

# Is cryotherapy effective in all women with low-grade cervical intraepithelial neoplasia?

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**Abstract. – OBJECTIVE:** This study was designed to investigate the incidence the pre-malignant and malignant cervical lesions at the 12-month follow-up investigation between cryotherapy and non-cryotherapy groups.

**PATIENTS AND METHODS:** A prospective cohort study was performed in women with CIN 1 and PCB, who were referred to the gynecology clinic at Imam Hospital affiliated to Mazandaran University of Medical Sciences (MAZUMS), Sari, Iran, from February 2015 to November 2019. Of 232 patients, 131 consented to cryotherapy and underwent the treatment, while 101 were unwilling to undergo the treatment. After 12 months, we performed a Pap smear, a colposcopy, and a histopathological investigation of the cervix in both groups. Primary and secondary outcomes were compared between groups. The primary outcome was the comparison of incidence premalignant and malignant cervical lesions in cryotherapy and non-cryotherapy groups. The secondary outcome was a comparison of the accuracy of the Pap smear test versus colposcopy for the detection of premalignant and malignant cervical lesions in women with or without a history of cryotherapy.

**PATIENTS:** Totally, abnormal cytological, positive colposcopic, and positive histopathological findings were reported in 41.56%, 20.26%, and 13.79 %, respectively. By histology biopsy, pre-malignant and malignant cervical lesions were reported in 28.24% (37/131) and 36.63% (32/101) of women in the cryotherapy and the non-cryotherapy group, respectively. This statistic did not differ significantly between groups ( $p = 0.78$ ).

Pap smears were abnormal in 39.7% and 44.5% of women in the cryotherapy and the non-cryotherapy group, respectively. A positive colpos-

copy was obtained in 27 (20.6%) and 19 (18.8%) women in the cryotherapy and the non-cryotherapy group, respectively. The diagnostic accuracy of the Pap smear test and colposcopy in detecting cervical neoplasia did not differ in women who had undergone cryotherapy and those who had not ( $p > 0.05$ ).

**CONCLUSIONS:** This prospective study showed that cryotherapy is no appropriate treatment for patients with CIN1 and PCB.

#### Key Words:

Cryotherapy, Pap smear, Cervical cancer, Postcoital bleeding, Colposcopy.

#### Abbreviations

PPV: Positive predictive value, NPV: Negative predictive value, LR+: Positive likelihood ratio, LR-: negative likelihood ratio, DOR: Diagnostic odds ratio, PCB: Postcoital bleeding, CIN: Cervical intraepithelial neoplasia, WHO: World Health Organization, LMICs: Low-income and middle-income countries, LEEP: Loop electrosurgical excision procedure.

#### Introduction

Cervical cancer is the second most frequent cause of death from gynecologic cancers<sup>1-3</sup>. Some women experience no symptoms due to a cervical intraepithelial neoplasia lesion (CIN) or carcinoma, while others frequently experience postcoital bleeding (PCB)<sup>4-6</sup>. Prevalence rates of 3.0-5.5% and 6.8%-17.8% have been reported for cervical cancer and CIN in women with PCB<sup>4,7</sup>.

Currently, we lack any precise guidelines or recommendations for the evaluation of PCB in women of reproductive age<sup>7</sup>. Although cryotherapy has been suggested for the management of CIN2 (+)<sup>8,9</sup>, its administration for PCB or CIN1 is still a debated issue<sup>8,10,11</sup>. According to the recommendations of the World Health Organization (WHO), cryotherapy is a standard approach for the treatment of patients with precancerous cervical lesions in see-and-treat programs in low-and middle-income countries (LMICs)<sup>8,12</sup>. The simplicity and effectiveness of cryotherapy are among its advantages, but it also has drawbacks<sup>13,14</sup>. The costs, difficulties in providing adequate refrigerant gas, the long duration of treatment, and equipment failure have caused frustration among treatment providers<sup>14,15</sup>. Cervical cryotherapy is widely used in clinics, but is liable to accelerate the process of metaplasia (conversion of squamous into glandular epithelium), resulting in the displacement of squamous glandular tissue into the cervix<sup>16,17</sup>. According to Sparks et al<sup>18</sup>, clinicians regarded cervical cryotherapy as adequate therapy and were negligent in performing subsequent follow-up colposcopies. Colposcopy has been suggested as the primary diagnostic procedure for evaluating women with a suspicious lesion in their cervix or women with a friable cervix<sup>19,20</sup>. Published studies on the management of PCB and CIN1 are scarce and inconclusive<sup>3,4,20,21</sup>. This study was designed to investigate the incidence the premalignant and malignant cervical lesions at the 12-month follow-up investigation between cryotherapy and non-cryotherapy groups. Also, the diagnostic accuracy of the Pap smear test and colposcopy for the detection of cervical neoplasia was compared in two groups.

