

Original Article

Effect of intrauterine device on cervicovaginal smears and its association with calcified bodies: a retrospective study

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Abstract: Background and aim: Intrauterine device (IUD) which is one of the most effective contraception methods might lead to alteration in genital system flora and to reactive cellular changes due to its local irritant action. Rather rare findings in cervicovaginal smears are amorphous calcified and psammoma-like bodies. In this study, in cervicovaginal smears, we investigated the effects of IUD on epithelial cells and flora as well as the association of amorphous calcified and psammoma-like bodies (PBs) with IUD use. Methods: Papanicolaou (PAP)-stained smears of 484 cases who use IUD and 216 cases who do not use IUD were studied. Calcified bodies, genital infection and reactive-dysplastic cellular alterations were statistically compared between groups. Results: Amorphous calcified bodies, inflammation, Actinomyces and Candida species, squamous metaplasia, cells with cytoplasmic balloon like vacuoles, papillary structures and multinuclear giant cells differed significantly in cases using IUD than cases not using IUD. In IUD users, amorphous calcified bodies were observed more frequently in smears with inflammation, Actinomyces, squamous metaplasia, papillary structures and multinuclear giant cells. Additionally, cases who did not use IUD had less amount of amorphous calcified bodies. Conclusions: IUD use, along with infection, leads to exaggerated alterations in cells. Amorphous calcified bodies as well as Actinomyces might be detected in cases using IUD. Therefore, such findings might be helpful in interpretation of abnormal cytological features.

Keywords: Intrauterine device, amorphous calcified body, cervicovaginal smear

Introduction

Intrauterine device (IUD) is among the most practical and effective contraception methods [1]. Efficacy of IUD is shown in various studies, though it also has some unwanted effects [2, 3]. IUD, with its tail extending to vagina, leads to foreign cell reaction, forms a solid surface for bacterial colonization and might alter the flora of female genital system [4, 5]. Besides, due to local irritation and pressure effect, it might cause dense inflammatory response and reactive cytological changes. Those changes might be observed in cervicovaginal smears as metaplasia, cells with cytoplasmic giant vacuoles, multinuclear giant cells, papillary structures, and cells with scanty cytoplasm, irregular chromatin, and large nucleus (IUD cells) that mimic high grade squamous intraepithelial lesion (HSIL) [2, 6]. In addition, secondary to mechanical irritation, atypical glandular and atypical squamous cells might be detected [3].

In cases with IUD, another rare finding in cervicovaginal smears is amorphous calcified bodies. Occasionally, some of those calcified bodies named psammoma-like bodies (PBs) might be seen as fragmented, small concentric calcified bodies surrounded by macrophages [7-9].

In our study, we aimed to investigate the association of amorphous calcified bodies and PBs found in cervicovaginal smear with IUD use along with the effect of IUD on epithelial cells and flora.

Materials and methods

Clinicopathological data

The smears belonging to 484 cases that were examined in our Pathology Department between 2009-2013 and data on duration of previous IUD use was available (69%) were examined as well as random 216 cases who had not

