MANAGEMENT OF ABNORMAL PAP SMEAR AND PRE-INVASIVE DISEASE OF THE CERVIX IN DEVELOPING COUNTRIES

Wale Oluborode

Department of Obstetrics and Gynaecology, Obafemi Awolowo University Teaching Hospital Complex

ABSTRACT:

Cervical cancer ranks as the third most common cancer after breast (1.38 million cases) and colorectal cancer (0.57 million cases).[1] In 2008, about 529,000 new cases of cervical cancer were diagnosed globally.[2] This disease is the fourth most common cause of cancer-death (275,000 deaths) ranking below breast (458 000 deaths), lung (427 000 deaths) and colorectal cancer (288 000 deaths).[1] Eighty-six percent of all cervical cancers and 88% of all deaths caused by cervical cancer occur in developing countries.[1] In sub-Saharan Africa, cervical cancer ranks the second most common cancer among women.[1,3] In the year 2012, out of the estimated 370,138 cancers in sub-Saharan African women, about 93,200 new cases of cervical cancer (25.2% of cancers) were recorded.[3] The lowest burden of cervical cancer was reported in Australia, Northern America and Western Europe with an age-standardised incidence rate of 5.0, 5.7 and 6.9/100 000, respectively.[1]

The low incidence of cervical cancer in these regions has been attributed to the establishment of an effective cervical cancer screening programme. A strong correlation between the initiation of cytology screening and a reduction in the incidence and mortality from cervical cancer have been demonstrated in countries like Denmark, Finland, Iceland, Norway and Sweden.[4,5] The introduction of these screening modalities was based on the knowledge that invasive cervical cancer is preceded by an interval of epithelial dysplastic changes, typically occurring at the transformation zone. While the age-standardised incidence rate of cervical cancer in Nigeria has increased to over 30/100 000,[1] much needs to be done to indigenize the experience from these successful screening programmes taking into cognizance the peculiarity of our environment.

Screening For Pre-Invasive Disease Of The Cervix

Protocol varies on the age of entry into the screening programme. According to American Society for Colposcopy and Cervical Pathology (ASCCP), cervical cancer screening should begin at age 21.[6] According to ASCCP, women under the age of 21 should not be screened regardless of the age of sexual initiation or other risk factors.[6] In the newly released American College of Obstetrics and Gynecology (ACOG) guideline,[7] women aged 21-29 should only have cytology screening every 3 years. HPV testing shouldn't be conducted in these women. While those between ages 30 through 65, should have cytology screening with human papillomavirus (HPV) co-testing every 5 years. A high-risk HPV DNA test is the preferred recommendation. Cytology alone every 3 years is also acceptable in these women. However, HPV testing alone is not recommended.[7]

After age 65, future screening recommendations

depend on past screening results. If previous tests have been negative, additional screening is not required. Negative tests in this case means 3 consecutive negative cytology results or 2 consecutive co-testing results in the past 5 years.[7] Women with a history of cervical intraepithelial lesions (CIN)2, 3, or adenocarcinoma must continue screening beyond age 65. In women with total hysterectomy and no history of CIN2 or higher, additional screening is not needed, but for those with high-grade lesions before hysterectomy, cytology screening should be continued every 3 years for the next 20 years. This is because, the risk of developing vaginal cuff cancer even years later still exists. Meanwhile, the role of HPV testing in this setting is unclear[6]

In the United Kingdom, the NHS Cervical Screening Programme (NHSCSP) recommends an entry into the screening programme by age 25. According to the NHSCSP,[8] cervical screening should take place between the ages of 25 and 64, at intervals of three or five years depending on the woman's age. According to the guideline,[8] women between ages 25 and 49 should have cytology screening three yearly, while those between the ages of 50 and 64 should be screened every five years. Only women with recent abnormal pap smear result or those who have not been screened since age 50 should continue cytology screening beyond 65years. The NHSCP does not recommend the use of HPV testing for routine use.

The success of cervical cancer screening programme in most developed countries has been tied to a combination of several approaches, such as, education, advocacy, legislation, vaccination, screening, early diagnosis and treatment. In low- and medium-income countries, there is however a considerable variation in their extent of implementation of these measures.[9] In achieving the successes experienced in high-income countries, low-and-medium-income countries should produce a blueprint for national cancer control using a framework that is socially and culturally sensitive[10]

In 2002, the Society of Gynaecology and Obstetrics of Nigeria (SOGON) constituted an expert committee on the prevention of cervical cancer.[11] The aim of this was to prepare a strategic plan for a National Cervical cancer prevention program in Nigeria. According to this protocol,[11] the entry age for cervical cancer screening in Nigerian women should be 30 years or two years after the first childbirth, and the screening interval should be every three years. Women who had a cytology screening should be managed according to the detected abnormality. Meanwhile, to maximize the participation of women, and to improve the efficiency of screening and treatment in our environment, it was proposed that women aged 30-64 years should have at least once in a life-time screening.[11]

