Original Article

DOI: 10.7860/JCDR/2020/44594.13995

Is there a Relationship between Combined Oral Contraceptive Use and Intrauterine Device Use with Abnormal Smear Results and Cervical Atypia?

Obstetrics and Gynaecology Section

SELÇUK KAPLAN

ABSTRACT

Introduction: The relationship between the use of contraceptive method and the presence of Human Papilloma Virus (HPV) persistent infection and precancerous cervical lesions has not been fully established.

Aim: To investigate the frequency of cervical atypia and risk factors affecting it in women using Combined Oral Contraceptive (COC) and Copper-Intrauterine Device Use (Cu-IUD).

Materials and Methods: A retrospective study was conducted in a tertiary centre between 2017 to 2019, involving 835 patients using Cu-IUD and 538 patients using COC. Age, obstetric data, high-risk HPV type positivity, education level, location, occupation, Body Mass Index (BMI), smoking, cervical cytology results and colposcopic biopsy results were noted for each group. Statistical Package for the Social Sciences (SPSS) version 22.0 program was used to analyse the data. Pearson chi-square test and multivariate binary logistic regression test were performed. Model compatibility was good in binary logistics test (omnibus test $p<0.001$). The $p<0.05$ value was considered statistically significant.

Results: The frequency of Cervical Intraepithelial Neoplasia I (CIN I) lesions increased in women using Cu-IUD ($p=0.038$), while the frequency of CIN II+ lesions increased in COC users. The use of COC increased the risk of CIN II+ ($p=0.014$). High-risk HPV type positivity was common in those using COC ($p<0.05$). In addition, age group 40-51 years, education level being primary, being multiparous, urban location, high risk HPV positivity were other risk factors for the presence of cervical atypia ($p<0.05$).

Conclusion: The risk of CIN I increased in those using Cu-IUD, while the risk of CIN II+ increased in those using COC.

Keywords: Contraception, Copper intrauterine devices, Human papillomavirus, Pap smear

INTRODUCTION

The most commonly used contraceptive methods in Turkey are Cu-IUD and COC [1]. Although high risk Human Papilloma Virus (HPV) positivity is the major risk factor for the development of cervical atypia, *Chlamydia trachomatis* infection, smoking, obesity, nulliparity and COC use are other risk factors [2,3]. These lesions are known as CIN grade II and III and Adenocarcinoma In Situ (AIS) [4]. It has been supported by many researches that the use of Cu-IUD reduces the risk of HPV infection [5,6]. In addition, Cu-IUD is stated to be a method that can be used not only as a contraceptive method but also to prevent HPV infection persistence [7]. In contrast, a new study investigating the frequency of development of precancerous cervical lesions in women using Levonorgesterone İntrauterine Device (LNG-IUD) and women using Cu-IUD has been shown to increase the risk of developing CIN II lesions and also in women using LNG-IUD, but there is no association with CIN III lesions [8]. Despite many different views the use of COC is still a risk factor for the development of precancerous cervical lesions today [8-10].

The aim of this study was to investigate the frequency of cervical atypia and risk factors affecting it in women using COC and Cu-IUD.

MATERIALS AND METHODS

This study was a retrospective study involving patients who reported to Adıyaman University Gynaecology and Family Planning polyclinics from January 2017 to December 2019. The study was approved by the Adıyaman University Non-Interventional Clinical Research Ethics Committee (No: 2019 / 9-1).

Sample Size Calculation

The minimum sample size for each of the two groups was calculated using the formula [11]. $n=D\ (z)^2\ p\ (1-p)/d^2$ where, n=minimum sample size at the 95% confidence level; Z=the standard deviation, D: design effect usually set at 2 [12]; d=precision: the difference between the true population rate and acceptable sample rate, set at 0.05; p=population prevalence from a previous study: 0.058 [13]. The minimum sample size (n) was calculated to be 168. In this study, considering the error rate of 20%, the sample finally taken in each group was 202.

Inclusion criteria: the use of Cu-IUD or COC as a contraceptive method, and accessibility to sociodemographic and obstetric data, cervical cytological reports, HPV test and colposcopic biopsy reports.