## Patients and Methods

A prospective cohort study was performed at Imam Hospital affiliated to Mazandaran University of Medical Sciences (MAZUMS), Sari, Iran, from February 2015 to December 2019.

The main purpose of the study was to investigate the incidence the premalignant and malignant cervical lesions at the 12-month follow-up investigation between cryotherapy and non-cryotherapy groups.

Based on the effectiveness of cryotherapy in curing 81.4% of women with CIN 1, as reported by Sankaranarayanan et al<sup>22</sup>, a minimum sample size of 220 patients was deemed appropriate ( $\alpha =$

0.05, power 0.9); 20% were added to compensate for potential loss to follow-up.

Women were enrolled in the study by a convenient sampling method. Inclusion criteria were as follows: 1) resistant PCB; 2) CIN 1 confirmed on histopathology; 3) currently not pregnant; 4) no more than one sexual partner in the course of their lives; 5) no smoking or alcohol; 6) no history of endometrial, ovarian, or cervical cancer; 7) no history of cervical manipulation (conization, ablation procedures, or the loop electrosurgical excision procedure (LEEP)); 8) no bleeding due to anatomical deformities in the hymen or perineum; 9) no history of diseases associated with immunocompromised conditions (e.g., diabetes mellitus, immune deficiency syndromes) or the use of corticosteroids or immunosuppressive drugs.

Women were excluded from the study if they were unwilling to cooperate, undergo a colposcopy biopsy at our center, or became pregnant.

The study objectives were explained to the patients, and their written informed consent was obtained. Of 268 patients, 142 consented to cryotherapy and underwent the treatment, while 126 were unwilling to undergo the treatment (Figure 1). Cryotherapy was administered without anesthesia by the double freeze technique. The latter consisted of freezing for 3 minutes, thawing for 5 minutes, and then re-freezing for 3 minutes. All cryotherapy sessions were performed at the clinic by a single gynecologist who was unaware of the outcome of the study. Women with HPV infection received quadrivalent HPV vaccinations (Gardasil). The vaccine was given as a series of intramuscular injections of 0.5 mL on day 1, month 2, and month 6.

General parameters including age, parity, duration of marriage, duration of PCB, cervicitis, history of uterine polyps, and HPV infection were registered. The data were obtained either directly from the patients or extracted from their medical records. All patients were followed for 12 months. The follow-up investigation at 12 months included a Pap smear, a colposcopy and a cervical biopsy.

All patients were placed in the dorsal lithotomy position, and the cervix was examined with a vaginal speculum. A standard specimen was taken with a spatula and a cotton swab. All samples were sent to the same cytology laboratory to be stained by the Papanicolaou technique and examined by a cytologist using the 2007 Bethesda system.

Patients were then asked to report for a colposcopy between day 8 and 12 from the start of