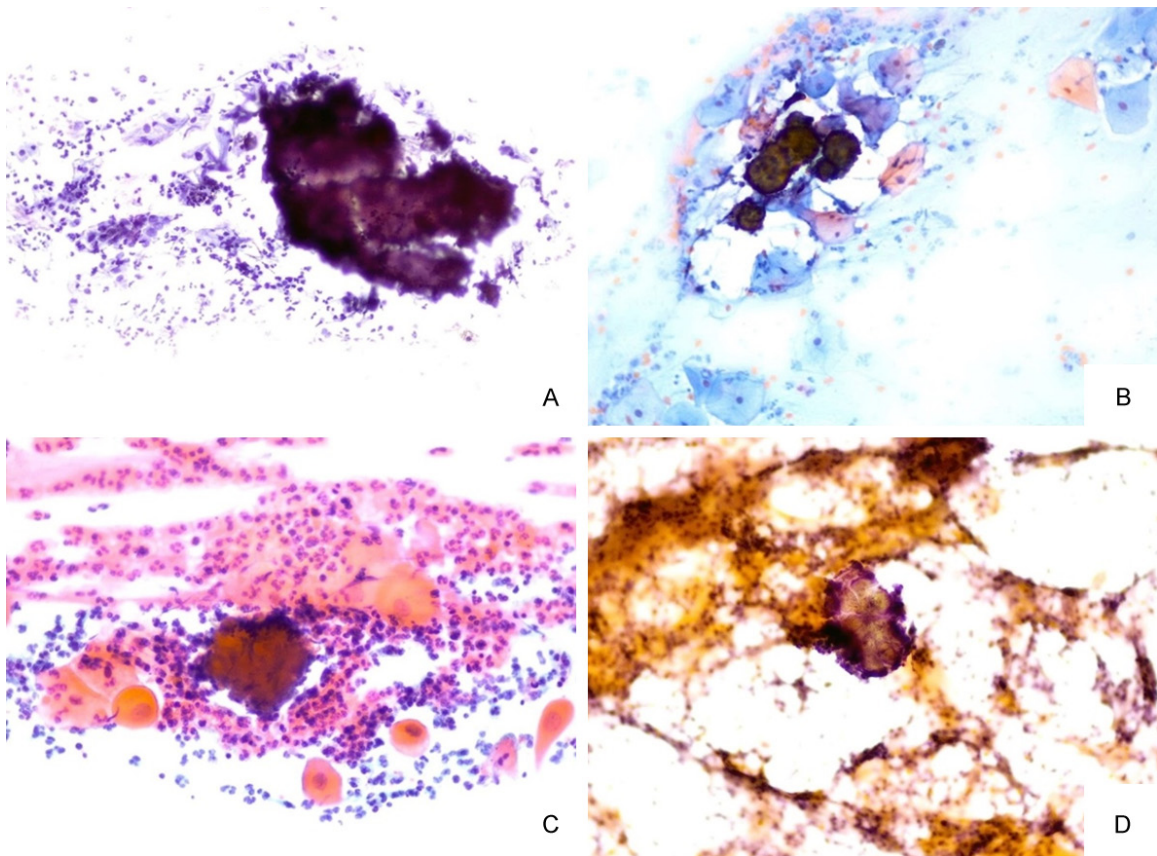


Figure 1. Calcified bodies in cervicovaginal smear. (A, B) Two-dimension calcified body that is fragmented and surrounded by polymorphonuclear leucocytes (A) and concentric calcification (B) (original magnification $\times 200$). (C) Small calcified fragment surrounded by polymorphonuclear leucocytes (original magnification $\times 400$). (D) Small concentric calcification resembling psammoma body (original magnification $\times 400$).

used IUD (31%). All of the study preparations were PAP-stained conventional smear samples. Inclusion criteria were to be in reproductive period and not having a history of drug use. Totally 700 smear preparations were re-evaluated according to Bethesda 2001 criteria, and density of inflammation, flora alterations including *Actinomyces*, bacterial vaginosis (BV), *Candida* species and *Trichomonas vaginalis* (TV), reactive and dysplastic changes occurring in squamous and glandular cells were examined [10]. Inflammation was graded as mild, moderate and severe depending on its density. Glandular cells that showed squamous epithelial cell alterations (atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells can not exclude HSIL (ASC-H), low-grade squamous intraepithelial lesion (LSIL) and HSIL) and nuclear enlargement, coarse chromatin, loss of polarity or pseudostratification were considered atypical glandular cells (AGC). Amorphous calcified structures and PBs that were reported in cytologies of cases using IUD were examined separately and recorded if they were found by themselves or together. Besides squamous metaplasia (SM) and tubal metaplasia (TM), cells with cytoplasmic giant vacuoles, multinuclear giant cells, papillary structures and IUD cells were examined.

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Statistical analysis

Our study was designed to detect 10% difference between 484 IUD positive and 216 IUD negative cases with $\alpha=0.05$ and $\beta=0.05$ error ratios. Power analysis was done with G*Power 3.1.

Categorical comparison between cases using and not using IUD was done by Chi-square test and if requirements for using Chi-square were not met, by Fisher's exact test. Since presence

