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Pelvic inflammatory disease and contraception: a cross-sectional study in tertiary center

Pelvik inflamatuvar hastalık ve kontrasepsiyon: üçüncü basamak merkezde kesitsel bir çalışma

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ABSTRACT

Aim: To investigate the relationship between the contraceptive methods used in the patient population treated for pelvic inflammatory disease (PID) in a tertiary center with clinical and laboratory features and clinical outcome of PID.

Material and Method: This is a cross-sectional study using the anamnesis, examination findings, microbiological and pathological evaluation results of vaginal and cytological samples recorded in the hospital database of 974 patients treated with a diagnosis of PID in a tertiary center between 2017 and 2019.

Results: Copper-intrauterine device (Cu-IUD) was the most commonly used contraceptive method in women with a history of PID. When the cervicovaginal culture results are evaluated; *E.coli* positivity was more frequent in patients using CU-IUD and levonorgestrel IUD (LNG-IUD) (<0.001). The frequency of reproduction was higher in Group B *Streptococcus* (<0.001) and other *Streptococcus* species (=0.006) in those using condoms. While *Staphylococcus* (=0.041) and *Chlamydia trachomatis* positivity was higher in combined oral contraceptives (COC) users, *C. Trachomatis* growth was frequent in depot medroxyprogesterone acetate (DMPA) users (<0.001). Re-hospitalization was more common in the DMPA group compared to the other groups (p=0.008).

Conclusion: Contraceptive methods may affect the genital flora and may be a predisposing factor for the development of PID or prevent the development of PID.

Keywords: Contraceptive agents, intrauterine devices, long-acting reversible contraception, pelvic inflammatory disease

ÖZ

Amaç: Üçüncü basamak bir merkezde pelvik inflamatuvar hastalık (PID) için tedavi edilen hasta popülasyonunda kullanılan kontraseptif yöntemler ile PID'nin klinik ve laboratuvar özellikleri ve klinik sonuçları arasındaki ilişkiyi araştırmak.

Gereç ve Yöntem: Üçüncü basamak bir merkezde 2017-2019 yılları arasında PID tanısı ile tedavi edilen 974 hastanın hastane veri tabanına kaydedilen anamnez, muayene bulguları, vajinal ve sitolojik örneklerin mikrobiyolojik ve patolojik değerlendirme sonuçlarının kullanıldığı kesitsel bir çalışmadır.

Bulgular: Bakır-rahim içi araç (Cu-RİA), PID öyküsü olan kadınlarda en sık kullanılan kontraseptif yöntemdir. Servikovajinal kültür sonuçları değerlendirildiğinde; *E.coli* pozitifliği CU-RİA ve levonorgestrel RİA (LNG-RİA) kullanan hastalarda daha sıktı (<0.001). Prezervatif kullananlarda Grup B *Streptococcus* (<0.001) ve diğer *Streptococcus* türlerinde (=0.006) üreme sıklığı daha yüksekti. *Staphylococcus* (=0.041) ve *Chlamydia trachomatis* pozitifliği kombine oral kontraseptif (COC) kullananlarda daha yüksek iken, *C. Trachomatis* büyümesi depo medroksiprogeteron asetat (DMPA) kullanıcılarında daha sık görülmüştür (<0.001). Diğer gruplarla karşılaştırıldığında (p=0.008).

Sonuç: Kontraseptif yöntemler genital florayı etkileyebilir ve PID gelişimi için predispozan bir faktör olabilir veya PID gelişimini önleyebilir.

Anahtar Kelimeler: Kontraseptif ajanlar, pelvik inflamatuvar hastalık, rahim içi araçlar, uzun etkili geri dönüşümlü kontrasepsiyon

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INTRODUCTION

Pelvic inflammatory disease (PID) is a serious complication of sexually transmitted infections and some gynecological procedures and is observed in 2-4% of women of reproductive age (1,2). PID is a term that includes upper genital tract infections such as endometritis, salpingitis, and oophoritis. It is caused by the spread of infections in the vagina and cervix to the uterine cavity (3). The diagnosis of PID should refer to the diagnostic criteria recommended by the Centers for Disease Control and Prevention (CDC), which consider abnormal vaginal discharge, fever, adnexal tenderness, cervicovaginal culture and laboratory data (1). Although PID is associated with sexually transmitted diseases, it can also be caused by endogenous infections of the vaginal flora. Risk factors for PID have been identified such as the use of an intrauterine device (IUD), curettage, multiple sexual partners, and sexually transmitted diseases (4), and barrier methods have been reported to be protective (5,6). PID is an important cause of gynecological morbidity (7); adhesion secondary to tubal infection leads to tubal infertility, ectopic pregnancy and chronic pelvic pain (8-10).

