

Frequency of intraepithelial lesions in the follow-up of women with unsatisfactory cervicovaginal cytology

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Abstract

Background: In Mexico, cervical carcinoma is the second leading cause of cancer death in women, which can be prevented if it is detected promptly with cervicovaginal cytology, however, this can be unsatisfactory even with neoplasia, so it is important to follow up to avoid underdiagnosing and delay treatment. In this hospital, this has not been previously studied. **Objective:** The objective of the study was to know the prevalence of lesions identified by cytology, colposcopy, biopsy, or hysterectomy, within 3 years after an unsatisfactory cytology. **Materials and methods:** Was reviewed the information about 156 cases of unsatisfactory cytologies during 2013 and 2014 that were followed up within next 3 years, at the General Hospital of Mexico "Dr. Eduardo Liceaga". **Results:** A total of 156 cases with follow-up were categorized the 1st year in 119 (76.3%) negative, 27 (17.4%) positive, 1 (0.6%) atypical squamous cells cannot exclude a high-grade lesion, and 9 (5.8%) inadequate; the 2nd year: 31 (79.5%) negative, 6 (15.5%) positive, and 2 (5.1%) unsatisfactory; the 3rd year: 12 (92.3%) negative and 1 (7.7%) carcinoma. According to the method by which the definitive diagnosis was made at follow-up, negative results were obtained by cytology 85 (54.5%), colposcopy with cytology 6 (3.8%), colposcopy with biopsy 20 (12.8%), and hysterectomy 8 (5.1%); positive results were obtained by cytology 7 (4.4%), colposcopy with cytology 8 (5.0%), electrosurgical loop 4 (2.4%), colposcopy with biopsy 8 (5.0%), and hysterectomy 1 (0.6%). **Conclusions:** Unsatisfactory cervicovaginal cytology is associated with the presence of preneoplastic and neoplastic lesions during their follow-up 3 years after this result.

Key words: Cytology. Cervicovaginal. Unsatisfactory. Inadequate. Follow-up. Cervical cancer.

Introduction

Cervical cancer is the fourth most frequent cancer in women worldwide; over 500,000 new cases are identified each year, and it is the fourth cause of cancer-related death among women in developing countries¹. Each year in the Americas, an estimated 83,200 women are newly diagnosed and 35,680 women die from this disease². In Mexico, since 2006, it is the second cause of death from cancer. An occurrence of 13,960

cases in women is estimated annually, with an incidence of 23.3 cases per 100,000 women³. Cervical cancer can be prevented and treated by timely detection with a cervical smear, which is the screening test used worldwide⁴.

According to the current Bethesda System 2014 to report the cervical cytology, an unsatisfactory or inadequate sample will be one that does not meet the required number of squamous cells, or in which more than 75% of squamous cells are not clearly visualized,

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as long as no abnormal cells are identified⁵⁻⁷, this is important since an inadequate smear is the most common cause of false negatives, in longitudinal studies, it was observed that a significant number of these women presented lesions or carcinomas later^{4,5,8,9}.

Studies in the United Kingdom, Norway, and South Africa concluded that after 2-5 years of follow-up, the risk of detecting high-grade lesions in women with an unsatisfactory Pap test was 1.6-4.0 times greater than in women with normal cytology^{6,10,11}.

In Colombia and Brazil, inadequate cytology was identified as an important factor that may explain the low impact of the health program and may contribute to overlook the diagnosis of precursor lesions, thereby modifying cervical cancer morbidity and mortality rates^{8,12}.

In our country, the importance of unsatisfactory cytologies at the public health level has been mentioned by González-Losa et al. who refer that one of the main problems in the effectiveness of the National Cervical Cancer Screening Program is the sampling of inadequate cytologies, an evaluation of the same, reports in 2010 an estimated 11-50% of cytological samples with this problem, as a consequence of the lack of quality in the taking of samples for evaluation¹³.