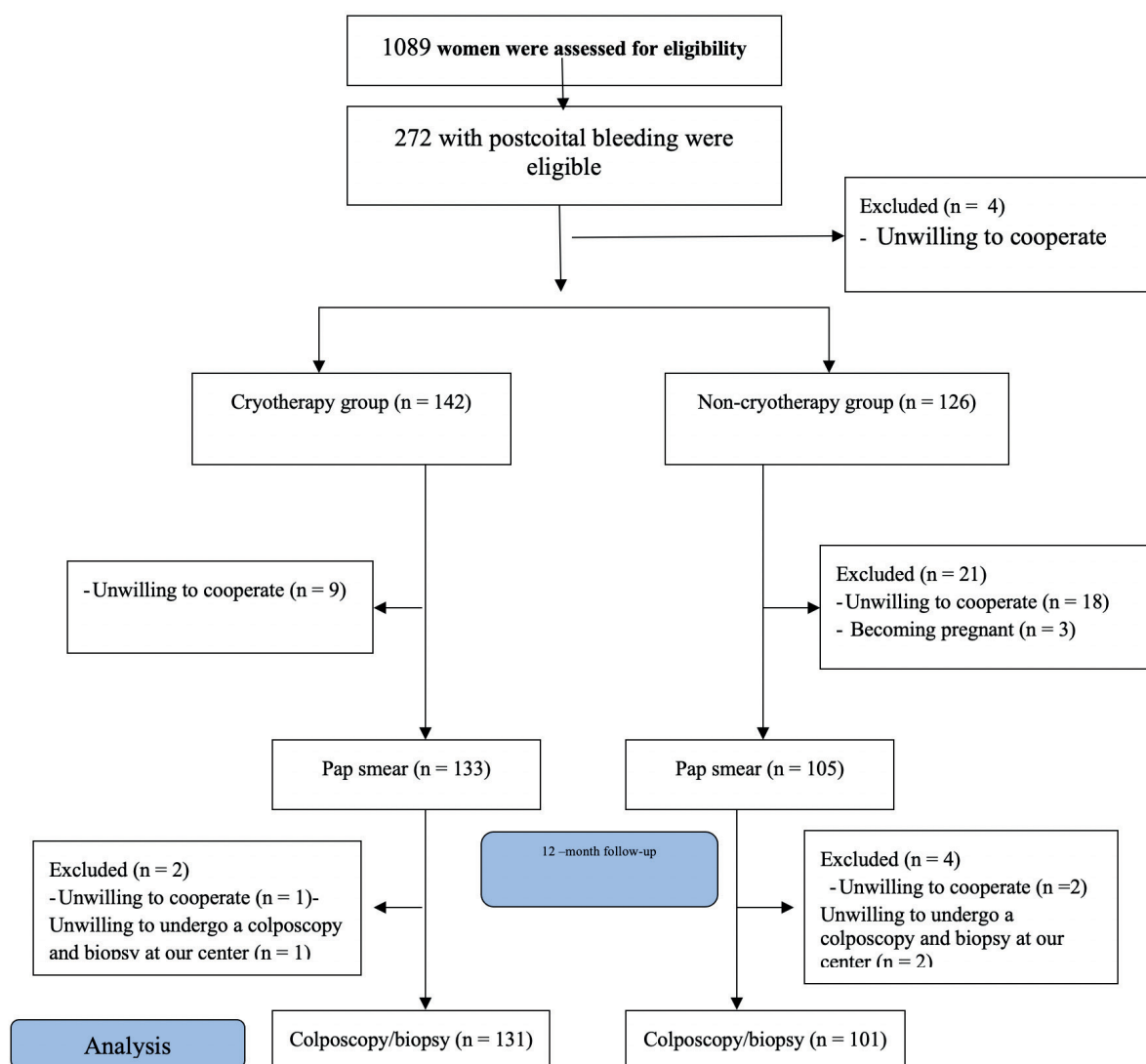


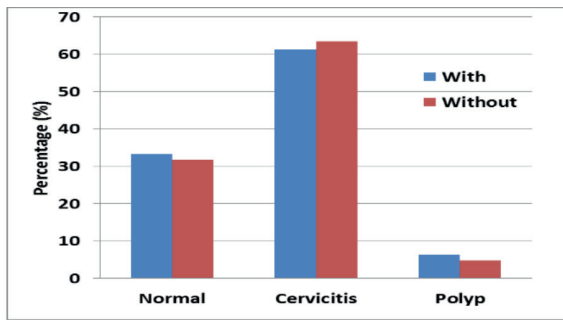
Figure 1. Flowchart of the study.

their menstrual period. Biopsy specimens were taken from all suspicious locations using separate instruments. The specimens were stained with hematoxylin and eosin. All of the lab tests were performed at the same laboratory, where the staff was unaware of the existence of the two groups. All procedures of cryotherapy, colposcopies, and Pap smears were performed by one person. The primary outcome was the difference between the cryotherapy and non-cryotherapy group in regard to the incidence of premalignant and malignant cervical lesions at the 12-month follow-up investigation, which included a biopsy and a histopathological examination. Three stages of CIN1, CIN2, or CIN3 are considered as premalignant lesions<sup>23</sup>.

The secondary outcome was a comparison of the accuracy of the Pap smear test versus colposcopy for the detection of premalignant and malignant cervical lesions in women with or without a history of cryotherapy. An ASCUS or a worse finding on the Pap smear test was considered abnormal. A CIN 2 lesion or worse on colposcopy and histopathology was considered positive. The biopsy was treated as the gold standard to establish the diagnostic accuracy of each test.