Copper intrauterine device (Cu- IUD) is one of the most effective birth control methods and is frequently used in all age groups (11). There are studies reporting an increased risk of PID in women using Cu-IUD (12,13). On the other hand, it has been reported that the risk of PID decreases in women who use levonorgestrel IUD (LNG-IUD) (14). It has been reported that the use of oral hormonal contraceptives reduces the risk of PID and the severity of inflammation decreases in these users (15). However, there is a lack of a current study that compares the effects of intrauterine, hormonal and barrier contraceptive methods on the clinical and outcomes of PID.

The purpose of our study in the light of this information; to investigate the relationship between the contraceptive methods used in the patient population treated for PID in a tertiary center with clinical and laboratory features and treatment outcome of PID.

MATERIAL AND METHOD

This is a cross-sectional study using the anamnesis, examination findings, and microbiological and pathological evaluation results of vaginal and cytological specimens recorded in our hospital database of patients admitted to our gynecology outpatient clinic in a tertiary center between January 2017 and December 2019. Ethics committee approval was received for this study from the Adiyaman University Non-interventional Clinical Researches Ethics Committee (No: 2020/6-23). This study was carried out in accordance with the Helsinki Declaration of Principles.

Among these patients, 1294 patients aged 18-45 years who had at least one minimum criteria and additional criteria were accepted as PID in accordance with the diagnostic criteria published in the latest guidelines by the United States Centers (1). In our center, patients who are diagnosed with severe disease, have nausea, vomiting and fever, have complications such as tubo-ovarian abscess, and those who do not comply with the outpatient regimen are hospitalized. Patients who were diagnosed with PID but had recently received outpatient oral antibiotic therapy, had a history of diabetes mellitus, had a history of minor or major surgery in the last 6 months, a history of immunosuppressive disease, or a history of immunosuppressive drug use in the last 6 months were excluded from the study. Based on these criteria, 974 female patients were included in the study. The patients were divided into the following groups according to the contraceptive method they used: copper IUD (Cu-IUD), combined oral contraceptive drug (COC), depot medroxyprogesterone acetate (DMPA), condom and LNG-IUD.

Clinical and Laboratory Tests Reviewed

Hospital entrance records taken from the electronic medical record database in our study center were made with service follow-up charts, laboratory results and discharge records.

Patient characteristics (age, parity, marital status, contraceptive method used, educational level) and PID clinical and laboratory characteristics (body temperature, C-reactive protein (CRP) serum level, white blood cell count (WBC), erythrocyte sedimentation rate (ESR) and physical examination findings (pelvic tenderness, fundal tenderness, cervical motion tenderness, abnormal cervical discharge) and cervicovaginal culture results) were noted. Cervicovaginal culture results; standard flora, *Escherichia coli* (*E. coli*), group B *Streptococcus*, *Enterococcus faecalis* (*E. faecalis*), *Staphylococcus* and its species, *Streptococcus* and species, *Chlamydia trachomatis* were noted for each group.

Clinical results such as hospitalization time and re-hospitalization were noted. Body temperature measured at admission was recorded as measured in degrees Celsius centigrade. 38 and above was accepted as fever. Hospitalization was accepted as re-hospitalization within the first 30 days after discharge (16). Clindamycin/gentamicin (900 mg IV clindamycin every eight hours plus a single daily dose (5 mg/kg) gentamicin) was administered, and after clinical improvement, the treatment regimen of oral clindamycin (450 mg orally four times daily) or doxycycline (100 mg twice daily) was administered.

Statistical Analysis

SPSS 22 (IBM SPSS version 22, IBM Corp., Armonk, NY) program was used to analyze the data. Pearson's Chi-square test was used for significance between groups and Fisher's exact test was used for categorical variables. Student t test and Mann-Whitney U test were used for analysis of continuous variables. A two-sided p value < 0.05 showed statistical significance. A value of p < 0.05 was considered statistically significant.

RESULTS

The demographic characteristics of the groups are given in **Table 1**. Accordingly, Cu-IUD was the most commonly used contraceptive method in women with a history of PID. Other preferred methods were COC, LNG-IUD, Condom and DMPA in order of frequency. The most preferred contraceptive method in the 18-25 age group was COC, the most preferred method in the 25-35 age group was Cu-IUD and the most preferred method in the 35-45 age group was LNG-IUD.

In the analyzes made according to the PID clinical and laboratory results; Fever was more frequent in Cu-IUD and DMPA groups (0.047). Pain and increased ESR, CRP, WBC values were common in those using COC and DMPA (p < 0.001). When the cervicovaginal culture results are evaluated; *E.coli* positivity was more frequent in patients using Cu-IUD and LNG-IUD (p < 0.001). The frequency of reproduction was higher in Group B

Streptococcus (p < 0.001) and other *Streptococcus* species (p = 0.006) in those using condoms. While *Staphylococcus* (p = 0.041) and *Chlamydia trachomatis* positivity was higher in COC users, *C. Trachomatis* growth was frequent in DMPA users (p < 0.001) (**Table 2**).