In the General Hospital of Mexico "Dr. Eduardo Liceaga," on average, approximately 10,000 cervicovaginal cytologies are performed annually, in 2015, there were 271 inadequate cytologies, in 2016, 201 were identified, and in 2017, 156 unsatisfactory cytologies were found, corresponding to 2.3%, 1.8%, and 1.6%, respectively. According to the Institute of Epidemiological Diagnosis and Reference in Mexico, there is a prevalence of 14.77% inadequate samples, of which < 5% are expected to present lesions at follow-up^{14,15}.

Therefore, because there are no precise reports of the frequency with which the precursor lesions and cervical carcinoma present in patients who have previously had inadequate samples nor on the follow-up given to them, it was considered pertinent to begin with the study of this situation, identifying the diagnosis issued by cytology, colposcopy, biopsy, electrosurgical loop, and hysterectomy, within 3 years after an unsatisfactory cervical-vaginal cytology.

Materials and methods

The study was retrospective, observational, and descriptive. We consulted the database of the cytopathology archive of the General Hospital of Mexico "Dr. Eduardo Liceaga." This study includes a total of

8212 patients during the period from 2013 to 2014. Patients were referred from the outpatient, emergency, or gynecology departments, and from the cervical cancer screening program. Most of the patients come from the Metropolitan area (Mexico City and State of Mexico) and nearby states. The hospital attends patients without social security and the cervical cancer screening program serves on average 100 women/day.

We selected 651 cervicovaginal cytologies with results of "inadequate sample" which correspond to 100% of the results of the period during 2013 and 2014, we searched and evaluated these cytological reports. The women included in this study were comparable to those excluded, they were aged between 19 and 90 years, had a diagnosis issued by a colposcopist and by the cytology department, with specification in the report of sample quality and presence or absence of injury. Subsequently, those patients who were followed up in the following 3 years were identified in the pathology file database by means of a new cytological study, colposcopy, biopsy, electrosurgical loop, and hysterectomy, and the diagnoses issued were collected. Cases in which the patients did not have a cytological report and had no follow-up were eliminated. A follow-up of 3 years (2014, 2015, and 2016) was sought because the 3 years considered by NOM 014-SSA2-1994¹⁶ are the years, in which the cytological control of the patients is carried out, that is, the year in which the inadequate sample is obtained and the two subsequent years of control are expected to be negative.

After data collection, descriptive statistical analysis was made by calculating percentages with statistical measures of central tendency, mean, mode, and median.

Results

In the Department of Cytopathology of the General Hospital of Mexico "Dr. Eduardo Liceaga," during the period from 2013 to 2014, a total of 8212 cervicovaginal cytologies were received, of which 651 (7.9%) were unsatisfactory and of these only 156 were followed (23.9%) (Fig. 1). The age range was a minimum of 19 years and a maximum of 90 years, the average age of women with inadequate cytology was 46.6 years (Fig. 2).

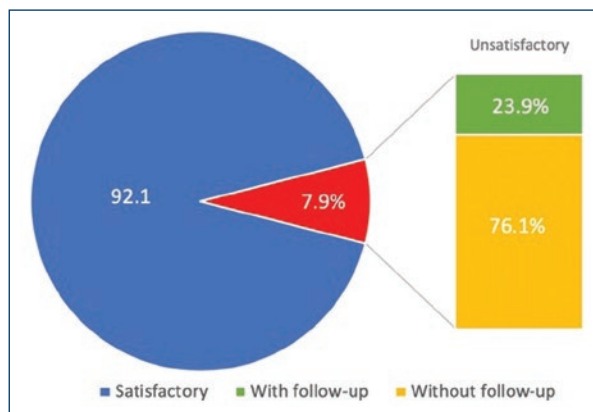
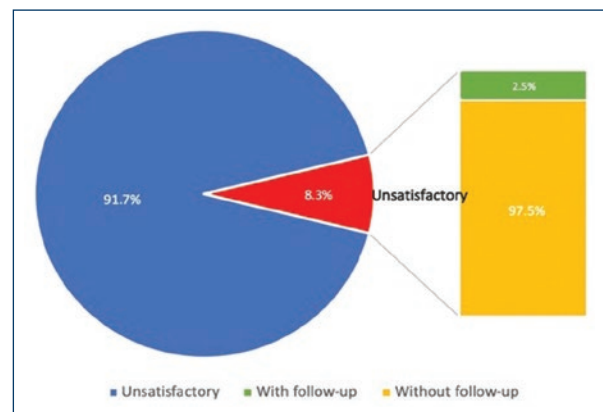
The 3-year follow-up of these patients was reviewed, 113 (72.4%) had cytology repeated and were categorized the 1st year and ordered by frequency in 119 (76.3%) negative, 27 (17.4%) positive, 1 (0.6%) atypical squamous cells cannot exclude a high-grade lesion,