### Statistical Analysis

Commercially available software (IBM SPSS Statistics version 21; IBM SPSS Statistics for Windows, Armonk, NY, USA) was used for data



**Figure 2.** Baseline non-malignant findings in the cryotherapy and the non-cryotherapy group.

analysis. Descriptive statistics (frequency and percentage) were used to present the data. Results for quantitative variables were reported in means  $\pm$  SD, and the independent *t*-test was used to compare quantitative variables between groups. The Chi-square test was used to compare the characteristics of categorical variables between groups. Ordinal categorical variables were reported in frequencies and percentages. The diagnostic outcome of the Pap smear was established on the basis of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio

(LR+), and negative likelihood ratio (LR-). The diagnostic odds ratio (DOR) for estimating the discriminative power of the diagnostic test was calculated according to the formula  $DOR = (TP/FN) / (FP/TN)$ . The level of significance was set to  $p = 0.05$ .

## Results

Of 1089 women referred to the gynecology clinic, 272 were eligible for the study. Forty (14.7%) were excluded because they were unwilling to cooperate ( $n = 23$ ), unwilling to undergo a colposcopy at our center ( $n = 18$ ), or became pregnant ( $n = 3$ ). The final analysis was based on data collected from 232 women. The mean age of the women was  $40.1 \pm 9.6$  years. A positive HPV infection was noted in 20.7% (48/232) of women. Of 232 patients, 131 (56.46%) consented to cryotherapy and underwent the treatment, while 101 (43.54%) were unwilling to undergo the treatment.

Differences in age, parity, the duration of marriage, duration of PCB, cervicitis, history of uterine polyps, and HPV infection did not differ significantly between groups. The baseline demographic and clinical characteristics of the groups are summarized in Table I.

**Table I.** Baseline demographic and clinical characteristic of the two groups of patients..

Variable		Cryotherapy group (n = 131)	Non-cryotherapy group (n = 101)	p-value
Age (y)	Min-Max	29-47	31-48	0.25*
	Mean $\pm$ SD			
Parity	Min-Max	41 $\pm$ 10.4	39.4 $\pm$ 8.8	
	Mean $\pm$ SD			
Duration of marriage	Min-Max	1-7	1-6	0.71*
	Mean $\pm$ SD	3.03 $\pm$ 0.1	3.6 $\pm$ 1.6	
Duration of PCB (m)	Min-Max	5-29	4-27	0.35*
	Mean $\pm$ SD	22.3 $\pm$ 7.6	24.3 $\pm$ 5.9	
Cervicitis, n (%)	Min-Max	6-21	7-14	0.05*
	Mean $\pm$ SD	13.5 $\pm$ 4.9	11.3 $\pm$ 3.2	
History of uterine polyps, n (%)	Yes	79 (60.31%)	64 (63.37%)	0.46**
	No	52 (39.69%)	37 (36.63%)	
HPV		10 (7.63%)	5 (4.95%)	0.93**
	Yes	121 (92.37%)	96 (95.05%)	
	Positive	23 (17.56%)	24 (23.76%)	0.064**
	Negative	108 (82.44%)	77 (76.24%)	

Abbreviations: Y; year, M; month N; number, SD; Standard deviation, PCB; Post coital bleeding. \*Student's *t*-test, \*\*Chi-squared test.

A large number of women in both groups had cervicitis; the difference between groups was not significant. Baseline cytological findings, cervicitis, and a history of uterine polyps in the two groups are shown in Figure 2.

As the primary outcome, by the histological result of the biopsy specimen, premalignant and malignant cervical lesions were reported in 28.24% (37/131) and 36.63% (32/101) of women in the cryotherapy and the non-cryotherapy group, respectively. Premalignant and malignant cervical lesions did not differ significantly between groups ( $p = 0.78$ ).

As a secondary outcome, cytological, colposcopic, and histopathological findings were compared in women with and without a history of cryotherapy. The Pap smear test was abnormal in 39.7% and 44.5% of women in the cryotherapy and non-cryotherapy groups, respectively. A positive colposcopy was obtained in 27 (20.6%) and 19 (18.8%) women of the cryotherapy and non-cryotherapy groups, respectively. Cytological and colposcopic findings did not differ significantly between groups. Abnormal cytological, positive colposcopic, and positive histopathological find-

ings were reported in 41.56% (96 of 232), 20.26% (47 of 232), and 13.79% (32 of 232), respectively.

Patients with an abnormal Pap smear and a positive cervical biopsy were significantly older than those with normal and negative findings ( $p = 0.001$ ,  $p = 0.001$ , respectively). The cytological, colposcopic, and histopathological findings in women with and without a history of cryotherapy are summarized in Table II.