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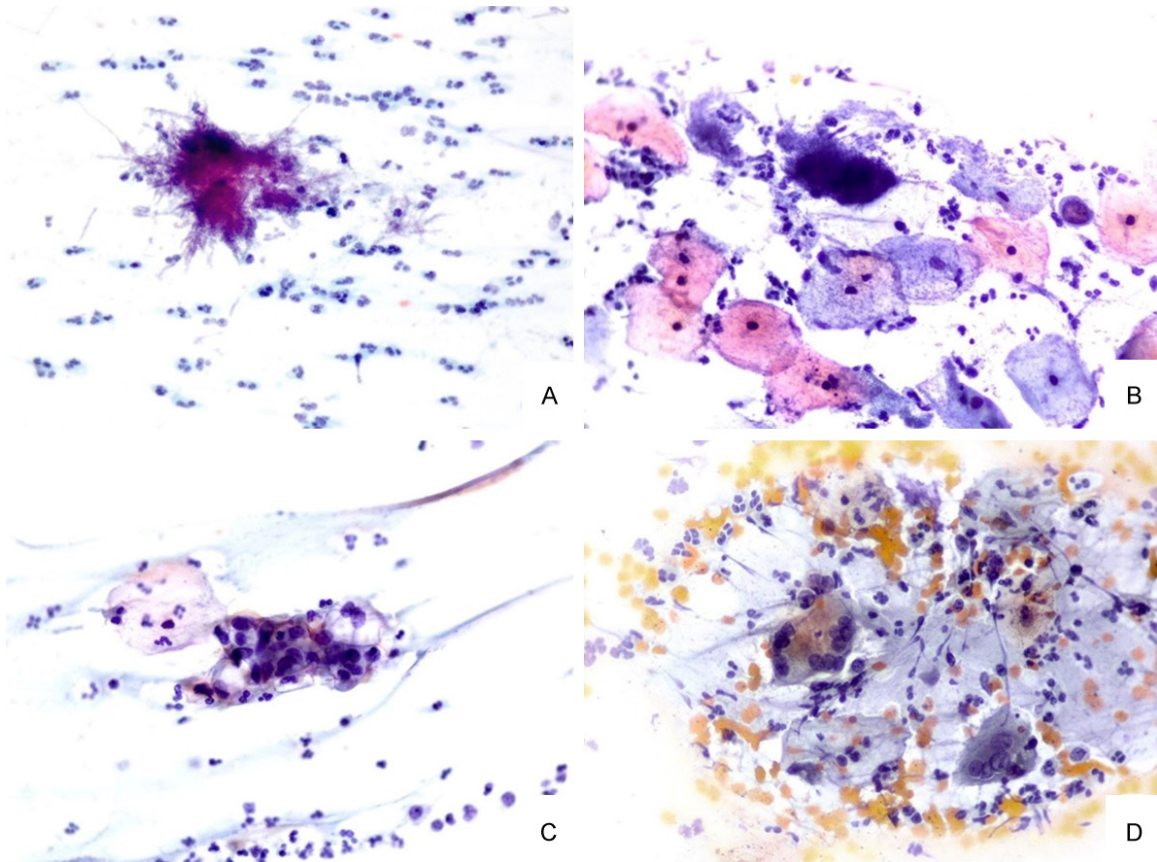


Figure 2. Reactive cytological changes associated with IUD. A. Actinomyces organisms with characteristic basophil spots surrounded by intertwined filament-type formations (original magnification $\times 400$). B. HSIL-like cells (IUD cell) on the right side and Actinomyces organisms on the left side (original magnification $\times 400$). C. Cluster of glandular cells with cytoplasmic vacuoles displacing nuclei (original magnification $\times 400$). D. Multinuclear giant cells (original magnification $\times 400$).

of calcified structures and alterations of flora in subgroups formed due to percentiles of durations of IUD use were categorical data, they were compared by Chi-square test.

Logistic regression analysis was done to show if parameters that are significantly high in cases using IUD compared to cases not using IUD were related with duration of IUD use. Results of logistic regression analysis were given with 95% confidence interval as relative risk (odds ratio) and significance (P) values. All statistical tests were performed with SPSS 17.0 (SPSS Inc., Chicago, USA) and significance level was $P < 0.05$ in all tests.

Results

Ages of the controls were between 18-51 (mean 37 ± 23), and ages of the cases in the study group were between 19-56 (mean 35 ± 7).

Results obtained from cases using IUD (Figures 1 and 2) and not using IUD as well as comparisons are presented in Table 1.

Since, in the IUD using group, median value of duration of IUD use was 48 months (25. percentile)-(75. percentile) duration of use was separated into 4 groups according to percentiles of distribution: < 24 months (I), 24-47 months (II), 48-83 months (III), ≥ 84 months (IV).

