Results of Prolonged Use of Intrauterine Device in Endometrium and Eosinophil Leukocytes

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INTRODUCTION

It is known to all gynecopathologists that the use of IUD (intrauterine device) causes histopathological changes in the endometrium. The histological features associated with the use of IUD are usually due to mechanical action. The micropapillary formation, focal reactive changes, nuclear enlargement, mild nuclear atypia, small nucleoli, and cytoplasmic vacuolization, as well as rarely stromal microcalcification, can be seen on the surface. Polymorphs, lymphocytes, histiocytes, plasma cells, foreign body type giant cells, and inflammatory cell infiltration can also be seen. Long-term use of IUD may also be associated with actinomyces infection 1.

Until today, there were several studies about the number of eosinophils in the endometrium.

These studies were generally performed in endometritis to help configuring out the confusion between plasma cells, which are the diagnostic cell of endometritis, and plasmacytoid stroma cells 2-3.

However, the relationship of eosinophil leukocytes with IUD has never been studied in the literature.

MATERIAL and METHOD

Ethical approval

This study was approved by the Ethical Committee in Konya Training and Research Hospital, Turkey (02 July 2020, 48929119/774)

Patients and study design

A single pathologist reviewed pathology preparations of 68 patients (38 using IUD and 30 not using IUD) who had abnormal uterine bleeding during the reproductive period and applied to our hospital between 2018-2020. Histopathological diagnosis in the curettage materials with a light microscope, eosinophil leukocyte, neutrophil, plasmocyte counts, and accompanying histopathological findings were re-evaluated in 10XHMF (High magnification fields) in compact areas without destruction findings. The methodology of this study is descriptive-analytical method, and data is analyzed using the statistical software SPSS 20.
RESULTS

In this study, a total of 68 patients with abnormal uterine bleeding in the reproductive period were examined. Thirty patients were not using IUD, while 38 had IUD. The patients' age range was between 25 and 46 years, with a mean age of 37.

In the histopathological diagnosis of 38 patients using IUD during curettage; endometritis was detected in 13 patients, proliferative endometrium in 5 patients, disorder proliferative endometrium in 4 patients, early secretory endometrium in 3 patients, endometrial polyp in 4 patients, progesterone effect in 3 patients, glandular stromal destruction in 3 patients, EnteroBIus vermicularis infestation in 1 patient. Six of our patients used the Mirena coil, while 32 of them used copper-wire IUD. The duration of IUD use in our patients varied between 3 months and 15 years, and the mean use was seven years (Table 1). In 31 of 38 patients (81%) with abnormal uterine bleeding and using IUD, eosinophils were detected in curettage materials. Among them, eosinophils were detected in 85% (11/13) of cases, which were detected to have endometritis and in 80% (20/25) of cases without endometritis (figure 1). While the average number of eosinophils observed in 10 HMF is 5.8 in patients with endometritis, it is 5 in patients without endometritis. The average duration of IUD use for eight patients who were observed to have no eosinophils was two years. The average duration of IUD use for patients who were found to have eosinophils was six years. In addition to these findings, actinomyces were observed in 2 patients (figure 2). EnteroBIus vermicularis was detected in 1 patient. Metaplastic changes were observed in 17 of our patients 14 eosinophilic, two squamous, one tubal) (figure 3). One patient had dystrophic calcification (figure 3). Pigment-laden histiocytes draw attention in 8 patients. (Table 1-2)

Eosinophils were observed in 11 (36%) of 30 patients in the control group with abnormal uterine bleeding who did not use IUD. Histopathological diagnoses in the control group were found as proliferative endometrium in 20 patients and disordered proliferative endometrium in 10 patients. Eleven patients who had eosinophils in the control group had an eosinophil average of two in 10 HMF.