The Pap smear and histopathological findings were consistent in 70.22% (92 of 131) and 71.28% (71 of 101) of women in the cryotherapy and non-cryotherapy groups, respectively ( $p = 0.58$ ). Colposcopic and histopathological findings were consistent in 64.88% (85 of 131) and 89.1% (90 of 101) of women in cryotherapy and non-cryotherapy groups, respectively ( $p = 0.218$ ).

The Pap smear and histopathological findings were consistent in 70.22% (92 of 131) and 71.28% (71 of 101) of women in cryotherapy and non-cryotherapy groups, respectively; the difference was not statistically significant ( $p = 0.58$ ). Colposcopic and histopathological findings were consistent in 64.88% (85 of 131) and 89.1% (90 of 101) of women with and without cryotherapy,

**Table II.** Outcomes of cytology and histopathology in the two groups.

Variable	Cryotherapy group (n = 131)	Non-cryotherapy group (n = 101)	p-value
Normal	79 (60.31%)	56 (55.45%)	0.35*
ASCUS	27 (20.69%)	25 (24.75%)	
HSIL	7 (5.34%)	8 (7.92%)	
LSIL	10 (7.63%)	9 (8.91%)	
ASC-H	7 (5.34%)	2 (1.98%)	
AGUS	1(0.76%)	1(0.99%)	
Normal	78 (59.54%)	68 (67.33%)	0.58**
CIN 1	26 (18.85%)	14 (13.86%)	
CIN 2	19 (14.5%)	10 (9.9%)	
CIN 3	8 (6.11%)	9 (8.91%)	
Positive	11 (8.4%)	8 (7.9%)	0.4**
Negative	120 (91.6%)	93 (92.1%)	
Normal	94 (71.75%)	69 (62.38%)	0.78*
CIN 1	19 (51.4%)	18 (47.4%)	
CIN 2	8 (21.6%)	6 (15.8%)	
CIN 3	5 (13.5%)	6 (15.8%)	
Micro-invasive cancer	5 (13.5%)	0	
Large SCC	0	2 (5.3%)	

Abbreviations: ASCUS; Atypical squamous cells of undetermined significance, HSIL; High grade squamous intraepithelial lesion; LSIL: Low-grade squamous intraepithelial lesion, ASC-H: High-grade squamous intra-epithelial lesion, AGUS: Atypical glandular cells of undetermined significance, CIN: Cervical intraepithelial neoplasia, SCC: Squamous cell carcinoma. \*Fisher's exact test, \*\*Chi-squared test.

**Table III.** Diagnostic accuracy of the Pap smear test and colposcopy in women with and without cryotherapy.

Groups		Sensitivity	Specificity	PPV	NPV	LR+	LR-
Pap smear	Non-cryotherapy	75%	69.6%	53.3%	85.7%	2.47	0.35
		64-82%	54-86%	41-80%	75-94%	2.2-5.5	0.13 - 0.49
	Cryotherapy	67.6%	71.3%	48%	84.8%	2.35	0.45
		57 - 87%	65-83%	39-68%	79-94%	1.1-4.6	0.19-0.59
		84.4%	91%	81.82%	92.64%	9.38	0.17
Colposcopy	Non-cryotherapy	76-93%	83-95%	49-90%	79-96%	5.4-15.4	0.09 - 0.32
	Cryotherapy	59.5%	67%	41.5%	80.7	1.8	0.29
		44 - 73%	58-82%	32-56%	73-89%	0.8-3.2	0.19-0.45

Abbreviations: PPV: Positive predictive value; NPV: Negative predictive value LR+: Positive likelihood ratio; LR-: Negative likelihood ratio.

respectively; the difference was not statistically significant ( $p = 0.218$ ).

The diagnostic accuracy of the Pap smear test and colposcopy was compared between the cryotherapy and the non-cryotherapy group. As shown in Table III, the sensitivity and specificity of the Pap smear in the cryotherapy and non-cryotherapy groups were 67.6% vs. 75%, and 71.3% vs. 69.6%, respectively. The sensitivity and specificity of colposcopy in women with and without cryotherapy were 59.5% vs. 84.4%, and 67% vs. 91%, respectively. The diagnostic accuracy of the Pap smear test and colposcopy in women with and without cryotherapy are shown in Table III.

DOR was calculated to estimate the discriminative power of the Pap smear test and colposcopy in diagnosing premalignant and malignant cervical lesions in women with or without cervical cryotherapy. The DOR of the Pap smear in detecting premalignant and malignant cervical lesions in patients with and without a history of cryotherapy was 5.16 (95% CI: 3.8 to 15.5) and 6.86 (95% CI 3.1 to 18.2), respectively. The DOR of colposcopy in detecting premalignant and malignant cervical lesions in patients with and without a history of cryotherapy was 3 (95% CI 1.8 to 5.2) and 56.7 (95% CI 31 to 98), respectively.