When hospitalization times of the patients were compared according to the groups, there was no significant difference (p > 0.05). However, re-hospitalization was more common in the DMPA group compared to the other groups (p = 0.008) (**Table 2**).

DISCUSSION

PID occurs with ascending spread of cervical infections. *N. Gonorrhoeae*, *C. Trachomatis* and anaerobic and facultative bacteria found in the vaginal flora were isolated in the fallopian tubes of women with acute PID (17). PID is affected by many mechanisms such as reduction in normal vaginal lactobacilli, development of bacterial vaginosis, reproduction of anaerobic microflora. The presence of bacterial vaginosis may affect the cervical barrier and cause the progression of microorganisms in the upper genital tract (18,19). It has been shown in various previous publications that the risk of PID increases with the use of IUD (20,21). In a recent study conducted in a large group of patients in Turkey bacterial colonization increases with use Cu-IUD, but the frequency of the PID has not been shown to increase with the IUD (22).

Table 1. Demographic characteristics of the patients

	Cu-IUD n=412	COC n=239	DMPA n=43	Condom n=117	LNG-IUD n=163
Age					
18-25	55 (13.4%)	151 (63.1%)	19 (44.2%)	47 (40.2%)	28 (17.2%)
25-35	263 (63.8%)	74 (31%)	15 (34.9%)	14 (12%)	31 (19%)
35-45	94 (22.8%)	14 (5.9%)	9 (20.9%)	56 (47.8%)	104 (63.8%)
Marital Status					
Married	354 (85.9%)	164 (68.6%)	9 (20.9%)	63 (53.9%)	146 (89.6%)
Divorced	58 (14.1%)	75 (31.4%)	34 (79.1%)	35 (29.9%)	17 (10.4%)
Single	-	-	-	19 (16.2%)	-
Obstetric History					
Gravida	3.19±1.90	2.34±2.00	3.66±1.91	2.12±1.81	2.07±2.00
Parity	2.56±1.54	1.67±1.35	2.88±1.42	1.87±1.23	1.74±1.09
Abortus	0.62±0.71	0.67±0.91	0.83±1.23	0.62±0.71	0.63±0.89
Educational Level					
Middle school and pre-school	151 (36.6%)	17 (7.1%)	4 (9.3%)	33 (28.2%)	86 (52.8%)
High school	138 (33.5%)	93 (38.9%)	9 (20.9%)	39 (33.3%)	29 (17.8%)
License	74 (18%)	81 (33.9%)	19 (44.2%)	17 (14.5%)	21 (12.9%)
Graduate	49 (11.9%)	48 (20.1%)	11 (25.6%)	28 (23.9%)	27 (16.5%)
Body Mass Index					
<25	69 (16.7%)	19 (7.9%)	21 (48.8%)	61 (52.1%)	47 (28.8%)
25-29.99	294 (73.4%)	173 (72.4%)	19 (44.3%)	35 (29.9%)	83 (51%)
>30	49 (11.9%)	47 (19.7%)	3 (6.9%)	21 (18%)	33 (20.2%)

Cu-IUD: Copper intrauterine device; COC: Combined oral contraceptives; DMPA: Depot medroxyprogesterone acetate; LNG-IUD: levonorgestrel intrauterine device

Table 2. Disease characteristics and treatment outcomes according to contraceptive method relationship

	IUD n=412	COC n=239	DMPA n=43	Condom n=117	LNG-IUD n=163	p
Clinical Features						
Fever (>38)	324 (78.6%)	207 (86.6%)	40 (93%)	63 (53.9%)	51 (31.3%)	0.047
Pain (lower abdominal, fundal, cervical motion)	247 (59.9%)	224 (93.7%)	37 (86%)	71 (60.7%)	84 (51.5%)	<0.001
Laboratory value (WBC, CRP ve ESR%)	379 (92%)	171 (71.5%)	43 (100%)	98 (83.8%)	102 (62.6%)	<0.001
Cervicovaginal Culture						
<i>Escherichia coli</i>	73 (17.8%)	9 (3.8%)	5 (11.7%)	13 (11.1%)	41 (25.2%)	<0.001
Group B <i>Streptococcus</i>	53 (12.9%)	29 (12.1%)	6 (14%)	24 (20.5%)	21 (12.8%)	<0.001
<i>Enterococcus faecalis</i>	28 (6.8%)	7 (2.9%)	1 (2.3%)	12 (10.3%)	19 (11.7%)	0.51
<i>Staphylococcus spp.</i>	17 (4.1%)	26 (10.9%)	-	3 (2.6%)	9 (5.5%)	0.041
<i>Streptococcus spp.</i>	8 (1.9%)	19 (7.9%)	2 (4.6%)	13 (11.1%)	5 (3.1%)	0.006
<i>Chlamidya trachomatis</i>	70 (17%)	47 (19.7%)	12 (27.9%)	8 (6.8%)	21 (12.9%)	<0.001
Standart flora	163 (39.5%)	102 (42.7%)	17 (39.5%)	44 (37.6%)	47 (28.8%)	0.17
Treatment Outcome						
Hospitalization duration	5.02±1.14	3.87±1.01	3.03±1.21	4.07±1.83	5.84±2.03	0.29
Re-hospitalization	109 (26.5%)	23 (9.7%)	19 (44.2%)	29 (24.8%)	47 (28.8%)	0.008

