 91.6%. This proportion is valid for the patients belonging to the study, 21 U.S. clinical centers; However, the number of patients is probably much higher in countries with high incidence of cervical cancer, for example, in Africa the incidence of HPV is 24% and in Latin America 16%\(^4\). The most important disadvantage is that in countries where the incidence of cervical cancer is greater, access to technology is precarious and the presence of molecular biology laboratories could be a luxury, in addition to the coverage of the target population of the screening fails to percentages greater than 50%. The option of direct vision with acetic acid and the realization of Pap test, which require less sophisticated equipment, are a much more realistic option. However, it is necessary to invest human resources and materials needed to improve these conditions.

The other aspect of the proposed algorithm would be more controversial, is the realization of colposcopy without cytology in patients who present HPV test positive for types 16 and/or 18, according to the authors of ATHENA, since this result has the same sensitivity when compared with Pap test with a report of ASC-US or more. In addition, justification is also based on knowledge of the etiology of the disease, where more than 70% of all cervical cancers are associated with one of the two types, mainly to 16. According to the analysis made in the ATHENA study, the number of colposcopies is not greater than that occurs in altered cytology cases, so the number of patients undergoing this procedure should not be increased. According to these results, only patients who are more likely to have CIN3 assessed. The direct reference without cytology to colposcopy seems an exaggerated strategy, taking into account the number of colposcopists available in each country, although the ATHENA study statistics seem to indicate otherwise.

It is also good to remember that HPV type 16, although it is more frequent in cervical cancer, also is in patients who have HPV infection without alterations in cytology, which could lead to one greater number of normal colposcopies. However, the court at age 25 appears to prevent the realization of colposcopies in patients with transient infection which, according to this study, is more common in women below this age. Another important aspect in the approach of the strategy is that the frequency to assess patients who are negative for HPV detection it is not specified, the treating physician should take the decision. This point needs to be clarified to the extent that tested this strategy as research.

The incorporation of the Cobas\(^\text{®}\) test in the screening of cervical cancer can be seen as a paradigm change in prevention of the disease, and it is necessary to conduct cost-benefit study to establish its application in countries with higher incidence of this pathology. The realization of a unique test that allows reducing the number of patients at risk without a doubt is useful and should be cost-effective. Analysis of the efficacy of this new algorithm requires their evaluation in time and in populations with a high incidence of cervical cancer and see if it results in a decrease in mortality from this disease. The challenge will be to train more physicians to perform colposcopies and conditioning laboratories for processing samples for HPV detection and genotyping of VPH16 and 18. Far from thinking that the end of the era of Pap test approaches, we see the Cobas\(^\text{®}\) test on the cytological sample as a sort of evolution of legacy of Papanicolaou. But still has not achieved the ideal screening method, we enter the era of molecular biology, also in the screening of cervical
cancer, as a way to give greater objectivity to the results, improve its efficacy in preventing and decide, with just a single test, safely, which patient can return home serene.

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References:

1. [www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm394809.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm394809.htm)