## Discussion

The published literature has clearly shown that PCB is a significant indicator of cervical cancer in women<sup>24</sup>. We still lack established guidelines for the management of women with CIN1 and PCB<sup>25</sup>. The aim of the present study was to evaluate the efficacy of cryotherapy in women with CIN1 and PCB. By histology biopsy, premalignant and malignant cer-

vical lesions were reported in 28.24% (37/131) and 36.63% (32/101) of women in the cryotherapy and the non-cryotherapy group, respectively.

Abnormal cytological findings were reported in 39.61% and 44.55% of women with and without cryotherapy, respectively. Colposcopic findings were positive in 20.6% and 18.1% of women in the cryotherapy and non-cryotherapy groups, respectively. Furthermore, 13.7% of women in the cryotherapy and non-cryotherapy groups had abnormal histopathological findings. Cytological, colposcopic, and histopathological findings did not differ between groups.

The double-freeze technique of cryotherapy is an accepted treatment for mild and focal moderate dysplasia of the cervix and PCB. The present investigation contrasted the data reported in previous studies concerning the positive effects of cryotherapy<sup>8,26,27</sup>. Sparks et al<sup>18</sup> retrospectively evaluated 268 women with PCB who had undergone cryotherapy and identified cervical cryotherapy as a risk factor for inadequate follow-up colposcopies. Furthermore, the efficacy of cryotherapy was deemed doubtful in a systematic review published in 2020. The latter investigation revealed that cryotherapy did reduce the risk of minor bleeding shortly after treatment but increased the risk of disease recurrence and infection<sup>28</sup>. Differences in study design, statistical analysis, and geographical location (developed or undeveloped countries), are the prime weaknesses of the published reports. Therefore, the subject calls for well-founded ethical studies of longer duration and appropriate design.

We compared the diagnostic accuracy of the Pap smear test and colposcopy for the detection of cervical neoplasia in patients with and without cryotherapy. The diagnostic accuracy of a test is measured by its sensitivity, specificity, PPV, NPV, LR,

ROC curve (AUC), and DOR<sup>29,30</sup>. The diagnostic value of the Pap smear and colposcopy in detecting cervical neoplasia was lower in the cryotherapy group than in the non-cryotherapy group, although the difference was not significant. In addition, the higher sensitivity and the higher NPV of colposcopy compared to the Pap smear was evidence of the greater diagnostic accuracy of the former. The present study revealed that colposcopy is superior to the Pap smear in detecting neoplastic lesions of the cervix in women with PCB.

These findings are in line with the data reported in previous studies<sup>31-34</sup>. In a cross-sectional study, Najib et al<sup>31</sup> reexamined 168 women during a 6-month period and noted the higher diagnostic accuracy of colposcopy compared to the Pap smear in detecting premalignant and malignant lesions of the cervix. According to some reports, the diagnostic accuracy of the Pap smear and colposcopy in detecting cervical neoplasia is influenced by HPV, HIV infection, and treatments<sup>31-33</sup>.

The main limitation of the present study is its observational design. The accuracy of the data registered in the present study should be evaluated in a randomized clinical trial.

## Conclusions

This prospective study showed that cryotherapy is no appropriate treatment for patients with CIN1 and PCB. The diagnostic accuracy of the Pap smear test and colposcopy in detecting cervical neoplasia colposcopy did not differ in women with or without cryotherapy. The diagnostic accuracy of colposcopy was superior to that of the Pap smear in detecting premalignant cervical lesions. In view of the fact that cervical cancer is the most common gynecological cancer in developing countries, we recommend colposcopy as a screening investigation for malignant and premalignant lesions of the cervix.

## Acknowledgments

This study was the result of a research project approved by the review board of Mazandaran University of Medical Sciences (MAZUMS). The authors would like to thank all participants.

## Ethics Approval and Consent to Participate

All steps of the study were performed in accordance with the Declaration of Helsinki (ethical principles for medical research involving human subjects) and the Committee of Science and Research Ethics at Mazandaran University of Medical Science (IR. MAZUMS. REC: 1390.181-89). The

participants were clearly informed about the purpose and background of the study, the fact that their participation in and withdrawal from the study would be voluntary, and the confidential management of their data. All participants gave their written informed consent and were free to discontinue their participation in any stage of the study, for any reason, or for no reason at all. All patient data were treated confidentially, were inaccessible to any person or organization, and were only reported collectively.

