review

Clinical Practice Guidelines on the Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention in Saudi Arabia

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BACKGROUND: Cervical cancer is the third most common gynecological malignancy in Saudi women with an estimated incidence rate of 1.9 cases per 100 000 women-years. More than 40% of cervical cancer cases are diagnosed at advanced stages due to lack of a routine screening program in Saudi Arabia. Thus, national guidelines for routine screening and treatment of precancerous cervical lesions are needed.

METHODS: The Saudi Centre for Evidence-Based Healthcare invited a panel of local experts and partnered them with a team from McMaster University in Canada for methodological support, to develop national clinical practice guidelines on the screening and treatment of precancerous lesions for cervical cancer. After the panel identified key clinical questions, the McMaster University working group updated existing systematic reviews that had been used for the 2013 WHO Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Recommendations were based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. Those recommendations took into account the available evidence, patient values and preferences, and resource use in the Saudi context. The panel provided recommendations on two major issues: screening for precancerous lesions (cervical intraepithelial neoplasia 2 & 3) and treatment of those lesions to prevent cervical cancer in women who tested positive after screening.

CONCLUSIONS: The Saudi expert panel recommends using the HPV DNA test followed by colposcopy or cytology (Pap test) followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer. The panel recommends cryotherapy or loop excision electrosurgery procedure (LEEP) over cold knife cone biopsy to treat women at risk of cervical cancer that tests positive for CIN2+. Universal screening for precancerous cervical dysplasia in women in Saudi Arabia is recommended using HPV testing and or cytology. Either cryotherapy or LEEP are preferred for treatment.

LIMITATIONS: National studies on cervical cancer screening modalities and treatment of precancerous cervical lesions, including HPV prevalence and its association with cervical cancer, are scarce.

An estimated 1% to 2% of women develop cervical intraepithelial neoplasia grade 2 and 3 (CIN 2 and 3) each year worldwide.[1] Those lesions could progress to cervical squamous cell carcinoma, which comprises 80% to 90% of cervical cancers.[2,3] Therefore, screening and treatment of CIN 2 and 3 (CIN2+) are important and successfully decrease cervical cancer incidence and mortality.[4] This reduction in mortality through established screening programs is attributed to 1) an increase in the detection of invasive cancer at early stages; and 2) the detection and treatment of precancerous lesions, which reduces the overall incidence of invasive cancer.[5]

One of the main risk factors for cervical cancer is human papilloma virus (HPV). A retesting of HPV-negative cases in a worldwide epidemiological study showed that nearly 100% of cervical cancer cases test positive for high-risk HPV genotypes.[6] Currently, one of the screening modalities for cervical cancer takes screening and detection of the HPV genotype into account.

Cervical cancer is reported to be the third most common gynecological malignancy in Saudi women with an estimated incidence rate of 1.9 cases per 100000 women-years. The number of new cervical cancer cases is 152 cases per year; 55 women die from cervical cancer per year.[7] A dramatic increase in the incidence of cervical cancer in Saudi Arabia is anticipated; the projected number of new cervical cancer cases and deaths in the year 2025 will be 309 and 117, respectively. Nonetheless, more than 40% of cervical cancer cases are diagnosed at advanced stages in Saudi women compared with 25% of cases in British Columbia, Canada. This is most probably attributed to the lack of national screening programs in Saudi Arabia.[8] Additionally, screening and treatment modalities for precancerous cervical lesions are variable and it is important to identify the appropriateness and cost effectiveness of those modalities among women in Saudi Arabia. For these reasons, the Ministry of Health in Saudi Arabia has developed national clinical practice guidelines for cervical cancer screening and treatment.

The objective of this paper is to provide concise guidance for clinicians based on the best current available evidence so as to reduce variability in clinical practice in the screening and treatment of precancerous cervical dysplasia (CIN2+). The target audience of these guidelines includes primary care physicians and gynecologists in Saudi Arabia.