When parameters frequently seen in IUD use were evaluated regarding duration of IUD use; significant difference was not found between groups for inflammation ($P = 0.65$), *Candida* species ($P = 0.27$), SM ($P = 0.43$), cells with cytoplasmic giant vacuoles ($P = 0.63$), papillary structures ($P = 0.26$) and multinuclear giant cells ($P = 0.23$). However, in case of presence of calcified bodies ($P < 0.001$) and Actinomyces ($P = 0.02$), there was a significant difference

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Table 1. Comparison between the groups using and not using IUD

		IUD (-) (n=216)	IUD (+) (n=484)	P
Calcified body	Calcified body (-)	212 (98.1%)	316 (65.3%)	<0.001 ^{a,*}
	PBs	0 (0%)	1 (0.2%)	0.69 ^b
	Amorphous body	4 (1.9%)	160 (33.1%)	<0.001 ^{b,*}
	PBs+Amorphous body	0 (0%)	7 (1.4%)	0.1 ^b
Inflammation	Inflammation (-)	28 (13%)	7 (1.4%)	<0.001 ^{a,*}
	Mild (+)	89 (41.2%)	169 (34.9%)	0.12 ^a
	Moderate (+)	87 (40.3%)	266 (55%)	<0.001 ^{a,*}
	Severe (+)	12 (5.6%)	42 (8.7%)	0.17 ^a
Flora alterations	BV	8 (3.7%)	27 (5.6%)	0.35 ^a
	Candida species	5 (2.3%)	34 (7%)	0.01 ^{a,*}
	TV	2 (0.9%)	3 (0.6%)	0.64 ^b
	Actinomyces	0 (0%)	48 (9.9%)	<0.001 ^{b,*}
Reactive cell alterations	SM	63 (29.2%)	249 (51.4%)	<0.001 ^{a,*}
	TM	3 (1.4%)	3 (0.6%)	0.37 ^b
	SM+TM	2 (0.9%)	8 (1.7%)	0.73 ^b
	Giant cell	0 (0%)	45 (9.3%)	<0.001 ^{b,*}
	Papillary structures	2 (0.9%)	19 (3.9%)	<0.001 ^{b,*}
	Vacuolar cells	8 (3.7%)	91 (18.8%)	0.03 ^{a,*}
	IUD cells	3 (1.4%)	13 (2.7%)	0.41 ^b
Epithelial cell abnormalities	ASC-US	6 (2.8%)	26 (5.4%)	0.17 ^a
	LGSIL	1 (0.5%)	4 (0.8%)	0.51 ^b
	HGSIL	0 (0%)	1 (0.2%)	0.69 ^b
	ASC-H	0 (0%)	0 (0%)	NA
	AGUS	0 (0%)	6 (1.2%)	0.18 ^b

^aChi-square test, ^bFisher's exact test. *P<0.05.

Table 2. Risk assessment of duration of IUD (months) use by logistic regression analysis

Result	Duration of IUD use (month)		
	OR (Odds Ratio)	95% Confidence Interval	P
Calcified body	1.004	1.000-1.009	0.04*
Inflammation	0.999	0.982-1.017	0.94
Flora alterations	1.007	1.002-1.012	0.004*
Reactive cellular alterations	1.002	0.998-1.006	0.36

*P<0.05.

regarding durations of IUD use. When calcified structures were compared in subgroups, there wasn't any significant difference between Group I-II (P=0.27) and Group III-IV (P=0.09), but difference was significant between Grup II-III (P=0.004). Therefore, calcified bodies increased in cervicovaginal smears of the cases using IUD longer than 48 months. In presence of Actinomyces, significant difference was not seen between pairs of groups (P>0.05), but when subgroups I and II and III and IV were combined and compared as IUD use <48

months and ≥48 months, a significant difference was detected (P=0.01). According to these results, in cases using IUD for longer than 48 months, Actinomyces rate was higher.

Risk evaluations regarding duration of IUD use of the parameters that had significant increase depending on IUD use are presented in **Table 2**.

Furthermore, in every 1 month

of increase in duration of IUD use, detection of calcified bodies increased 0.4% and flora alterations increased 0.7% (P=0.04).

Relations between parameters that increased significantly by IUD use and presence of calcified bodies are shown in **Table 3**.