## Availability of Data and Materials

The datasets generated and analyzed for the study are available from the corresponding author with permission from Mazandaran University of Medical Science (MAZUMS), Sari, Iran.

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## Conflict of Interest

The Authors declare that they have no conflict of interests.

## References

- 1) Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, Freddie Bray. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Global Health* 2020; 8: 191-203.
- 2) Ferrante JM, Fyffe DC, Vega ML, Piasecki AK, Ohman-Strickland PA, Crabtree BF. Family physicians' barriers to cancer screening in extremely obese patients. *Obesity* 2010; 18: 1153-1159.
- 3) Karimi-Zarchi M, Allahqoli L, Nehmati A, Kashi AM, Taghipour-Zahir S, Alkatout I. Can the prophylactic quadrivalent HPV vaccine be used as a therapeutic agent in women with CIN? A randomized trial. *BMC Public Health* 2020; 20: 1-7.
- 4) Cohen O, Schejter E, Agizim R, Schonman R, Chodick G, Fishman A, Hershko Klement A. Post-coital bleeding is a predictor for cervical dysplasia. *PLoS one* 2019; 14: e0217396.
- 5) Straughn J, Yashar C. Patient education: Cervical cancer treatment; early-stage cancer (Beyond the Basics). Nov 15, 2018 ed: UpToDate, Inc. and/or its affiliates. All Rights Reserved, 2020.
- 6) Allahqoli L, Abed Saeedi Z, Azin A, Hajaan S, Alavi Majd H, Molavi N. Socially damaged women's perception of sexually transmitted infections: a qualitative study. *Life Sci J* 2014; 11: 244-250.
- 7) Batish A, Sathiyathan S. Should women with postcoital bleeding be referred for colposcopy?. *Nepal J Obstet Gynaecol* 2016; 11: 5-7.