METHODS

This clinical practice guideline was part of the larger initiative of the Saudi Arabia Ministry of Health to provide guidance for clinicians to ensure high quality of care and reduce variability in clinical practice across the country. For this purpose, the Saudi Arabia Ministry of Health, through the Saudi Centre for Evidence-Based Healthcare, partnered with the McMaster University Working Group to provide methodological support and contacted a panel of national experts in the field of screening and treatment of cervical cancer. The detailed methodology is published online through the Saudi Arabian Ministry of Health website.[9]

The invited expert panel selected clinical questions using a formal prioritisation process. The McMaster University working group updated existing systematic reviews related to the clinical questions. The reviews had been used for the 2013 WHO Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention.[10] The group also conducted systematic searches for information specific to the Saudi context, including searches for information about patient values and preferences, and cost and resource use. Based on the updated systematic reviews, the panel prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. The panel assessed the quality of evidence using the system described by the GRADE working group.[11] Evidence on the diagnostic accuracy of screening strategies, and the effects of screening and treatment strategies on critical and important health outcomes, was sought from randomized controlled trials; however, no such studies were found and it was necessary to use clinical decision modelling techniques to combine studies that reported separately on these two aspects and obtain estimates of the effects of the different screening and treatment strategies.

The quality of evidence is classified as "high", "moderate", "low", or "very low" based on considerations of risk of bias, directness, consistency and precision of the available evidence for a specific health care problem.[12] The definition of each category is as follows:

High: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

According to the GRADE approach, the strength of a recommendation is either strong or conditional (weak) and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades – either strong or conditional – of the strength of recommendations is essential for sagacious clinical decision-making.

Based on this information and the input of Saudi Arabia panel members, the group prepared the evidence-to-recommendation tables that served the guideline panel in following the structured consensus process and transparently document all decisions made during the meeting. The guideline panel met in Riyadh on December 4, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organisation (WHO) rules.

ANALYSIS OF THE EVIDENCE AND RECOMMENDATIONS

The panel provided recommendations on two major issues; I: Screening for precancerous lesions to prevent cervical cancer (Questions 1-3) and II: Treatment of CIN2+ lesions for preventing cervical cancer in women who tested positive after screening (Questions 4-6). The recommendations were made taking into account the available evidence, resource use, and the Saudi context. The full document related to this guideline development and recommendations is available online.[13]

I. Screening for precancerous lesions to prevent cervical cancer

Question 1: Should an HPV test followed by colposcopy be preferred over visual inspection with acetic acid (VIA) followed by colposcopy to screen for CIN2+ in asymptomatic women at risk of cervical cancer?

Summary of findings: There was moderate quality evidence on the diagnostic accuracy of the screening strategies (5 cohort and cross- sectional studies, 8921 patients,[14-18] and very low quality evidence on the effects of the screening strategies on health outcomes (clinical decision models were used to combine studies providing information on diagnostic accuracy and health outcomes.)

Assuming a 2% probability of having CIN2+, HPV testing has the benefit of more true positives and fewer false negatives. Mortality due to cervical cancer, cervical cancer incidence, CIN2+ recurrence, and undetected CIN2+ rates are lower when patients are screened with the HPV test. The guideline panel agreed that the benefits of the HPV test over VIA are large.

The HPV test followed by colposcopy results in fewer true negatives and more false positives. Adverse effects such as major bleeding, major and minor infections, and unnecessary treatments are slightly smaller after screening with VIA followed by colposcopy; however, the differences are not clinically significant for most of these outcomes. The guideline panel agreed that the harms of the HPV test followed by colposcopy compared with VIA followed by colposcopy are small.

Values and Preferences: The guideline panel agreed that most women would prefer to be screened with the HPV test over VIA because the procedure takes less time to be administered. They also agreed that there is probably not important uncertainty and/or variability on women's values and preferences.

Resource use: The guideline panel agreed that even though there are extra resources needed to screen

Table 1. Interpretation of strong and conditional (weak) recommendations.

Implications	Strong Recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggests course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

women with HPV test over VIA (considering resources needed for implementation), these resources are probably small and are worth the benefits. Once the program is implemented, the HPV test would be cheaper.

Other considerations: Health inequities would be reduced if the HPV test is implemented, and this would be an option acceptable to all key stakeholders. Since resources may be the only constraint for implementing HPV testing, and these are not perceived to be a problem in Saudi Arabia, the HPV screening is a feasible option to implement. On the other hand, VIA is not an acceptable option nor it is feasible to implement, and therefore, health inequities would increase if it were implemented.

