The possible association of uterine fibroid formation with copper intrauterine device use: a cross-sectional study

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Background: Fibroids are the most common pelvic tumors in females, affecting approximately 30%–50% of women of fertility age. Intrauterine devices (IUDs) are widely used in the world. Copper-IUDs which are one of the common causes of intrauterine chronic inflammation might create a suitable microenvironment for fibroid growth. This study aimed to find an answer to investigate whether there is an association between fibroids and copper (Cu) T-IUD use. *Methods*: This cross-sectional study was conducted with 788 participants. The participants were divided into two groups based on fibroid presence (study group) or absence (control group). For this study, usage of IUDs was defined as Cu T-IUD use for at least one year. Medical and obstetric history, oral contraceptive (OC) and/or IUD use and duration of use, as well as smoking, were questioned. *Results*: In participants who had fibroids, IUD use was found to be statistically significantly higher (55.5% vs 43.4%) (*P* = 0.001). In addition, according to multiple logistic regression analysis, having fibroids was found to be significantly related to age, number of abortions, smoking, and duration of Cu T-IUD use. A statistically significant correlation was not found between fibroid diameter, parity, and duration of OC use; however, a statistically weak correlation was found between fibroid size and duration of Cu T-IUD use. *Conclusions*: This study points to the association of Cu T-IUD use, inflammation, and fibroids. Our results can provide a steppingstone for the development of additional studies investigating this hypothesis. If inflammation is the preliminary event and copper IUDs cause inflammation, preventive health strategies may be implemented to lessen the possibility of fibroid development.

Keywords

Contraception; Etiology; Inflammation; Intrauterine device; Uterine fibroid; Leiomyoma

1. Introduction

Uterine fibroids are the most common pelvic tumors in females, affecting approximately 30%–50% of fertility-age women [1–4]. Originating from smooth muscle cells in the myometrium, fibroids are composed of collagen, fibronectin, and proteoglycan [5]. Most fibroids are asymptomatic; however, patients may have symptoms of bleeding, pain, and a sense of pressure [6]. Uterine hemorrhage-related anemia, infertility, and recurrent pregnancy losses have also been related to fibroids. As such, uterine fibroid-related hemorrhage

and pain may seriously impact a woman's quality of life and can lead to a severe public health problem. In addition to being the most common cause of hysterectomies, many women undergo myomectomies each year [6, 7]. All these factors lead to fibroids being responsible for a heavy economic burden.

The etiology of fibroids is still not clear despite many studies investigating the complex pathophysiology. Genetic and environmental factors, inflammation, steroid hormones, and growth factors are considered to affect the fibrotic process and angiogenesis in fibroid growth [8]. Copper (Cu) T-380A IUDs that effectively provide long-term, reversible contraception are widely preferred among women in developing countries [9–11]. Intrauterine foreign bodies lead to an inflammatory response in the uterus by inducing an inflammatory reaction via macrophages and leukocytes. Protic *et al.* [12] showed the presence of inflammatory cells in uterine fibroid tissues and suggested chronic inflammation as a potential abnormal tissue regeneration of myofibroblasts. It has been suggested that uterine irritation (menstruation, infection, DNA damage, use of talc, and IUDs) can initiate an inflammatory state in which increased cytokines, chemokines, and growth factors stimulate fibrous tissue formation and also smooth cell proliferation, causing fibroid formation [13]. Thus, Cu IUDs, which are a common cause of intrauterine chronic inflammation, might create a suitable microenvironment for fibroid growth. This study aimed to find an answer to investigate whether there is an association between fibroids and Cu IUD use.

2. Material and methods

This cross-sectional study was conducted with 788 participants admitted to the Family Planning Outpatient Clinic between December 2018 and October 2019. Women who applied to the family planning clinic for routine care, having information about contraception or smear control were included. Cases and controls were selected from the same population having a similar likelihood of a fibroid diagnosis. Participants were divided into two groups based on fibroid presence (study group) or fibroid absence (control group). IUD usage was defined as Cu-T 380A IUD use for at least one

year. The medical records of the participants were checked. Patients who had fibroids before IUD insertion, in addition to those having hormone therapy, gynecologic surgery, malignancy, adenomyosis, a history of pelvic inflammatory disease (PID), genital infection, endometriosis, ovarian diseases, Levonorgestrel IUD use, or multiple uterine fibroids were excluded from the study. Demographic characteristics, medical and obstetric history, oral contraceptives (OC) and/or IUDs use, and smoking status were questioned. Smoking status was assessed as never smoked or smoked at least one pack/year. The size and location of fibroids were measured by two clinicians. Ultrasound examinations were performed with a Mindray DC-80A trans-vaginal 3.5 MHz transducer (Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China). The International Federation of Gynecology and Obstetrics (FIGO) classification system was used for evaluation [14].