Exclusion criteria: Subjects under the age of 21, having received corticosteroid and/or other immunosuppressive treatment in the past one year, having diabetes mellitus, history of malignancy, history of chemotherapy/radiotherapy, history of cervical pathology (colposcopic biopsy, Loop Electrosurgical Excision Procedure (LEEP) konisation, cold ablation etc.,) were excluded. Patients who did not give information about the contraceptive methods they used or who did not have regular follow-up data were also excluded from the study.

In the light of these criteria, 1373 patients whose data were fully accessed were included in the study. Eight hundred thirty five patients included in the study used Cu-IUD (Group A) as contraceptive use method and 538 patients were using COC (Group B). Demographic characteristics such as age, obstetric data (parity), education level, occupation, smoking history, BMI, and duration of contraceptive use were noted. The genital examination findings of the patients were noted. The presence of genital wart, cervical cytology results, HPV tests results and colposcopic biopsy results were also noted.

Cervical cytology results were classified according to the Bethesda system. The corresponding epithelial cellular abnormalities, most

notably: Atypical Squamous Cells of Undetermined Significance (ASCUS), Low Grade Squamous Intraepithelial Lesions (LSIL), High-Grade Squamous Intraepithelial Lesions (HSIL), Atypical Squamous Cells cannot exclude HSIL (ASC-H) and Atypical Glandular Cells (AGC) were reported according to the Bethesda system [14]. Colposcopic biopsy was performed on those whose cytology results were abnormal and/or infected with high-risk HPV types [3]. Biopsy results were classified into three grades: CIN I, CIN II and CIN III equivalent to mild, moderate and severe dysplasia respectively; and carcinoma in situ [4]. Here, CIN II+ is used for patients with moderate to severe dysplasia and carcinoma insutu.

STATISTICAL ANALYSIS

The data were analysed with SPSS v22 (SPSS Inc., Chicago, USA). Qualitative data were expressed as frequency, percentage, median (minimum-maximum), and mean±standard deviation. Pearson chi-square test and binary logistic regression test were used for data analysis. A p-value of <0.05 was considered statistically significant.

The omnibus test was performed to determine the compatibility of the binary logistic regression test model and its value in predicting the analysis. Omnibus test showed the compatibility of the model (p<0.001).

RESULTS

All women participating in the study were married, monogamous and sexually active. The age distribution of the participants ranged from 21-51 years, and the mean age was 39.19±14.9 years for the group using Cu-IUD and 31.83±12.71 years for the group using COC [Table/Fig-1]. The prevalence of cervical atypia was 17.96% (150) in those using Cu-IUD and 17.65% (95) in those using COC.

Variables	Cu-IUD (n=835)	COC (n=538)
Mean age (years)	39.19±14.91	31.83±12.71
21-29	102	257
30-39	289	179
40-49	271	67
>50	173	35
Parity		
≤1	283	244
≥2	552	294
Mean duration of usage (year)	5.92±2.27	3.04±1.82
Residence		
Rural	683	251
Urban	152	287
Educational level		
Lower secondary school	178	41
Secondary school and above	381	97
Undergraduate	233	293
Graduate	43	107
Occupation		
Unemployed	293	58
Officer	107	118
Worker	229	124
Health employee	114	121
Teaching	92	117
HrHPV positivity		
Present	65	95
Absent	770	443
Genital wart		
Present	114	42
Absent	721	496
BMI (kg/m²)		
<25	294	137
25-29.99	351	327
≥30	190	74
Smoking		
Present	327	241
Absent	508	297

[Table/Fig-1]: Sociodemographic and obstetric data in Cu-IUD and COC users.
Cu-IUD: Copper intrauterine device users; COC: Combined oral contraceptive users; BMI: Body mass index; HrHPV: High risk human papillomavirus

While comparing the women using COC and women using Cu-IUD, positivity of high-risk HPV types was common among women using COC p<0.001. In addition, when the colposcopic biopsy results were examined, the incidence of CIN I was higher in women using Cu-IUD, and the frequency of CIN II+ was higher in women using COC (p=0.006) [Table/Fig-2].