Discussion

In cervicovaginal smears of the women using IUD as a contraceptive method, amorphous cal-

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Table 3. Association of calcified bodies observed in IUD users with significant parameters

		Calcified body (-)	Calcified body (+)
Inflammation (P=0.002) ^{a,*}	Inflammation (-) (n=7)	7 (100%)	0 (0%)
	Mild (n=169)	122 (72.2)	47 (27.8%)
	Moderate (n=266)	168 (63.2%)	98 (36.8%)
	Severe (n=42)	19 (45.2%)	23 (54.8%)
Actinomyces (P=0.04) ^{a,*}	Absent (n=48)	291 (66.7%)	145 (33.3%)
	Present (n=436)	25 (5.2%)	23 (4.9%)
Candida species (P=0.41) ^a	Absent (n=450)	296 (65.8%)	154 (34.2%)
	Present (n=34)	20 (58.8%)	14 (41.2%)
SM (P<0.001) ^{a,*}	Absent (n=235)	176 (74.9%)	59 (25.1%)
	Present (n=249)	140 (56.2%)	109 (43.8%)
Vacuolar cells (P=0.40) ^a	Absent (n=393)	260 (66.2%)	133 (33.8%)
	Present (n=91)	56 (61.5%)	35 (38.5%)
Papillary structures (P=0.003) ^{a,*}	Absent (n=679)	518 (76.3%)	161 (23.7%)
	Present (n=21)	10 (47.6%)	11 (52.4%)
Giant cell (P<0.001) ^{a,*}	Absent (n=655)	511 (78%)	144 (22%)
	Present (n=45)	17 (37.8%)	28 (62.2%)

^aChi-square test. *P<0.05

calcified bodies accompanying reactive cellular alterations and rarely, PBs might be recognized [3, 8, 9, 11, 12]. Studies reveal that those amorphous calcified bodies are derived from a progressively calcifying layer that cover IUD surface [13-15]. This in utero calcification process that is found on surface of more than 50% of IUDs, and that begins as early as 6th month was first described at 1980s [16, 17]. Its content and morphological features were investigated by methods such as electron microscopy, X-ray microprobe and ultramicrochemical stone analysis. Calcified shell layer was made of high amount of acellular structure composed of calcium carbonate, and cellular structure composed of erythrocytes, polymorphonuclear leucocytes and also, fibrillary material [13-15, 17, 18]. Moreover, studies revealed that inflammation accelerated formation of calcified layer and with longer duration of use, broader area of deposits were found on the surface of IUD [14, 15]. However, it was stated that amount of calcified layer depended on not only surface width, but also on personal metabolic differences [15]. Interestingly, on literature survey, scant amount of studies were focused on such calcified structures observed in cervicovaginal smears [3, 7]. Generally, available studies were done on calcified layers on IUDs that were taken out [13-15]. However, apart from PBs detected in smears related with IUD use, we didn't find a study that investigated the associ-

ation between amorphous calcified structures and cellular alteration due to IUD use.

Although PBs were seen in 1.4% of cases using IUD, in cases that had a duration of use of 24 months or more, PBs were described more frequently [7]. In another study including 1000 cases, only 3 cases included PBs [11]. PBs, although rare in cervicovaginal smears, might reflect ovarian and in a lower degree endometrial and peritoneal neoplasia [19, 20]. Age of the case (over 45), clinical features (postmenopausal bleeding and abnormal clinical findings) and accompanying cellular atypia in cervical smears are important factors suggesting malignancy in presence of PBs [19-22]. In some studies, PBs were related with benign conditions such as chronic salpingitis, tuberculosis endometritis, endometrial hyperplasia, endometrial polyp, peritoneal endosalpingiosis, ovarian inclusion cysts and adenofibroma [12, 20, 23]. In our study, 0.2% cases who use IUD included PBs, 33.1% had amorphous calcified structures and 1.4% had both PBs and amorphous calcified structures. For the cases that did not use IUD, 1.9% showed amorphous calcified structures. There was a significant relation between amorphous calcified bodies and cases using IUD but not between cases not using IUD (P<0.001).

Our study results revealed a significant relation between amorphous calcified structures and

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duration of IUD use ($P=0.004$). Results showed that such structures were more frequent in cases using IUD for more than 48 months. Besides, for every 1 more month of IUD use, presence of calcified bodies in smears also significantly increased ($P=0.04$).

