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Original Research

Utility of colposcopy in the management of ASCUS and LSIL in women younger than 25-year-old: A retrospective multicenter study

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Summary

Objective: We aimed to analyze the colposcopy-guided biopsy results in women aged 21-24 years with clinical suspicion for cervical lesion and/or cytological abnormality. *Methods:* This was a retrospective cohort study conducted on 461 patients undergoing colposcopic examination and biopsy between the ages of 21-24. The colposcopy-guided biopsy results of women with atypical squamous cells of undetermined significance (atypical squamous cells of undetermined significance) cytology were cervical intraepithelial neoplasia (cervical intraepithelial neoplasia) 2 in 9 patients and cervical intraepithelial neoplasia 3 in 5 patients. *Results:* The colposcopy-guided biopsy results of women with low-grade squamous intraepithelial lesion (low-grade squamous intraepithelial lesion) cytology were cervical intraepithelial neoplasia 2 in 17 patients, cervical intraepithelial neoplasia 3 in 10 patients, and invasive cancer in 1 patient. One of the high-grade squamous intraepithelial lesion (high-grade squamous intraepithelial lesion) patients had invasive cervical cancer. The cytology results of women with cervical intraepithelial neoplasia 1 after 6 months from colposcopy-guided biopsy were atypical squamous cells of undetermined significance (n = 11), and low-grade squamous intraepithelial lesion (n = 6). The cytology results of women with cervical intraepithelial neoplasia 1 after 12 months were atypical squamous cells of undetermined significance in 2 women, and low-grade squamous intraepithelial lesion in 2 women. The cytology results after 12 months from colposcopy-guided biopsy were high-grade squamous intraepithelial lesion in 16 of 433 women who underwent follow-up (3.7%). There were no significant statistically differences between cervical intraepithelial neoplasia 2 patients with and without treatment in terms of cytology results at 6 months (p = 1.00). However, there were significant statistically differences between cervical intraepithelial neoplasia 2 patients with and without treatment in terms of cytology results at 12 months (p= 0.042). *Conclusions:* Colposcopic examination should perform in women aged 21-24 years with atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion due to the possibility of high-grade squamous intraepithelial lesion and invasive cancer.

Key words: Cervical intraepithelial neoplasia; Colposcopy; Human papillomavirus.

Introduction

Cervical cancer is common among women worldwide. The presence of screening and human papillomavirus (HPV) vaccination programs decreased the incidence and mortality rates. While a fall in cervical cancer rates resulting from screening strategy, when and whom to screen, and frequency are still debated. The benefits and harms of cervical cancer screening vary with age. The age-adjusted incidence of cervical cancer in women under 20 years is very low. Adolescents are also more likely to spontaneously clear HPV infection and the most of low-grade lesions as well as many high-grade lesions in adolescent women, will resolve spontaneously [1, 2].

Avoiding of unnecessary diagnostic procedures and treatment in this age group, cervical cancer screening be initiated no earlier than age 21. International guidelines vary: United Kingdom screening policy and was based on evidence that screening at ages 20–24 provided no population benefit in terms of cancer prevention [3]. World Health Organization guidelines for screening and treatment of precancerous lesions for cervical cancer prevention recommendations apply to women 30 years of age and older because of their higher risk of cervical cancer and may extend to younger and older women depending on their baseline risk of cervical intraepithelial neoplasia (CIN) 2^{+}. United States professional organizations suggest initiating screening at age 21, regardless of the age of initiation of sexual activity [4-7]. However, a recently updated guideline for management of abnormal cervical cancer screening test and cancer precursors advised that women aged 21-24

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years need less invasive management for minor cytological abnormalities and even cervical intraepithelial lesions CIN 2/3 can be managed conservatively [8]. Women over age 30 were invited for population-based screening via HPV DNA and conventional cytology in Turkey [9]. The opportunistic cervical cancer screening be initiated as United States professional organizations. But the management of cervical cytological abnormalities in women aged 21-24 years depends on the institutional decision whether follow up or colposcopy intervention.

In this multicenter study we analyzed the colposcopy and biopsy results in women aged 21-24 years with clinical suspicion for cervical lesion and/or cytological abnormality for defining necessity of both intervention and follow up.

Materials and Methods

Study design and setting

This was a retrospective cohort study conducted on a sample of patients undergoing colposcopic examination and biopsy because of clinical suspicion for cervical lesion or/and abnormal cytology result which was performed at four tertiary gynecology and obstetrics education and research hospital between January 2009 and March 2019.

Table 1. — *Demographic and clinical characteristics of the patients.*

	n = 461
Age (year)	22.65 ± 1.30
Number of biopsies (median, range)	2 (0-7)
Cytology results	
Normal	54 (11.7%)
ASCUS	195 (42.3%)
LSIL	190 (41.2%)
HSIL	22 (4.8%)
HPV status	
Not screened	132 (28.6%)
Positive	67 (14.5%)
Negative	262 (56.8%)

ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; HPV: human papillomavirus.