Variables	COC (n=538)	Cu-IUD (n=835)	p-value
HPV results			
Negative	443	770	<0.001
HrHPV positivity	95	65	
Cytology results			
Negative	403	700	<0.001
ASCUS	105	55	
LSIL	15	70	
HSIL	15	10	
Colposcopic biopsy			
Negative	443	685	0.006
CIN I	46	103	
CIN II+	49	47	

[Table/Fig-2]: High risk HPV frequencies, cytology results and colposcopic biopsy results in patient groups using Cu-IUD and COC as a contraceptive method.
CIN: Cervical intraepithelial neoplasia; Cu-IUD: Copper intrauterine device users; COC: Combined oral contreceptive users; HrHPV: High risk human papilloma virüs

Frequency of CIN I and CIN II and above (CIN II+) lesions were increased in women aged 40-51 years, women with positive high-risk HPV test results, multiparous women, urban residents (p<0.001) [Table/Fig-3].

When the relationship between the contraceptive method and cervical atypia was investigated, the frequency of CIN I lesions increased in women using Cu-IUD (p=0.038), while the frequency of CIN II+ lesions increased in COC users (p=0.014) [Table/Fig-3].

DISCUSSION

In this study, compared to women using Cu-IUD and using COC as a contraceptive method, the risk of CIN I in women using Cu-IUD and CIN II+ in women using COC was found to be increased. Moreover, being in the age group of 40-51 years for the development of CIN lesions, positivity of high-risk HPV types, secondary education level, multiparity, being unemployed and urban location were identified as risk factors.

It has been reported in previous publications that there is a negative relationship between the use of Cu-IUD and the development of cervical cancer [6,15]. In a new meta-analysis examining the relationship between Cu-IUD use and cervical cancer; cervical cancer has been reported to be less common in women using Cu-IUD [8]. In a study between a group of women using Cu-IUD and two women who did not use contraceptive methods; there was no significant relationship between abnormal cytological results and Cu-IUD [16]. This study is different from the earlier studies. Firstly, the study was done at single centre and includes homogeneous group of patients. Earlier studies have included large group of patients, patients who had multiple

	CIN I	CIN II+	OR_1 (%95 CI)	OR_2 (%95 CI)	p1	p2
Age						
21-39	21	17	0.08 (0.05-0.13)	0.12 (0.07-0.21)	<0.001	<0.001
40-51	128	79	11.75 (7.29-18.92)	8.06 (4.71-13.78)		
Contraceptive						
IUD	103	47	1.47 (1.02-2.12)	0.59 (0.39-0.90)	0.038	0.014
COC	46	49	0.67 (0.47-0.97)	1.68 (1.10-2.54)		
Parity						
≤1	21	13	0.23 (0.14-0.37)	0.23 (0.12-0.42)	<0.001	<0.001
≥2	128	83	4.29 (2.67-6.90)	4.30 (2.37-7.80)		
HPV positive						
HrHPV DNA +	47	83	6.33 (4.19-9.55)	167.08 (86.94-321.08)	<0.001	<0.001
HrHPV DNA -	102	13	0.15 (0.10-0.23)	0.006 (0.003-0.012)		
Education level						
≤Primary	34	44	0.25 (0.16-0.37)	0.80 (0.53-1.22)	<0.001	0.317
≥Secondary	115	52	3.99 (2.68-5.95)	1.23 (0.81-1.87)		
Residence						
Rural	43	23	0.15 (0.10-0.24)	0.12 (0.07-0.20)	<0.001	<0.001
Urban	106	73	6.33 (4.04-9.24)	8.60 (5.29-13.97)		
Occupation						
Unemployed	126	77	2.00 (1.26-3.18)	1.42 (0.84-2.38)	0.003	0.181
Employed	23	19	0.49 (0.31-0.79)	0.70 (0.41-1.17)		

[Table/Fig-3]: Binary logistic regression test results for colposcopic biopsy.
CIN: Cervical intraepithelial neoplasia; Cu-IUD: Copper intrauterine device users; COC: Combinedoral contreceptive users; HrHPV: High risk human papilloma virüs; OR: Odds ratio; C.I.: Confidence interval; p1: Risk factors p-values investigated for CIN I; p2: Risk factors p values investigated for CIN II+

partners and a different age at first intercourse. All women in this study were married and monogamous. This homogeneity may have implications on the results. A recent large-scale study has shown to increase the risk of CIN II+ in women using LNG-IUD, and there was a tendency to diminish the risk of CIN II+ in women using Cu-IUD [10]. The results of this study are coherent with the previous study, as the risk of CIN II+ is shown to decrease in women using Cu-IUD.