IUD negatively influences female genital system flora by causing an inflammatory response [4, 5]. Some studies report that long term IUD use increased cervical infection risk [24, 25] and calcified layer on IUD increased bacterial and fungal infection risk significantly [15]. In literature, in cases using IUD, specific cervicovaginal infection was seen at a rate of 29% [4, 5]. In our study specific infection rate was 23.1%. For every 1 month longer IUD use, flora alterations in cervicovaginal smear increased 0.7% ($P=0.004$). In our study, since there was a significant relation between moderate inflammation and IUD use ($P=0.001$) and also since 63.7% of the cases had moderate and severe inflammation, we conclusively stated that IUD increased the risk of infection. In literature, BV (12-42%), TV (7.6-32%), *Candida* species (6.4-28%) and *Actinomyces* (2-11%) were respectively reported as causes of specific cervicitis in IUD users [6, 26]. In another study, *Actinomyces* significantly increased after 24 months [7, 27]. In our study causes of infection were respectively, *Actinomyces* (9.9%), *Candida* species (7%), BV (5.6%) and TV (0.6%). Incidence rates of *Actinomyces* and *Candida* species were in accordance with literature and we found a relation between IUD use and *Actinomyces* and *Candida* species ($P<0.001$). In our study which was done on cases living in areas with low social and economical levels, prevalence rates of BV and TV were less than reported in literature, and this was suggested to be related with monogamy or unconscious antibiotic use. According to our results duration of use was also significant. There was a relation between IUD and presence of *Actinomyces* ($P=0.002$) and use of more than 48 months led to an increase in presence of *Actinomyces* ($P=0.01$).

Cellular alterations related with IUD use occur after chronic irritation of minimum 10-12 weeks or more IUD use [2]. SM and TM, hyperplastic papillary endocervical cell groups, multinuclear giant cell forms, cells with balloon like cytoplasmic vacuoles and IUD cells are some of those alterations [2, 6, 28]. Especially, IUD cells might

be HSIL-like and occasionally bizarre looking. Major source of those cells is endometrial surface epithelium [2, 29]. In our study, most frequently observed reactive responses in IUD users were significantly more SM (51.4%) and cell with balloon like cytoplasmic vacuoles (18.8%), multinuclear giant cell forms (9.3%) and papillary structures (3.9%) which were detected more often than cases not using IUD (respectively $P<0.001$, $P<0.001$, $P=0.03$, $P<0.001$). Those results were in consistency with literature data [6, 30].

The relation of presence of IUD with development of cervical and endometrial neoplasia is under investigation for a long time. As a result, it is reported that IUD is not related with occurrence of high grade dysplasia or carcinoma, and also, Copper-IUD has a decreasing effect on invasive cervical cancer risk [31]. As well, presence of IUD does not carry a significant risk for endometrial carcinoma [32, 33]. By stimulating inflammatory response, it eliminates abnormal or precancerous endometrial epithelial cells and has an lowering effect on estrogen receptor concentration [34, 35]. To be acquainted with alterations in endocervical and endometrial cells that are localized near IUD bodies is important in order to discriminate dysplastic and neoplastic lesions [2]. Consensus on effect of IUD on squamous cells is that, presence of IUD is not related with development of squamous atypia [28, 36]. However, some authors suggest that long term IUD use leads to development of dysplasia and hyperplasia [37]. Our study had a retrospective design and it did not cover a period that might show a statistical significance for neoplasia. In our study, similar to the literature, there wasn't any significant difference in cases using IUD compared to control group for development of cervical dysplasia. In cases using IUD, although squamous intraepithelial lesion rate was high (6.4%), there wasn't any statistically significant difference with control group (3.3%). Besides, in 1.2% of cases using IUD, AGC were observed with no statistically significant difference than control group. Observation of high ASCUS rate in study group might reflect reactive cellular alterations that are derived from inflammation and vaginal flora alterations.

As a conclusion, in our study, the rate of amorphous calcified bodies, inflammation, Actino-

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myces and *Candida* species, SM, cells with cytoplasmic balloon like vacuoles, papillary structures and multinuclear giant cell forms differed significantly in cases using IUD than cases not using IUD. In IUD users, smears with amorphous calcified bodies, inflammation, *Actinomyces*, SM, papillary structures and multinuclear giant cell forms were observed in a high percent. Cytomorphologic findings due to IUD were emphasized and also amorphous calcified bodies observed in smears were investigated. To keep in view that such bodies as well as presence of *Actinomyces* are suggestive of IUD use might prevent diagnosis of false positive dysplasia/neoplasia in smears with exaggerated cytomorphologic alterations.

Disclosure of conflict of interest

None.

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