Implementation considerations: to implement this recommendation, the panel notes that resources such as equipment, maintenance, and trained professionals are needed. Also, there would be a need to implement a system to transport samples from villages to main centers.

Recommendation 1: The Saudi Expert Panel recommends the use of the HPV test followed by colposcopy over VIA followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer. (strong recommendation, moderate quality evidence for diagnostic test accuracy and very low quality evidence for health outcomes evidence).

Remark: In settings where colposcopy is not available, cytology is an alternative for women who test positive on the HPV test (evidence not assessed).

Question 2: Should the HPV test followed by colposcopy be preferred over cytology followed by colposcopy to screen for CIN2+ in asymptomatic women at risk of cervical cancer?

Summary of findings: There was low quality evidence on the diagnostic accuracy of the screening strategies (11 cohort and cross-sectional studies, 39050 patients),[17-27] and very low quality evidence on the effects of the screening strategies on health outcomes (clinical decision models were used to combine studies providing information on diagnostic accuracy and health outcomes). Assuming a 2% probability of having CIN2+, HPV testing results in more true positives and fewer false negatives. Mortality due to cervical cancer, cervical cancer incidence, CIN2+ recurrence, and undetected CIN2+ rates are lower when patients are screened with the HPV test.[10] The guideline panel agreed that the benefits of the HPV test followed by colposcopy over cytology followed by colposcopy are large. The HPV test followed by colposcopy results in fewer true negatives and more false positives. Adverse effects such as major bleeding, major and minor infections, and unnecessary treatments are slightly smaller after screening with cytology followed by colposcopy; however, the differences are not clinically significant for most of these outcomes. The guideline panel agreed that the harms of HPV testing followed by colposcopy compared with cytology followed by colposcopy are small.

Values and Preferences: The guideline panel agreed that most women would prefer to be screened with the HPV test over cytology because the results of the HPV test can be obtained faster, there is no need to undergo a speculum exam and the procedure can be done by a nurse or the patient herself. They also agreed that there is probably not important uncertainty and/or variability in women's values and preferences.

Resource use: The guideline panel agreed that patients may incur less costs if HPV testing is implemented since there would be no need to visit a gynaecologist to collect the sample. Resources may be needed for implementation of an HPV testing program, but the benefits are worth the costs.

Other considerations: The fact that the screening could be done by health professionals other than gynecologists makes it easier to reach women in remote areas, which would reduce health inequities. HPV testing would be an option acceptable to all key stakeholders. Since resources may be the only constraint for implementing HPV testing, and these are not perceived to be a problem in Saudi Arabia, HPV screening is a feasible option to implement.

Implementation considerations: To implement this recommendation, the panel notes that resources such as equipment, maintenance, and trained professionals are needed. Also, there would be a need to implement a system to transport samples from villages to main centres.

Recommendation 2: The Saudi Expert Panel suggests using HPV testing followed by colposcopy over cytology followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer. (conditional recommendation, low quality evidence for diagnostic test accuracy and very low quality evidence for health outcomes evidence).

Remark: In settings where colposcopy is not available, cytology is an alternative for women who test positive on the HPV test (evidence not assessed).

Question 3: Should VIA followed by colposcopy be preferred over cytology followed by colposcopy to screen for CIN2+ in asymptomatic women at risk of cervical cancer?

Summary of findings: There was low quality evidence on the diagnostic accuracy of the screening strategies (11 cohort and cross- sectional studies, 12089 patients),[15-18; 28-34] and very low quality evidence on the effects of the screening strategies on health outcomes (clinical decision models were used to combine studies providing information on diagnostic accuracy and health outcomes). The guideline panel agreed that the benefits of VIA over cytology are probably small, since benefits seem to be clinically insignificant when comparing both options. Assuming a 2% probability of having CIN2+, VIA followed by colposcopy results in fewer true negatives, fewer true positives, more false negatives and more false positives. Mortality due to cervical cancer, cervical cancer incidence, CIN2+ recurrence, and undetected CIN2+ rates are higher when patients are screened with VIA. Adverse effects such as major bleeding, major and minor infections, and unnecessary treatments are slightly smaller after screening with cytology followed by colposcopy; however, the differences are not clinically significant for most of these outcomes. The guideline panel agreed that the harms of VIA followed by colposcopy compared with cytology followed by colposcopy are large.