Table 1. Follow-up of unsatisfactory cytology at 1, 2, and 3 years according to result

Result	Frequency: % (n) 95% CI					
	1 st year		2 nd year		3 rd year	
Negative	73.7 (115)	[0.62, 0.771]	76.9 (30)	[0.556, 0.843]	92.3 (12)	[0.737, 1.063]
≤ Leibg ^a	9 (14)	[0.03, 0.121]	10.3 (4)	[0.006, 0.194]	0 (0)	0
≥ Leiag ^b	9 (14)	[0.03, 0.121]	5.1 (2)	[−0.018, 0.118]	7.7 (1)	[−1.316, 1.456]
Unsatisfactory	8.3 (13)	[0.03, 0.121]	7.7 (3)	[−0.009, 0.149]	0 (0)	
Total	100 (156)		100 (39)		100 (13)	

a. They include all cases with the result of atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesion (LSIL)

b. They include all cases of atypical squamous cells cannot exclude a high-grade lesion (ASC-H), high-grade squamous intraepithelial lesion (HSIL), carcinoma, and adenocarcinoma.

**Figure 1.** Total cervicovaginal cytologies performed in 2013-2014 with unsatisfactory results.**Figure 2.** Follow-up of unsatisfactory cytology at the 1st year with unsatisfactory result.

and 9 (5.8%) inadequate; during the 2nd year of follow-up: 31 (79.5%) were negative, 6 (15.5%) positive, and 2 (5.1%) unsatisfactory; and in the last year, there were 12 (92.3%) negative and only 1 (7.7%) positive (Table 1).

According to the method by which the definitive diagnosis was made at follow-up, negative results were obtained by cytology 85 (54.5%), by colposcopy with cytology 6 (3.8%), by colposcopy with biopsy 20 (12.8%), and by hysterectomy 8 (5.1%). A total of 28 (17.3%) women presented abnormality in subsequent studies, mainly detected by colposcopy with cytology 8 (5.0%) and 15 (9.6%) were confirmed by biopsy, loop, or hysterectomy (Table 2).

Discussion

Inadequate cervicovaginal cytologies are presented in less than 2% annually in the General Hospital of

Mexico “Dr. Eduardo Liceaga,” in this study of 8212 cytologies performed during the period from 2013 to 2014, the unsatisfactory represented 7.9%, a percentage that is not less low than that reported in other series with a range of 0.8-11.7%^{6,10,11,17}.

The average age of 49.6 years is higher than in other studies 37.7-39.1 years^{6,17} since 96% of our population is older than 40 years, although women younger than 19 years were identified, it should be considered that the women’s cancer prevention and control program are aimed at women aged 25-64 years^{16,18}.

A total of 156 (23.9%) were subsequently monitored, and according to guidelines^{19,20,21}, most 72.4% had their cytology repeated after the unsatisfactory cytological result, only 11 cases (10.9%) were again inadequate. It is unknown why the other women in the total population were not followed.