Table 1. Results of our patients using IUD

| IUD-Usage-duration | M-C-IUD | Pathologic diagnosis | NPL/10 HPF | Plasmocyte/10 HPF | EOS/ 10 HPF | Metaplasia |
|--------------------|---------|---------------------|------------|------------------|-------------|------------|
| 10 year +          | M-C-IUD | Progesterone effect | 0          | 0                | 8           | 0          |
| 10 year +          | M-C-IUD | Endometritis        | 15         | 5                | 5           | Squamous metaplasia |
| 3 year             | M-C-IUD | DPE                 | 5          | 0                | 5           | Eosinophilic metaplasia |
| 2 year +           | M-C-IUD | Progesterone effect | 0          | 2                | 0           | Tubal metaplasia |
| 3 month            | M-C-IUD | Endometrial polyp   | 5          | 0                | 0           | 0          |
| 12 year +          | M-C-IUD | Proliferative endometrium | 10         | 0                | 3           | Eosinophilic metaplasia |
| 3 year             | M-C-IUD | Endometritis        | 5          | 5                | 3           | 0          |
| 4 year +           | M-C-IUD | Progesterone effect | 3          | 1                | 3           | 0          |
| 9 year             | M-C-IUD | Early secretory endometrium | 5         | 0                | 3           | Eosinophilic metaplasia |
| 1 year             | M-C-IUD | Endometrial polyp   | 10         | 0                | 0           | 0          |
| 5 year             | M-C-IUD | Endometritis        | 1          | 3                | 1           | Eosinophilic metaplasia |
| 14 year            | M-C-IUD | DPE                 | 5          | 0                | 0           | Eosinophilic metaplasia |
| 5 year             | M-C-IUD | Early secretory endometrium | 20         | 5                | 10          | 0          |
| 10 year            | M-C-IUD | DPE                 | 20         | 5                | 5           | 0          |
| 7 year +           | M-C-IUD | Progesterone effect | 10         | 3                | 10          | 0          |
| 12 year            | M-C-IUD | Endometritis        | 5          | 4                | 5           | Eosinophilic metaplasia |
| 15 year            | M-C-IUD | Endometritis        | 10         | 10               | 10          | Eosinophilic metaplasia |
| 4 year             | M-C-IUD | Endometritis        | 10         | 5                | 5           | Eosinophilic metaplasia |
| 4 year +           | M-C-IUD | Endometritis        | 10         | 10               | 3           | Eosinophilic metaplasia |
| 3 year +           | M-C-IUD | Progesterone effect | 5          | 5                | 5           | 0          |
| 5 year             | M-C-IUD | Endometritis        | 10         | 5                | 15          | Eosinophilic metaplasia |
| 5 year             | M-C-IUD | Progesterone effect | 10         | 5                | 10          | 0          |
| 4 year +           | M-C-IUD | Early secretory endometrium | 0         | 0                | 0           | 0          |
| 3 year +           | M-C-IUD | Endometrial polyp   | 10         | 5                | 10          | Eosinophilic metaplasia |
| 1,5 year           | M-C-IUD | Endometrial polyp   | 15         | 2                | 10          | 0          |
| 5 year             | M-C-IUD | PE                  | 5          | 0                | 5           | 0          |
| 7 year             | M-C-IUD | Endometritis        | 5          | 5                | 5           | 0          |
| 1 year             | M-C-IUD | Endometrial polyp   | 5          | 3                | 5           | 0          |
| 4 year +           | M-C-IUD | Early secretory endometrium | 1         | 2                | 4           | 0          |
| 1,5 year           | M-C-IUD | PE                  | 5          | 5                | 0           | 0          |
| 5 year             | M-C-IUD | PE                  | 5          | 2                | 7           | 0          |
| 4 year             | M-C-IUD | Endometritis        | 2          | 7                | 2           | Eosinophilic metaplasia |
| 18 year            | M-C-IUD | DPE                 | 10         | 2                | 10          | Eosinophilic metaplasia |
| 2 year             | M-C-IUD | G/S br.             | 0          | 0                | 0           | Eosinophilic metaplasia |
| 11 year            | M-C-IUD | G/S br.             | 5          | 5                | 5           | Eosinophilic metaplasia |
| 10 year            | M-C-IUD | G/S br.             | 7          | 5                | 3           | 0          |
| 5 year             | M-C-IUD | PE                  | 5          | 0                | 4           | Eosinophilic metaplasia |

(M-C-IUD: Mirena- coil intrauterine device, PE: Proliferative endometrium, DPE:Disorder proliferative endometrium, G/S br.(Glandulo stromal breakdown)
DISCUSSION