Participants

Four-hundred sixty-one patients undergoing colposcopic examination and biopsy between the ages of 21-24 were included in the study. Data were collected retrospectively from the electronic medical database system of four hospitals that included ages, liquid-based smear results, HPV results, pathology reports, and follow-up (6 months, 1 year) records. Patients were informed prior to colposcopy and a signed written consent were taken for possible risks and allowing to use their data, in obedient to declaration of Helsinki. All colposcopic examinations and biopsies were performed by high-level skilled advanced colposcopist. A data worksheet was recorded at the end of colposcopy. All pathological specimens were performed by specialized gyneco-pathologists. After colposcopic biopsy patients were followed by cytology every 6 months for 12 months. The trial was approved by the local ethical committee (approval number: 274/2018).

Statistical analysis

Data were analyzed by SPSS (Version 20.0. 2011, IBM SPSS Statistics for Windows; IBM Corp. Armonk, NY, United States of America). The histogram and normality plots and Shapiro-Wilk normality test were used for data distribution analysis. Descriptive statistics (mean, standard deviation, median, range, percentage) were used in the analysis of quantitative data. Kruskal–Wallis tests and Fisher's exact tests were used to compare groups. A p-value 0.05 was considered as statistically significant.

Results

Demographic characteristics including ages, median number of cervical biopsies, cytology results, and HPV status were presented in Table 1; and colposcopy-guided biopsy results of 461 patients were presented in Table 2. Two patients (0.43%) had invasive cervical cancer. Endocervical curettage was performed in 294 (63.8%) patients. The results of endocervical curettage were normal in 273 (92.9%) women, CIN 1 in 13 (4.4%) women, CIN 2 in 4 (1.4%) women, CIN 3 in 3 (1%) women, and invasive cancer in 1 (0.3%) woman. Sixty-seven cases (14.5%) were positive for HPV (HPV 16 or/and 18, n = 45; other HPV types, n = 22). Twenty-eight (6.1%) of 461 patients underwent surgical procedures including cervical excisional procedure (n = 26) (5.7%) and radical hysterectomy (n = 2) (0.4%). Loop electrosurgical excision procedure (LEEP) was performed in all patients with CIN 3 (n = 19), and 7 of 32 patients with CIN 2. All of the patients who underwent LEEP had negative surgical margin both the endocervical and ectocervical margins. Mean cone size documented from the pathology reports of the patients was 1.62 ± 1.43 cm3. None of the patients with CIN 1 (n = 144) underwent excisional procedure. The cytology results of women with CIN 1 after 6 months from colposcopy-guided biopsy were atypical squamous cells of undetermined significance (ASCUS) (n = 11), and low-grade squamous intraepithelial lesion (LSIL) (n = 6). Additionally, the cytology results of women with CIN 1 after 12 months were ASCUS in 2 women, and LSIL in 2 women. Twenty-eight patients who underwent cervical excisional procedure or radical hysterectomy had any high-grade lesion throughout the follow-up period. The cytology results after 12 months from colposcopy-guided biopsy were high-grade intraepithelial lesion in 16 of 433 women who underwent follow-up (3.7%). The cytology results of 32 patients with CIN 2 after 6 and 12 months were presented in Table 3. There were no significant statistically differences between CIN 2 patients with and without treatment in terms of cytology re-

Table 2. — *Colposcopy-guided biopsy results of the patients.*

		Cervical biopsy results (n = 461)				
		No lesion (n = 264)	**CIN 1 (n = 144)**	**CIN 2 (n = 32)**	**CIN 3 (n = 19)**	**Invasive cancer (n = 2)**
Cytology results	**Normal (n = 54)**	40	13	1	-	-
	ASCUS (n = 195)	134	47	9	5	-
	LSIL (n = 190)	83	79	17	10	1
	HSIL (n = 22)	7	5	5	4	1
		57.30%	31.20%	6.90%	4.10%	0.40%

ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; CIN: cervical intraepithelial neoplasia.

Table 3. — *The cytology results of CIN 2 patients after 6- and 12-months follow-up.*

	Patients underwent follow up (n=25)	**Patients underwent LEEP (n=7)**	***p***
Patients with abnormal cytology results at 6 months follow up	1	0	1
Patients with abnormal cytology results at 12 months follow up	0	2	0.042

LEEP: Loop electrosurgical excision procedure.

sults at 6 months ($p = 1.00$). However, there were significant statistically differences between CIN 2 patients with and without treatment in terms of cytology results at 12 months ($p = 0.042$) (Table 3).