For screening to be successful, the test must be affordable. Also, the screening test, diagnosis and treatment should be provided on-site, preferably all in one or two visits (to ensure wide coverage).[9] This is rarely the case in our environment. The complex inputs of sample collection, processing, reading and reporting of smears and quality assurance which has contributed to the success of cytology screening in high income countries is lacking in our environment. Studies from cytology screening projects in low-and-medium income countries in South and Central America, over the last three decades, have yielded only limited success in preventing cervical cancer[12, 13]. Therefore, down-

staging cytology screening to visual inspection with acetic acid (VIA) triage and the use of 'single-visit approach' becomes important to achieve a high coverage in our environment.

The 'single-visit approach' adopted by the expert committee[11] therefore entails treating VIA-positive women, with no evidence of invasive cancer, by cryotherapy at the same screening session. The cost-effectiveness of this approach has been confirmed using computer-based models of a variety of cervical cancer screening strategies in India, Kenya, Peru, South Africa and Thailand. It was discovered that there was a reduction in the lifetime risk of cancer by *about* 25%–36% and a reduction in the cost per year of life saved to <$500.[14] The "single-visit approach"; which can be implemented by midlevel providers, is justified in routine practice in low income countries, based on the available evidence of its safety, acceptability and effectiveness.[9] From a randomized trial in India, a 25% reduction in cervical cancer incidence and a 35% reduction in cervical cancer mortality were found following a single round of VIA screening provided by trained nurses.[15] It is however important to note that VIA is a subjective test that suffers from high false positive rates, low to moderate specificity and reproducibility, and the quality assurance procedures of this screening modality is yet to be standardized.[9]

Treatment of Abnormal Screening Test

Screening is ineffective, if the detected pre-clinical disease is not managed appropriately. Therefore, to reduce the incidence and mortality from cervical cancer, several working groups and expert committees, based on available scientific evidence, have arrived at consensus guidelines to guide practitioners on the management for screened cervical abnormalities.

Unsatisfactory cytology specimens are unreliable for detecting epithelial abnormalities.[16] In most cases, they are as a result of insufficient squamous cells,[17] although when conventional Pap tests are employed, specimens can also be rendered unsatisfactory by obscuring blood, inflammation, or other processes.[18] According to the 2012 ASCCP Consensus Guidelines,[16] women with an unsatisfactory cytology result with negative or no HPV test result should have a repeat cytology in 2-4 months while correcting, when possible, the problem that caused the unsatisfactory smear. Treating the obscuring inflammation when a specific infection is present is important. For women who had a co-testing (combined cytology and HPV tests), and have a positive HPV test and unsatisfactory cytology test, either a repeat cytology in 2-4 months or colposcopy is acceptable. Invasive cancers do bleed on contact, it may also be associated with inflammatory processes. According to the NHSCSP guidelines,[8] women with persistent inadequate samples (after three consecutive inadequate samples) should undergo colposcopy to exclude invasive cancer, as inadequate results may be associated with lesions that are not exfoliating.

Atypical Squamous Cell of Undetermined Significance (ASC-US) is the most common cytologic abnormality,[16] it represents a category of morphologic uncertainty. Thus HPV testing for the management of ASC-US cytology tests helps to objectively stratify the risk for the development of worse cervical cancer precursor lesions.[6] Despite this, ASCUS carries a low risk

for CIN 3+, partly because one third to two thirds of women with ASCUS have HPV-negative test.[19,20]

For women with ASC-US cytology, where HPV testing is possible, reflex HPV testing is preferred.[16] Alternatively, when there is no HPV result, a repeat cytology at 1 year would be acceptable.[16] For women with HPV-negative ASC-US, whether from reflex HPV testing or co-testing, repeat co-testing at 3 years is recommended while women with HPV-positive ASC-US, whether from reflex HPV testing or co-testing should have a colposcopy.[16] If colposcopy does not identify CIN, a repeat co-testing at 12 months is recommended. In women with ASC-US cytology and no HPV result; after repeating cytology at 1 year, a result of ASC-US or worse is an indication for colposcopy.[16] However, if the cytology result is normal, a return to cytology testing at 3-year intervals is recommended.[16]

Atypical Squamous Cell cannot exclude HSIL (ASC-H) confers a higher risk for CIN 3+ over time than ASC-US or low-grade squamous intraepithelial lesion (LSIL),[21,22] although the risk is lower than that of high-grade squamous intraepithelial lesion (HSIL).[16] The high rate of HPV detection in women with ASC-H makes reflex HPV testing unsuitable.[23] In addition, the 5-year cancer risk among HPV-negative women with ASC-H is 2%. This also is high to justify observation.[21] Therefore, in women with ASC-H cytology, colposcopy is recommended regardless of HPV result.[16]