- 8) Agah J, Sharifzadeh M, Hosseinzadeh A. Cryotherapy as a method for relieving symptoms of cervical ectopy: a randomized clinical trial. *Oman Med J* 2019; 34: 322-326.
- 9) Wesley RS, Muwonge R, Sauvaget C, Thara S, Sankaranarayanan R. Effectiveness of cryotherapy for histologically confirmed cervical intraepithelial neoplasia grades 1 and 2 in an Indian setting. *Int J Gynaecol Obstet* 2013; 123: 16-20.
- 10) Lewis K, Sellors J, Dawa A, Tsu V, Kidula N. Report on a cryotherapy service for women with cervical intraepithelial neoplasia in a district hospital in western Kenya. *Afr Health Sci* 2011; 11: 370-376.
- 11) Taylor SN, Lensing S, Schwebke J, Lillis R, Mena LA, Nelson AL, Rinaldi A, Saylor L, McNeil L, Lee JY. Prevalence and treatment outcome of cervicitis of unknown etiology. *Sex Transm Dis* 2013; 40: 379-385.
- 12) Pinder LF, Parham GP, Basu P, Muwonge R, Lucas E, Nyambe N, Sauvaget C, Mwanahamuntu MH, Sankaranarayanan R, Prendiville W. Thermal ablation versus cryotherapy or loop excision to treat women positive for cervical precancer on visual inspection with acetic acid test: pilot phase of a randomised controlled trial. *Lancet Oncol* 2020; 21: 175-184.
- 13) Asrani S, Reddy PB, Dhirawani RB, Jain S, Pathak S, Asati P. Cryosurgery: a simple tool to address oral lesions. *Contemp Clin Dent* 2018; 9(Suppl 1): S17-S22.
- 14) Basu P, Mittal S, Vale DB, Kharaji YC. Secondary prevention of cervical cancer. *Best Pract Res Clin Obstet Gynaecol* 2018; 47: 73-85.
- 15) Maza M, Schocken CM, Bergman KL, Randall TC, Cremer ML. Cervical precancer treatment in low-and middle-income countries: a technology overview. *J Glob Oncol* 2017; 3: 400-408.
- 16) Çekmez Y, Şanlıkan F, Göçmen A, Vural A, Türkmen SB. Is cryotherapy friend or foe for symptomatic cervical ectopy? *Med Princ Pract* 2016; 25: 8-11.
- 17) WHO, IARC. Prevention of cervical cancer through screening using visual inspection with acetic acid (VIA) and treatment with cryotherapy. A demonstration project in six African countries: Malawi, Madagascar, Nigeria, Uganda, the United Republic of Tanzania, and Zambia, 2012.
- 18) Sparks RA, Scheid D, Loemker V, Stader E, Reilly K, Hamm R, McCarthy L. Association of cervical cryotherapy with inadequate follow-up colposcopy. *J Fam Pract* 2002; 51: 526-528.
- 19) Fraser IS, Petrucco OM. Management of intermenstrual and postcoital bleeding, and an appreciation of the issues arising out of the recent case of O'Shea versus Sullivan and Macquarie pathology. *Aust N Z J Obstet Gynaecol* 1996; 36: 67-73.
- 20) Shapley M, Jordan J, Croft PR. A systematic review of postcoital bleeding and risk of cervical cancer. *Br J Gen Pract* 2006; 56: 453-460.
- 21) Lili E, Chatzistamatiou K, Kalpaktsidou-Vakiani A, Moysiadis T, Agorastos T. Low recurrence rate of high-grade cervical intraepithelial neoplasia after successful excision and routine colposcopy during follow-up. *Medicine* 2018; 97: e9719.
- 22) Sankaranarayanan R, Rajkumar R, Esmy PO, Fayette JM, Shanthakumary S, Frappart L, Thara S, Cherian J. Effectiveness, safety and acceptability of 'see and treat' with cryotherapy by nurses in a cervical screening study in India. *Br J Cancer* 2007; 96: 738-743.
- 23) WHO. Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva: World Health Organization, 2013; pp. 1-58.
- 24) Gulumser C, Tuncer A, Kuscu E, Ayhan A. Is colposcopic evaluation necessary in all women with postcoital bleeding? *Eur J Obstet Gynecol Reprod Biol* 2015; 193: 83-87.
- 25) Tarney CM, Han J. Postcoital bleeding: a review on etiology, diagnosis, and management. *Obstet Gynecol Int* 2014; 2014: 192087.
- 26) Nicholas J Shaheen, Bruce D Greenwald, Anne F Peery, John A Dumot, Norman S Nishioka, Herbert C Wolfsen, J Steven Burdick, Julian A Abrams, Kenneth K Wang, Damien Mallat, Mark H Johnston, Alvin M Zfass, Jenny O Smith, James S Barthel, Charles J Lightdale. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. *Gastrointest Endosc* 2010; 71: 680-685.
- 27) Çekmez Y, Şanlıkan F, Göçmen A, Vural A, Türkmen SB. Is cryotherapy friend or foe for symptomatic cervical ectopy? *Med Princ Pract* 2016; 25: 8-11.
- 28) Hurtado-Roca Y, Becerra-Chauca N, Malca M. Efficacy and safety of cryotherapy, cold cone or thermocoagulation compared to LEEP as a therapy for cervical intraepithelial neoplasia: systematic review. *Rev Saude Publica* 2020; 54: 1-13.
- 29) Maxim LD, Niebo R, Utell MJ. Screening tests: a review with examples. *Inhal Toxicol* 2014; 26: 811-828.
- 30) Šimundić AM. Measures of diagnostic accuracy: basic definitions. *EJIFCC* 2009; 19: 203-211.
- 31) Najib Fs, Hashemi M, Shiravani Z, Poordast T, Sharifi S, Askary E. Diagnostic accuracy of cervical pap smear and colposcopy in detecting premalignant and malignant lesions of cervix. *Indian J Surg Oncol* 2020; 11: 453-458.
- 32) Karimi-Zarchi M, Peighambari F, Karimi N, Rohi M, Chiti Z. A comparison of 3 ways of conventional pap smear, liquid-based cytology and colposcopy vs cervical biopsy for early diagnosis of premalignant lesions or cervical cancer in women with abnormal conventional pap test. *Int J Biomed Sci* 2013; 9: 205-210.
- 33) Karimi-Zarchi M, Zanbagh L, Shafii A, Taghipour-Zahir S, Teimoori S, Yazdian-Anari P. Comparison of Pap smear and colposcopy in screening for cervical cancer in patients with secondary immunodeficiency. *Electron Physician* 2015; 7: 1542-1548.
- 34) Fatahi Meybodi N, Karimi-Zarchi M, Allahqoli L, Sekhavat L, Gitas G, Rahmani A, Fallahi A, Hassanlouei B, Alkatout I. Accuracy of the triple test versus colposcopy for the diagnosis of premalignant and malignant cervical lesions. *Asian Pac J Cancer Prev* 2020; 21: 3501-3507.