Although the majority were negative at the 1st year of follow-up, up to 17.4% did present subsequent

Table 2. Method and outcome at the 1st year follow-up of unsatisfactory cervicovaginal cytologies

Method	Frequency: % (n) 95% CI								Total
	Negative		≤ Leibg ^a		≥ Leig ^b		Unsatisfactory		
Cytology ^c	82 (82)	[0.721,0.878]	4 (4)	[0.002, 0.077]	3 (3)	[−0.003, 0.063]	11 (11)	[0.052, 0.168]	100 (100)
Biopsy ^d	53.3 (24)	[0.362, 0.637]	20 (9)	[0.102, 0.298]	22.2 (10)	[0.102, 0.298]	4.4 (2)	[−0.016, 0.096]	100 (45)
Hysterectomy	81.8 (9)	[0.565, 1.035]	9.1 (1)	[−0.078, 0.258]	9.1 (1)	[−0.078, 0.258]	0 (0)		100 (1)

a. They include all cases with the result of atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesion (LSIL)

b. They include all cases of atypical squamous cells cannot exclude a high-grade lesion (ASC-H), high-grade squamous intraepithelial lesion (HSIL), carcinoma, and adenocarcinoma

c. They include all cases cytology and cytology with colposcopy

d. They include all cases in which were performed biopsy, cytology with biopsy, and electrosurgical loop.

abnormality, a considerably high percentage compared to that reported in the literature from 1.1 to 9.4%^{6,17}. In the following 2 years of follow-up, 15.5% and 7.7%, respectively, of diagnoses with lesions were observed, of which 16.7% presented squamous abnormalities. The predominant lesions in the 1st year were low grade (9.0%), high grade (4.5%), and carcinoma (2.6%); in the 2nd year were observed mainly lesions of low grade in 10.3%, those of high grade, and the carcinoma presented both in 2.6%; for the 3rd year, only one case with carcinoma was identified, percentages higher than those reported by Adam et al.¹¹

This demonstrates that it is likely to observe cervical lesions after unsatisfactory cytologies, however, in the absence of current statistics of the prevalence of intraepithelial lesions after inadequate cervical-vaginal cytologies in our country, it is difficult to know whether our results are statistically significant.

Conclusions

It is concluded that inadequate specimens contribute to the increase of undiagnosed precursor and neoplastic lesions since they cannot be ruled out, but are even associated with them, therefore, it is necessary to repeat the sampling and follow-up in these cases to make an early diagnosis, provide timely treatment, and favor the survival of hospital patients, which affects morbidity and mortality rates due to cervical cancer^{8,12}. Likewise, the clinical significance and prognosis of an unsatisfactory cytology is not fully known and studies are required to provide more information about it. Furthermore, it is suggested to emphasize the need to train the personnel responsible for improve cytological sampling, and in their interpretation, to have a high degree of intra- and inter-observer concordance.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The data in this article correspond to unlinked information and cannot be related to any particular patient, it is not possible to establish the identity of anyone, therefore confidentiality is not at risk and there is not need to get an informed consent.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66:7-30.
2. Pan American Health Organization. Plan of Action for Cervical Cancer Prevention and Control 2018-2030. 56th Directing Council, 70th Session of the Regional Committee of WHO for the Americas. Washington, DC: PAHO; 2018. Available from: http://www.paho.org/hq/index.php?option=com_docman&view=download&category_slug=56-directing-council-english-9964&alias=45803-cd56-9-e-poa-cervical-cancer-803&Itemid=270&lang=en. [Last accessed on 2019 Dec 15].