Women with a result of **LSIL** cytology and positive HPV test on co-testing, and those with LSIL cytology with no HPV test should be referred for colposcopy.[16] However, those with a negative HPV test on co-testing should, preferably repeat co-testing after one year, although an immediate referral for colposcopy is acceptable.[16] If co-testing at 1 year shows normal cytology and negative HPV, the co-testing is repeated after 3 years. However, if co-testing result is either ASUS or worse, or HPV positive, colposcopy is recommended.[16]

According to the ASCCP guideline, women with no identifiable lesion on colposcopy and those with CIN 1 should have a co-test (cytology and HPV test) a year later. A normal cytology and HPV test, means that follow-up testing should be done 3 years later.[16] If CIN 1 persists for at least 2 years, either a continued follow-up or treating with abalative or excisional technique is acceptable. An histology result of CIN2,3 is managed by either excisional or ablative techniques.[16]

HSIL is associated with a high incidence of CIN 2+ on colposcopy. CIN2+ is found in 60% of these women.[24,25,26] and this might justify an immediate excision of the transformation zone in those who are likely to be lost to follow-up;[16] as is the case in most developing countries.

For women with HSIL cytology, acceptable pathways of management are: colposcopy or immediate loop electrosurgical excision.[16] If colposcopy is the elected option and CIN2/3 lesions were identified, both excision and ablation are acceptable treatment modalities. However, if CIN 2/3 is not identified, the women could either be observed by ensuring cytology and HPV testing after 12 and 24 months.[16] Otherwise a diagnostic excision procedure would still be acceptable.[16] For women on observation, a diagnostic excision procedure is recommended when cytologic result is HSIL at either the 1-year or 2-year visit.[16] After treatment, co-testing should be done at 12 and 24 months. If both co-tests are negative, retesting in 3 years is

recommended. If all tests are negative, routine screening is recommended for at least 20 years, even if this extends screening beyond 65 years of age.[16]

An interpretation of **Atypical Glandular Cell (AGC)** is poorly reproducible[27] and uncommon[28]. It has been associated with metaplasia, polyps and also neoplasias such as, adenocarcinomas of the endometrium, cervix, ovary, fallopian tube.[29] Women with AGC-not otherwise specified (AGC-NOS) should have colposcopy with endocervical sampling, regardless of their HPV result.[16] Those with CIN 2/3 following colposcopic evaluation could either have an ablative or a diagnostic excisional procedure. If no CIN 2/3 was observed, co-testing at 12 months and 24 months is recommended,[16] and if both contests are negative, follow-up co-testing in 3 years is recommended.[16] In the event of an abnormal 12 or 24 month follow-up test, a colposcopy should be done. For women with AGC "favor neoplasia" (AGC-FN) or endocervical adenocarcinoma in-situ cytology, colposcopy with endocervical sampling is also recommended, regardless of the HPV result.[16] Once an invasive disease has been ruled out during the initial colposcopic workup, a diagnostic excisional procedure is recommended.[16]

Cytology screening programs have lead to a remarkable decline in the prevalence of cervical cancer in developed countries.[30] This, however is not without a considerable financial, technical and logistic inputs, which often time is lacking in most low and medium income countries. The challenges and difficulties in implementing cytology screening in low-and-medium-income country have stimulated the search for alternative methods of screening such as visual inspection with acetic acid (VIA) or with Lugol's iodine.[31,32]

VIA is a useful alternative for low-resource settings, but standardized training and careful monitoring of test positivity and detection rates are essential to ensure optimal performance.[33] It is a simple and inexpensive test, that can be provided by midwives, nurses and other health workers. Providers can be trained in 5-10days.[33] VIA does not require a laboratory infrastructure, and the consumables required for this procedure are cheap and are universally available. The test results are immediately available. This permits treatment with cryotherapy without additional recalls.

Treatment with cryotherapy is done if the observed lesion does not extend into the endocervical canal or onto the vaginal walls, if no evidence of invasive cancer is present, and the lesion involves less than 3 quadrants of the transformation zone, provided the whole lesion could be covered by the cryoprobe. Local anesthesia or analgesics are not required prior to the procedure[33]

Compared to cytology, VIA has a higher sensitivity but lower specificity.[34] Its accuracy at detecting cervical neoplasia has been extensively studied and found to be satisfactory.[34,35] Frequently repeated screening, although more effective, may not be feasible or may be too costly for implementation in most low resource countries.[13] Therefore, a logical first step in low resource countries is to achieve a high level of coverage of the target population with a good-quality, highly sensitive test and good-quality treatment.

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