Values and Preferences: The guideline panel agreed that women would consider VIA an advantage of over cytology because of the the time needed to get results; however, when considering the procedure itself, cytology would be preferred. They also agreed that there is probably not important uncertainty and/or variability on women's values and preferences.

Resource use: The guideline panel agreed that VIA followed by colposcopy is cheaper than cytology followed by colposcopy; however, since there are not benefits for VIA followed by colposcopy over cytology followed by colposcopy; costs are irrelevant.

Other Considerations: VIA is not currently implemented in Saudi Arabia. All physicians would need to be trained to perform this screening test, which makes it infeasible to implement and would probably cause health inequities in terms of people who would have access to trained physicians. Therefore, this would not be an acceptable option from the point of view of key stakeholders.

Implementation considerations: There is a need to expand the structure to perform cytology on a large scale in Saudi Arabia.

Recommendation 3: The Saudi Expert Panel suggests using cytology followed by colposcopy over VIA followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer (conditional recommendation, low quality evidence for diagnostic test accuracy and very low quality evidence for health outcomes evidence).

II. Treatment of CIN2+ lesions for preventing cervical cancer in women who test positive after screening.

Question 4: Should cryotherapy be preferred over cold knife conization (CKC) to treat women at risk of cervical cancer who test positive after screening?

Summary of findings: There was very low quality evidence on the effects of the screening strategies on health outcomes (clinical decision models were used to combine studies providing information on diagnostic accuracy and health outcomes). After treatment with cryotherapy, there is a slightly higher mortality, cervical cancer incidence and CIN2+ recurrence rate; however, the guideline panel considered the differences clinically insignificant. After treatment with cryotherapy, there is a lower rate of major bleeding, major and minor infections and premature deliveries, irrespective of the screening strategy used (see tables in full version).[13] The difference in these outcomes was considered to be clinically important, and thus the guideline panel agreed that the benefits of cryotherapy compared with CKC probably outweigh the harms.

Values and Preferences: The guideline panel agreed that most women would prefer to undergo treatment with cryotherapy because it can be done as an outpatient. The only disadvantage is an increase in watery vaginal discharge after treatment with cryotherapy, which may lead to a need further control visits. They also agreed that there is probably not uncertainty and variability in these values and preferences.

Resource use: the guideline panel agreed that cryotherapy would be cheaper than CKC, and thus it would be a cost-saving alternative.

Other considerations: The guideline panel agreed that inequities would be reduced if cryotherapy was implemented and that this is an option acceptable to all key stakeholders. Both options would be feasible to implement.

Recommendation 4: The Saudi Expert Panel recommends using cryotherapy over CKC to treat women at risk of cervical cancer who tested positive for CIN2+. (strong recommendation, very low quality evidence for health outcomes evidence).

Question 5: Should Loop Electrical Excision Procedure (LEEP) be preferred over CKC to treat women at risk of cervical cancer who test positive after screening?

Summary of findings: There was very low quality evidence on the effects of the screening strategies on health outcomes (clinical decision models were used to combine studies providing information on diagnostic accuracy and health outcomes) After treatment with LEEP, there is a slightly higher mortality, cervical cancer incidence and CIN2+ recurrence rate; however, the guideline panel considered the differences clinically insignificant (see tables in full version).[13] After treatment with cryotherapy, there is a lower rate of major bleeding, minor infections and premature deliveries; and a higher rate of major infections irrespective of the screening strategy used (see tables in full version).[13] The difference in these outcomes was considered clinically important, and thus the guideline panel agreed that the benefits of LEEP compared with CKC probably outweigh the harms.

Values and Preferences: The guideline panel agreed that most women would prefer to receive treatment with LEEP over CKC due to the lower rate of complications and the possibility of performing the procedure in an outpatient clinic. There is probably no uncertainty and variability in these values and preferences.

Resource use: The guideline panel agreed that LEEP would be cheaper than CKC, and thus it would be a cost-saving alternative.

Other considerations: The guideline panel agreed that inequities would be reduced if LEEP was implemented and that this is an option acceptable to all key stakeholders. Both options would be feasible to implement.

Recommendation 5: The Saudi Expert Panel recommends using LEEP over CKC to treat women at risk of cervical cancer who test positive for CIN2+ (strong recommendation, very low quality evidence for health outcomes evidence).