In previous studies, Bagchi S et al., and Nayak SR et al., the increase in the frequency of ASCUS and LSIL in Cu-IUD users has been shown to be 2 and 3 years of use, respectively [17,18]. Similarly, the frequency of CIN I lesions increased in those using Cu-IUD in this study (the average usage time of Cu-IUD in the present study was 5 years).

A recent meta-analysis of 33 substances including COC, Depot Medroxyprogesterone Acetate (DMPA), Cu-IUD, LNG-IUD and other methods; could not ascertain a clear relationship between COC and HPV infection [19]. Nielsen A et al., has reported that high-risk HPV infections are more common in COC users, and have shown that COC change susceptibility or immune response to HPV infections [20]. A recent study in Nigeria reported that the incidence of CIN II lesions increased in COC users [21]. Moreover, in a recent study by Xu H et al., COC use has been shown to increase the risk of CIN II and III [22]. In a study by Loopik DL et al., it was shown that the risk of CIN III increased in COC users compared to IUD users [23]. Moreover, in another study, Adhikari I et al., stated that the risk of ASCUS and LSIL decreases the risk of CIN I and cytological atypia with the use of COC, and that COC use may be protective against CIN I lesions [9]. In this study, the risk of CIN I was decreased in COC users.

The strength of the study lies in evaluating not only the contraceptive methods, but also the other risk factors associated with cervical atypia; and it is among the few studies from Turkey.

Limitation(s)

This research had some limitations. First, the present study was retrospective and single-centered study. There may be deficiencies in the retrospective analysis of the data. When the sexual behaviours of the patient groups were questioned, they all stated that they were married and monogamous. This homogenicity of the group should be considered before applying this data to larger homogeneous population.

CONCLUSION(S)

It has been shown that the use of Cu-IUD decreases the risk of CIN II+ lesions by increasing the risk of CIN I, while the use of COC decreases the risk of CIN I by increasing the risk of CIN II+. In addition, although the most important risk factor for the development of cervical atypia is the positivity of high-risk HPV types, it should be remembered that sociodemographic features are also important risk factors.

Acknowledgement

The author would like to thank the Adiyaman University Pathology Department for providing access to the data.

REFERENCES

[1] Gavas E, İnal S. Türkiye'de kadınların aile planlaması yöntemleri kullanma durumları ve tutumları: Sistematikderleme. Sağlıkve Yaşam Bilimleri Dergisi, Yıl. 2019, Cilt 1, Sayı 2, s.37-43.
[2] de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al., Human papillomavirus genotype attribution in invasive cervical cancer: A retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11:1048e-56.
[3] Castellsague X, Munoz N. Chapter 3: Cofactors in human papillomavirus carcinogenesis-Role of parity, oral contraceptives, and tobacco smoking. J Natl Cancer Inst Monogr. 2003:20-28.
[4] Buckley CH, Butler BE, Fox H. Cervical intraepithelial neoplasia. J Clin Pathol. 1982;35:14459413.
[5] Averbach SH, McCune KS, Shiboski S, Moscicki AB. The effect of intrauterine devices on acquisition and clearance of human papillomavirus. American Journal of Obstetrics and Gynaecology. 2017;216(4):386.e1-386.e5.
[6] Gonzalez MA, Nasarre BL, Salazar F, Varillasa D, Cristobala I. Influence of intrauterine dispositive in human papillomavirus clearance. European Journal of Obstetrics and Gynaecology. 2019;232:65-69.
[7] Cortessis VK, Barrett M, Wade NB, Enebish T, Perrigo JL, Tobin J, et al. Intrauterine device use and cervical cancer risk: A systematic review and meta-analysis. Obstet Gynaecol. 2017;130:1226-36.
[8] Averbach S, Silverberg MJ, Leyden W, Smith-McCune K, Raine-Bennett T, Sawaya GF. Recent Intrauterine device use and the risk of precancerous cervical lesions and cervical cancer. Contraception. 2018;98(2):130-34.
[9] Adhikari I, Eriksson T, Luostarine T, Lehtinen M, Apter D. The risk of cervical atypia in oral contraceptive users. Eur J Contracept Reprod Health Care. 2018;23(1):12-17.
[10] Ajah LO, Chigbu CO, Ozumba BC, Oguanuo TC, Ezeonu PO. Is there any association between hormonal contraceptives and cervical neoplasia in a poor Nigerian setting? Onco Targets Ther. 2015;8:1887-92.
[11] Le CT. Introductory Biostatistics, New Jersey: Wiley İnterscience; 2003;451-54.
[12] Basol G. Scientific research process and method. Kılıc, O. Cinoglu, M. (Editors). Scientific research methods. 2008. Pp. 113-43. Istanbul: Licance Publishing.
[13] Ajah LO, Chigbu CO, Ozumba BC, Oguanuo TC, Ezeonu PO. Association of Intrauterine Device (IUD) and cervical neoplasia- A study in a poor nigerian population. J Clin Diagn Res. 2016;10(6):QC05-QC8. doi:10.7860/JCDR/2016/18328.8049).
[14] Bergeron C. The 2001 Bethesda system. Salud Publica Mex. 2003;45:(3):340-44.
[15] Moscicki A, Schiffman M, Franceschi S. The natural history of human papillomavirus infection in relation to cervical cancer in: David Jenkins, XavierBosch (Eds.) Human Papillomavirus: Proving and Using a Viral Cause for Cancer book 1st Edition; Academic Press (1stpp: 149-160).