The study was approved by the Local Ethics and Clinical Investigation Committee. The sample size was calculated by the simple random sampling method. Informed consent was obtained from all patients. Statistical analyses were made using the Statistical Package for the Social Sciences (SPSS; Version 22.0, IBM, Chicago, IL, USA). The normality distribution of the data was evaluated with a Shapiro-Wilks test. Descriptive statistics (mean, standard deviation, frequency) were provided. A Chi-square test was used for comparison of qualitative data and Student's t-test was used for normally distributed variables. Associations between the normally distributed data were tested by Pearson correlation analysis. The Enter option was used in multiple logistic regression analyses of the association between fibroid status and independent variables. Fibroid status was divided into those with (1) or without (0) fibroids as a dependent variable. Independent variables were age, number of abortions, smoking status, duration of IUD use, parity, and OC use. $P < 0.05$ was considered statistically significant.

3. Results

This study initially included 840 participants, but 52 women were excluded due to having hormone therapy, PID, multiple fibroids, or gynecologic surgery. Of the remaining 788 participants, the mean ages of women in the study and control groups were 45.7 ± 7.6 years and 43 ± 8.3 years, respectively. The mean parity and abortus number were higher in the study group ($P = 0.004$, $P = 0.012$; $P < 0.05$). Of participants, 25.8% (n = 200) had smoked during some period of their lives. There was no significant difference between groups in terms of OC history ($P = 0.406$; $P > 0.05$). The demographic characteristics of groups are shown in Table 1.

Of the participants, 49.1% (n = 387) had IUDs. The mean duration of Cu IUD use was 9.14 ± 6.29 years. After IUD insertion, participants were followed up annually. Overall, 344 women had fibroids and 444 women did not. The size of fibroids varied between 5–120 mm (mean 31.36 ± 18.86 mm).

In women who had fibroids, IUD use was found to be sig-

Table 1. Demographic characteristics of groups.

	Fibroids		P value
	Yes	No	
	Mean ± SD	Mean ± SD	
Age (years)	45.7 ± 7.6	43 ± 8.3	[1]0.000**
Parity	2.3 ± 1.3	2.1 ± 1.3	[1]0.004*
Abortus	0.4 ± 0.8	0.2± 0.6	[1]0.012*
Body mass index	28.3 ± 5.3	27.2 ± 5.3	[1]0.015*
Oral contraceptive use	n (%)	n (%)	
Yes	55 (16)	81 (18.2)	[2]0.406
No	289 (84)	444 (81.8)	

[1]Student's t-test; [2]Chi-square test, *$P < 0.05$; **$P < 0.001$.

Table 2. Association of fibroids with intrauterine device use.

	No IUD use	Cu IUD use	P value
	n (%)	n (%)	
Study Group	153 (44.5)	191 (55.5)	[1]0.002*
Control Group	248 (55.9)	196 (44.1)	
Submucosal (FIGO 1 + 2)	20 (51.3)	19 (48.7)	
Intramural (FIGO 3 + 4)	85 (40.1)	127 (59.9)	[1]0.117
Subserosal (FIGO 5 + 6)	48 (51.6)	45 (48.4)	

[1]Chi-square test; *$P < 0.05$.

FIGO, International Federation of Gynecology and Obstetrics.

nificantly higher (55.5% vs 44.1%) ($P = 0.002$; $P < 0.05$) (Table 2). A statistically significant weak correlation was found between fibroid size and duration of IUD use (Table 3); however, having fibroids was found to be significantly related to the duration of IUD use ($P = 0.039$; $P < 0.05$) in multiple logistic regression analysis (Table 4). No statistically significant difference was found between those who had submucosal, intramural, and subserosal fibroids regarding IUD use ($P = 0.117$; $P > 0.05$) (Table 2).

Having fibroids was found to be significantly related to age, number of abortions, smoking status, and duration of IUD use in multiple logistic regression analysis (Table 4). A statistically significant relationship was not found between having fibroids and parity, or duration of OC use (Table 4). A negative and statistically insignificant correlation was found between fibroid size and duration of OC use (Table 3).

In multiple logistic regression analysis, having fibroids was found to be significantly related to smoking ($P = 0.002$; $P < 0.05$). No statistically significant difference was found between participants who had submucosal, intramural, and subserosal fibroids regarding smoking status ($P = 0.083$; $P > 0.05$).