Cu-IUD: Copper intrauterine device; COC: Combined oral contraceptives; DMPA: Depot medroxyprogesterone acetate; LNG-IUD: levonorgestrel intrauterine device WBC: White Blood Cell; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate

There are some factors preventing the full understanding of the role of Cu-IUD in the development of gynecological infections. Many genital infections are asymptomatic. One of the most important examples among these is *C. Trochomatis*. It is difficult under these conditions to determine whether PID, which develops secondary to this microbial agent, which can cause tubal infertility and chronic pelvic pain, due to the upper genital tract infection that causes tubal damage and adhesions (23), is caused by Cu-IUD (24). In addition, in another study, it was shown that *C. Trochomatis* positivity did not contribute to the development of PID in Cu-IUD users (24). Considering our study results, the most common contraceptive method used in patients with a history of PID was Cu-IUD. This finding is not a surprise when compared with the data in previous studies, but the fact that Cu-IUD is one of the contraceptive methods frequently used in our country may explain the high number of patients in the group. However, although *C. Trochomatis* was the most common bacterium grown in cervicovaginal culture in this study, there was no correlation with *C. Trochomatis* positivity in PID patients using Cu-IUD.

In a previous study examining microbial cultures in patients with PID, the most frequently grown bacteria were *E. Coli* (26.4%) and other *Enterococcus* species (24%) (25). In another study, *S. Aureus* was the most common bacteria (26). In another study conducted with a large patient population in Asia, bacteria that multiplied frequently in PID patients; *E. coli*, *Proteus mirabilis*, *S. aureus*, Group B *Streptococcus* and *Klebsiella pneumoniae* (27). In our study, the second most common bacterium that multiplied in cervicovaginal cultures was *E. Coli* after *C. Trochomatis*. It has been reported in various publications that oral hormonal contraceptive methods

have positive effects on the vaginal microflora and reduce the risk of PID (28,29).

Estrogen in the content of COC increases the amount of glycogen in vaginal epithelial cells and increases the growth of *Lactobacillus* bacteria and contributes to the reproduction of healthy vaginal microbial flora (30-33). In a study conducted among women using COC as a contraceptive method and women using a barrier method, it was shown that *Lactobacillus* reproduce more in the vaginal microflora of COC users (31). In the data in our study, *C. Trochomatis* and *Staphylococcus* positivity were found in the cervicovaginal cultures of PID patients using COC. These changes can be explained depending on the effects of COC on flora.

Information on the effects of progesterone-containing contraceptive methods on the vaginal microflora is still contradictory. In a study examining the vaginal flora of patients using oral contraceptive drugs containing progesterone and using LNG-IUD; It has been determined that due to atrophy caused by progesterone, glycogen content in vaginal epithelial cells decreased and vaginal microflora was negatively affected (34). However, some studies have shown that the use of LNG-IUD has no effect on vaginal microflora (35,36). In a study conducted with DMPA users, it was stated that there was a decrease in the prevalence of lactobacilli in the vaginal microflora, while another study reported that it had no effect on microflora (37,38). In our study, positivity of *E. Coli* in cervicovaginal culture in PID patients using LNG-IUD, positivity of group B *Streptococcus* in condom users and *C. Trochomatis* positivity in DMPA users were frequent. These findings may be related to the negative effects of progesterone and barrier methods mentioned in publications on the vaginal microflora.

In addition, considering the re-hospitalization rates of the patients, we found that this rate increased in DMPA users. This may be related to the persistent infection of *C. Trachomatis*, which is the most common agent in patients using DMPA.

This study has some limitations. Firstly our study is single-centered, and common contraceptive methods used among patients admitted to our center were investigated. Secondly, the study is a cross-sectional study. The data registered in the hospital database were analyzed retrospectively. In the light of these findings, the data should be considered before generalizing to the society.

CONCLUSION

In women presenting with acute PID clinic, contraceptive methods may have an impact on treatment selection and results. It should be kept in mind that contraceptive methods to be chosen in patients with a history of PID may affect the genital flora and may be a predisposing factor for the development of PID or prevent the development of PID.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was received for this study from the Adiyaman University Non-interventional Clinical Researches Ethics Committee (No: 2020/6-23).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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