[16] Castellsague X, Diaz M, Vaccarella S, de Sanjosé S, Muñoz N, Herrero R, et al. Intrauterine device use, cervical infection with human papillomavirus, and risk of cervical cancer: A pooled analysis of 26 epidemiological studies. Lancet Oncol. 2011;12:1023-31.
[17] Bagchi S, Sah S, Agrawal T. Effect of intrauterine copper device on cervical cytology and its comparison with other contraceptive methods. Int J Reprod Contracept Obstet Gynaecol. 2016;5(8): 2795-98.
[18] Nayak SR, Chaitanya LL, Radhika P. Clinicocytological study in copper-T users J Obstet Gynaecol India. 2007;57(3):231-33.
[19] Deese J, Pradhan S, Goetz H. Contraceptive use and the risk of sexually transmitted infection: Systematic review and current perspectives. Open Access Journal of Contraception. 2018;9:91-112.
[20] Nielsen A, Kjaer SK, Munk C, Osler M, Iftner T. Persistence of high-risk human papillomavirus infection in a population-based cohort of Danish women. J Med Virol. 2010;82:616-23.
[21] Nyam YE, Anzaku AS, Emmanuel I, Maradona IE, Kenneth EC, Haruna DP, et al. Innocent Comparative Study of Precancerous Lesions of the Uterine Cervix Among Users and Non-Users of Combined Oral Contraceptive Pills in Jos, Nigeria. International Journal of Clinical Oncology and Cancer Research. 2018;3(3):35-40.
[22] Xu H, Egger S, Velentzis LS, O'Connell DL, Banks E, Darlington-Brown J, et al. Hormonal contraceptive use and smoking as risk factors for high-grade cervical ıntraepithelial neoplasia in unvaccinated women aged 30-44 years: A case-control study in new South Wales, Australia. Cancer Epidemiol. 2018;55:162-69. doi: 10.1016/j.canep.2018.05.013.
[23] Loopik DL IntHout J, Melchers WJG, Massuger LFA, Bekkers RLM, Siebers AG. Oral contraceptive and intrauterine device use and the risk of cervical intraepithelial neoplasia grade III or worse: A population-based study. European Journal of Cancer. 2020;124:102e-109.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Obstetrics and Gynaecology, Adıyaman University, Adıyaman, Merkez, Turkey.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Selçuk Kaplan,
Altınşehir Mahallesi Ikidam Cad. Zümrüt Gold City 5 kat: 4 No:7, Adıyaman, Merkez, Turkey.
E-mail: kaplan_2384@hotmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 10, 2020
- Manual Googling: Jun 20, 2020
- iThenticate Software: Aug 17, 2020 (13%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Apr 09, 2020**
Date of Peer Review: **May 15, 2020**
Date of Acceptance: **Jun 23, 2020**
Date of Publishing: **Sep 01, 2020**