Question 6: Should cryotherapy be preferred over LEEP to treat women at risk of cervical cancer who tested positive after screening?

Summary of findings: There was very low quality evidence on the effects of the screening strategies on health outcomes (clinical decision models were used to combine studies providing information on diagnostic accuracy and health outcomes). There are no differences in benefits after treatment with cryotherapy compared with LEEP. After treatment with cryotherapy, there is a lower rate of major bleeding and major infections. Differences in premature deliveries and minor infections are clinically insignificant irrespective of the screening strategy used. The guideline panel agreed that the benefits of cryotherapy compared with LEEP probably outweigh the harms.

Values and Preferences: The guideline panel agreed that most women would prefer to undergo treatment with cryotherapy over LEEP; and that there is probably no uncertainty and variability in these values and preferences.

Resource use: The guideline panel agreed that cryotherapy would be cheaper than LEEP, and thus it would be a cost-saving alternative.

Other considerations: The guideline panel agreed that inequities would be reduced if cryotherapy was implemented and that this is an option acceptable to all key stakeholders. Both options would be feasible to implement.

Implementation considerations: LEEP is a valid alternative particularly in settings where there are experienced physicians and the equipment is available.

Recommendation 6: The Saudi Expert Panel suggests using cryotherapy over LEEP to treat women at risk of cervical cancer who test positive for CIN2+ (conditional recommendation, very low quality evidence for health outcomes evidence).

DISCUSSION AND IMPLEMENTATION

The main aim of cervical cancer screening is to prevent morbidity and mortality from cervical cancer. Thus, screening strategies should identify cervical cancer precursors likely to progress to invasive cancers (potentially maximizing the benefits of screening) and avoid the detection and unnecessary treatment of transient HPV infection and its associated benign lesions that will likely become cancerous (minimizing the potential harms associated with screening). Cytology (the Pap test) has been widely used as the sole screening method for precancerous lesions of the cervix. Incorporation of HPV testing into cervical cancer screening strategies has the potential to allow both increased disease detection (improving benefits) and decreasing harms such as the psychosocial impact of screening positive, additional clinical visits and procedures, and treatment of lesions that may resolve. In the development of these evidence-based guidelines, we considered the tradeoffs of desirable and undesirable consequences of screening while considering different screening modalities.[35-45]

These clinical practice guidelines are the result of an initiative of the Saudi Ministry of Health to promote the practice of evidence-based medicine across Saudi Arabia. The guidelines are expected to reduce practice variations and health inequities in Saudi Arabia.

It should be noted that no guidelines or recommendations could take into account all unique features of individual clinical circumstances. Hence, clinicians, patients, third-party payers, institutional review committees, other stakeholders, or courts should never view these recommendations as dictates. Additionally, the values and preferences of individual patients should be taken into consideration in the diagnosis and treatment of CIN2+ lesions especially when considerable variability among patients is expected.

Our guidelines may also alert the public and the appropriate government agencies to the prevalence of HPV and assist in the decision to recommend HPV screening, triage, and vaccination as well as aid in the prediction of the disease progression. The panel considers it necessary to perform periodic and formal evaluations of adherence to the recommendations of this guideline and any new evidence in this field. Finally, the panel considers it necessary to undertake local research on the values and preferences of the Saudi population related to such issues as well as the development of a national register of local data on the incidence and outcomes of CIN2+.

LIMITATIONS

National studies on cervical cancer screening modalities and treatment of precancerous cervical lesions, including HPV prevalence and its association with cervical cancer in Saudi Arabia, are scarce. Moreover, future studies on the performance of different screening modalities should take into account patient acceptability, population uptake of screening, quality of screening, quality of the supportive services like pathology, and the cost of screening.

CONCLUSION

Universal screening for precancerous cervical dysplasia in women in Saudi Arabia is recommended. It should be initiated within 3 years after marriage and up to 65 years of age; however, further research on the threshold age for screening in Saudi Arabia is warranted. HPV testing and or cytology are recommended as screening modalities. Either cryotherapy or the loop electrical excision procedure are preferred for treatment of CIN2+ lesions. A national registry with data on the incidence and treatment of cervical dysplasia and its progression to cancer is needed.

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