Discussion

Historically, a population based cervical screening program in Turkey was started in 2004 using the Papanicolaou (Pap) smear. However, organized population screening achieved annual coverage rates of only 1–2%. In 2013 a new HPV based screening strategy was developed for increased compliance rates. Women aged between 30 and 65 years ($\sim$ 16 million) are invited for HPV based screening by primary level health staff every five years. All screening processes are free of charge for the eligible individuals. Women under 30-year-old is still under opportunistic screening by Pap smear test and all of our cases referred colposcopic examination of our out patients colposcopy clinic. Thus, we could not demonstrate the abnormal cytology rates in this age group but the most of the abnormal cytology results under the age of 25 year were low-grade cytological abnormality. Abnormal Pap smear rate was reported 12% on 133,947 women aged 21–24 undergoing screening between 2003–2010 at Kaiser Permanente Northern California (KPNC) and 1.4% of them had high grade squamous intraepithelial lesion (HSIL) [10]. Abnormal Pap and/or HPV test result rates were 12.3% and 13.3% among women aged 25-29 and 30-64, and high grade cytologic findings are detected higher compared the women younger 25-year-old. (7.5% and %13.7, respectively) [11]. HSIL cytologic abnormality was detected 4.8% of the women under the age of 25 year with abnormal cytology results in present study. This rate is slightly higher compared the previous study and probably it can be related to use of referred cytologic abnormality for this analysis. Only one invasive cancer was diagnosed in women HSIL cytology and was clear cell pathology. $CIN2^+$ lesion rates were 41% of the HSIL cytology in our cohort. $CIN2^+$ lesions were detected in 10% of the patients with all kind of abnormal cytology or high-risk HPV DNA (+) women in present study.

In recent report, 41% of the patients had $CIN2^+$ lesion on biopsy results and cumulative 5-year risk of $CIN3^+$ and cancer for women aged 21-24 was calculated as 28% and was comparable to in those of older women. Another study published at 2010, which also included KPNC data, showed that untreated CIN 2 lesions less progression to CIN 3 was not common in the 1–2 years following the CIN-2 diagnosis [12]. In a database review, Fuchs *et al*. reported that 39% of adolescents with untreated CIN 2 showed regression to normal with 92% showing CIN 1 or less after 3 years. Only 8% had CIN 2 persistence or progression. Certainly, rates of cervical cancer are low in adolescents and young women supporting that progression of CIN 2 to cancer in this age group is extremely rare [13]. Surgical intervention was performed in 7 women with CIN 2 biopsy results. In addition to high regression rate of the observation group, significantly higher abnormal cytology results were detected in treatment group compared with observation group at 12th month cytologic evaluation. Nevertheless, it cannot be speculated that surgical excision could negatively affect the 12 months cytology. Seven patients who underwent LEEP had more than 1 involved quadrant according to initial pathology reports. So, it might affect the decision on the management and surgery might be preferred rather than follow up. In addition, more than 1 involved quadrant in patients who underwent LEEP could negatively affect the 12 months cytology.

Patients with clinical suspicion for cervical lesion but without abnormal cytology result had no CIN 3 or invasive cancer on the colposcopy directed biopsy specimen. On the other hand, 4.6% and 2.6% of the patients with AS-

CUS cytology had CIN 2 and CIN 3 lesions, respectively. Additionally, one of the patients with LSIL cytology had invasive cancer, 17 of the patients with LSIL cytology had CIN 2, and 10 of the patients with LSIL cytology had CIN 3.

Not all younger patients with ASCUS or LSIL were received a colposcopic examination. Reflex HPV testing could be performed for women aged 21-24 years with minor cytological abnormalities. But HPV testing is performed only at a few tertiary centers in women younger than 30 years of age in Turkey. Therefore, a colposcopic examination could be preferred. As the colposcope becomes more widespread in clinical practice, using a colposcope would be more attainable. Therefore, we recommend colposcopic examination when considering women aged 21-24 years with abnormal cytology including ASCUS, LSIL, and HSIL as a credible and feasible strategy.

The present study has some limitations which have to be pointed out. First, retrospective design and small number of cohorts can be viewed as limitations of the study. Additionally, not all of the patients included in this study tested for HPV and information about HPV subtype could not be presented for patients.

Conclusions

The management of cervical cytological abnormalities in women aged 21-24 years depends on the institutional decision whether follow up or colposcopy intervention. Reflex HPV testing could be a choice for women aged 21-24 years with minor cytological abnormalities. However, our current data demonstrated that colposcopy in addition to cytology is associated with increased detection of premalignant lesions of the cervix uteri even if not high-grade cytology. With the increased accessibility of colposcopy, colposcopic examination could be performed in women aged 21-24 years with ASCUS or LSIL due to possibility of high-grade squamous intraepithelial lesion and cervical invasive cancer.

Author contributions

Concept – B.P.G., B.G., C.K.K., M.E., D.S.A.; Design – B.P.G., B.G., C.K.K., M.E., I.A.O.; Analyses – B.P.G., C.K.K., M.E., S.G., E.K., I.A.O., D.S.A.; Supervision – B.P.G., B.G., S.G., E.K., S.S., D.S.A.; Materials – B.P.G., B.G., S.G., E.K., I.A.O., S.S.; Writer – B.P.G., B.G., S.S..

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Conflict of interest

The authors declare no conflict of interest.

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