3. Secretaría de Salud. Hoja de Datos Sobre Cáncer de Cuello Uterino. Available from: http://www.gob.mx/cms/uploads/attachment/file/487307/Hoja_de_Datos_2019_CACU.pdf. [Last accessed on 2019 Dec 15].
4. Gallegos V, Gallegos M, Velázquez GP, Escoto SE. Cáncer cervicouterino: causas de citología no útil. *Rev Latinoamer Patol Clin*. 2011; 59:23-27.
5. Nayar R, Wilbur DC. El Sistema Bethesda para informar la citología cervical: definiciones, criterios y notas aclaratorias. 3rd ed. Argentina, Buenos Aires: Ediciones Journal; 2017.
6. Hock YL, Ramaiah S, Wall ES, Harris AM, Marston L, Marshall J, et al. Outcome of women with inadequate cervical smears followed up for five years. *J Clin Pathol*. 2003;56:592-5.
7. Ramos-Ortega G, Díaz-Hernández MC, Rodríguez-Moctezuma JR, Domínguez-Gómez FG. Satisfactory cervical cytology. Circular exocervical cytologic smears against longitudinal exocervical smears. *Rev Med Inst Mex Seguro Soc*. 2014;52:696-703.
8. Amaral RG, Manrique EJ, Guimarães JV, Sousa PJ, Mignoli JR, Xavier Ade F, et al. Influence of adequacy of the sample on detection of the precursor lesions of the cervical cancer. *Rev Bras Ginecol Obstet*. 2008; 30:556-60.
9. Gavranović L, Novak SR, Bolanca IK. Causes and frequency of unsatisfactory cervicovaginal smears. *Acta Med Croatica*. 2011;65 Suppl 1:115-9.
10. Nygård JF, Sauer T, Nygård M, Skare GB, Thoresen SO. CIN 2/3 and cervical cancer in an organised screening programme after an unsatisfactory or a normal pap smear: a seven-year prospective study of the Norwegian population-based screening programme. *J Med Screen*. 2004; 11:70-6.
11. Adam Y, McIntyre JA, De Bruyn G. Incidence of cytological abnormalities within 24 months of a normal cervical smear in Soweto, South Africa. *S Afr Med J*. 2012;103:34-9.
12. Cendales R, Wiesner C, Murillo RH, Piñeros M, Tovar S, Mejía JC. Quality of vaginal smear for cervical cancer screening: a concordance study. *Biomedica*. 2010;30:107-15.
13. González-Losa MR, Amaro-Camacho A, Domínguez-Reyes M, Castro-Sansores C. Calidad de la toma de muestra de citología cervical de la Unidad Médica de medicina familiar No. 57 del instituto mexicano del seguro social. *Rev Biomed*. 2006;17:102-6.
14. González-Mena LE, Peña-Alonso YR. Resultados, metas y logros 2012-2018. Cáncer Cervicouterino. Indre Coordinación de Patología. Curso Patricia Alonso 2019, Fundamentos de la Citología Cervicovaginal, Mérida Yucatán, Mexico, 2019.
15. Secretaría de Salud. Lineamientos Para la Vigilancia Por Laboratorio de Cáncer Del Cuello Del Útero: laboratorio de Citología. Secretaría de Salud; 2016. Available from: https://www.gob.mx/cms/uploads/attachment/file/159057/lineamientos_para_la_vigilancia_por_laboratorio_de_cancer_del_cuello_del_uterio.pdf. [Last accessed on 2019 Dec 15].
16. Secretaría de Salud. Modificación a la Norma Oficial Mexicana NOM 014-SSA2-1994, Para la Prevención, Detección, Diagnóstico, Tratamiento, Control y Vigilancia Epidemiológica del Cáncer Cérvico Uterino. Secretaría de Salud; 2007. Available from: <http://www.salud.gob.mx/unidades/cdi/nom/m014ssa294.pdf>. [Last accessed on 2019 Dec 15].
17. López-Alegría F, Lorenzi DR, Poblete OQ. Follow-up of women with inadequate pap smears: a prospective cohort study. *Sao Paulo Med J* 2015;133:20-7.
18. Secretaría de Salud. Programa de Acción Específico: prevención y control del cáncer de la mujer 2013-2018. Secretaría de Salud; 2015 Available from: https://www.gob.mx/cms/uploads/attachment/file/10046/prevencionycontrol-delcancerdelamujer_2013_2018.pdf. [Last accessed on 2019 Dec 15].
19. Sen C, Brett MT. Outcome of women referred to colposcopy for persistently inadequate smears. *Cytopathology*. 2000;11:38-44.
20. Hollingworth J, Kotecha K, Dobbs SP, Shaw PA, Ireland D. Cervical disease in women referred to colposcopy following inadequate smears. *Cytopathology*. 2000;11:45-52.
21. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis*. 2013;17:S1-27.