Eosinophils are inflammatory cells that are popularly known to be involved in allergy-related responses. However, eosinophils are also known to play an important role in the pathogenesis of late-type inflammation. Previous studies have shown that eosinophils are absent in the normal endometrium, except for immediately before menstruation, or they may be associated with endometrial instrumentation. Also, inflammatory infiltration can sometimes be accompanied by eosinophils in endometritis. Adegbuyega et al. stated that eosinophil leukocyte infiltration in the endometrium may occur in curettage materials after surgical intervention and may sometimes be seen without an underlying abnormality. In the study of Phillips et al., only patients using Mirena coils were examined, and it was found that 59 of 75 samples had stromal inflammatory cell infiltration, which is usually with a mixture of lymphocytes, neutrophils, histiocytes, and eosinophils.

In the study in which Perlman et al. aimed to find the

| Table 2. Pathological effects of long-term use of IUD |
|------------------------------------------------------|
| Metaplastic changes | 19/38 cases |
| Eosinophilic metaplasia | 15 |
| Squamous metaplasia | 2 |
| Tubal metaplasia | 1 |
| Hemosiderin pigments | 8/38 cases |
| Actinomyces | 2/38 cases (5 and 18 years usage of copperwire coil) |
| Distrophic calcification | 1/38 case (four years usage of mirena coil) |
| Endometritis | 13/38 cases |
| Enterobius vermicularis | 1/38 case (four years usage of mirena coil) |
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rate of eosinophils in endometritis, eosinophils were found in 68% in the endometritis group and 38% in the control group (1). In our study, this rate was found to be 85% in the endometritis group who were using IUD, and 80% in the group using IUD without endometritis.

The eosinophil presence rate (36%) found in our control group was found to be similar to that of the control group in the study of Perlman et al. In our study, the rate of eosinophil monitoring rate of 36% for non-endometritis and non-IUD control group indicates that IUD use alone may cause an increase in the number of eosinophil leukocytes without endometritis. The reason for separately evaluating endometritis and non-endometritis groups in the group using IUD is to prevent misleading because eosinophils may accompany plasma cells in endometritis.

As per our findings, the average duration of IUD use for seven patients, for whom no eosinophils were detected in the histopathological examination, was two years. The average duration of IUD for patients who had eosinophils was 7.5 years. Although the use of IUD does not always cause an increase in eosinophils in the endometrium, we can say that the rate of eosinophils increases as the duration of IUD use increases.

In our study, we added neutrophils along with eosinophils and observed that neutrophils usually accompany (30/31) eosinophils. However, we know that lymphocytes and neutrophils may be a regular component of the endometrium, depending on the menstrual cycle stage. Also, we did not detect any eosinophilic micro-abscess in any of our patients.

In addition, metaplastic changes have been observed in 17 of our cases, and 8 of them had hemosiderin pigment-laden histiocytes, and in the literature, metaplastic changes and hemosiderin pigments were associated with the use of IUD in endometrial curettage materials 5.

The dystrophic calcification observed in one of our cases was found to be seen in 10% of the patients using Mirena coil in the literature. In our results, it was observed in only one out of six patients who were using the Mirena coil 5. In a recent study, they stated that endometrial benign calcifications may be multifactorial but progesterone plays an important role 6. The fact that the only case we detected calcification used mirena coil for four years supports this thesis.

Once again, Enterobius vermicularis was present in one of our cases, which was associated with chronic pelvic inflammatory diseases in the literature, and its association with IUD has not been previously defined 2-7.

Although at low rates, hyperplasias have been reported in the literature related to Mirena coil use. There were no findings suggesting malignancy or hyperplasia in our patients 5.

Our study is valuable since it is the first study in the literature investigating the number of eosinophils in curettage materials of patients using an intrauterine device (IUD).

CONCLUSION
The prolonged use of IUD causes many histopathological changes in the endometrium. According to the results of our study, the use of IUD does not always cause an increase in eosinophils in the endometrium but is accompanied by high rates. Also, we can say that the number of eosinophils increases as the IUD usage time increases. It should be kept in mind that increased eosinophil leukocytes monitored by gynecopathologists in curettage materials, may be associated especially with prolonged IUD use.

Conflict of interest
The authors declare that they have no conflict of interest.

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