4. Discussion

Uterine fibroids are found in connection with a fibrotic disorder characterized by increased wound healing and elevated collagenous extracellular matrix (ECM) [15, 16]. Fibroids are an important public health issue, as they are very common and one of the most common reasons for hysterectomies and a primary cause of morbidity in premenopausal

Table 3. Correlation between fibroid diameter and study variables.

		Fibroid diameter (mm)
Parity	r	0.03
	P	0.615
OC duration (years)	r	−0.09
	P	0.106
Cu IUD use (years)	r	0.11
	P	0.046*

Pearson Correlation Analysis; *$P < 0.05$.

OC, Oral contraceptive; IUD, Intrauterine device.

Table 4. Parameters related to fibroids in logistic regression analysis N = 788.

Variables	Beta value	OR	95% CI	P value
Age	0.037	1.04	1.02–1.06	0.000*
Parity	0.045	1.05	0.92–1.19	0.486
Abortus	0.278	1.32	1.06–1.64	0.013*
Smoking	0.552	1.74	1.22–2.48	0.002*
OC use duration (years)	−0.029	0.97	0.91–1.04	0.377
Cu IUD use duration (years)	0.025	1.03	1.00–1.05	0.039*

Hosmer–Lemeshow goodness-of-fit test $P = 0.326$, Nagelkerke $R^2 = 0.08$.

OC, Oral contraceptive; IUD, Intrauterine device; *$P < 0.05$.

women [6, 7]. Although there have been many studies in recent years on the pathophysiology of fibroids, the etiology is still not understood. This study found that the percentage of Cu IUD use was higher in women who had fibroids (55.5% vs 43.4%) ($P = 0.001$). In addition, having fibroids was found to be significantly related to age, number of abortions, smoking, and duration of Cu IUD use.

Currently, it has not been identified exactly which factors play a role in the initiation of the transformation of myometrial cells into fibroids and how this process is regulated. Factors likely to be responsible for initiating nonhereditary genetic changes in fibroids include intrinsic abnormalities of the myometrium, elevated estrogen receptors in the myometrium, hormonal changes, and responses to ischemic injury during menstruation or inflammation [5]. Injury and repair processes due to the menstrual cycles are thought to affect myometrial stem cells which become dysregulated and transform into fibroid smooth muscle [17].

Wegienka et al. [13] suggested a hypothesis that could explain the role of inflammation in fibroid formation. According to this hypothesis, uterine irritation (menstruation, infection, DNA damage, talc, IUD use) is the first stage that initiates the inflammatory state. Increased cytokines, chemokines, and growth factors stimulate fibrous tissue formation and also smooth muscle cell proliferation, causing fibroid formation [13]. It is suggested that inflammation plays a role in tissue repair and remodeling by affecting endometrial receptivity [18]. Chronic inflammation leads to abnormal tissue regeneration, overproduction of ECM proteins, and fibroid growth.

In their study, Protic et al. [12] showed the presence of inflammatory cells in uterine fibroids that induce excessive ECM production, tissue remodeling, and fibroid growth. They found the presence of an increased number of Cluster of Differentiation 68 (CD68) positive macrophages in fibroids alongside high amounts of myofibroblasts and collagen. The information they found in their study supports the hypothesis about the relationship between inflammation and fibroid formation. They suggested that fibroids originate from stem cells that are present in the uterus and are activated by an unknown inflammatory stimulus [12]. Smooth muscle cells respond to injury and ischemia with increased cell proliferation and ECM production, due to the release of growth factors such as transforming growth factor-beta (TGF-β). It has been shown that the TGF-β, which has both mitogenic and fibrogenic features, is excessively produced in uterine fibroids [15, 19].

It is known that IUDs used worldwide are a common cause of intrauterine chronic inflammation [20]. The global rate of IUD use is approximately 12% [21]. Their insertion is performed in family planning clinics without any charge. Since it is the most preferable contraceptive method among Turkish women, the IUD rate of use was higher (49.1%) in our study. Intrauterine foreign bodies induce inflammatory reactions through macrophages and leukocytes that travel to the uterus. A sterile inflammatory reaction develops when the uterus is subjected to a foreign body. This effect begins just after the application and rapidly disappears after IUD removal. Local irritation and pressure effects due to IUDs also lead to intense inflammatory responses and various reactive cytological changes [20]. Copper significantly changes endometrial cell mechanisms. Endometrial edema, vascular congestion, and necrosis develop through IUD-induced local inflammatory effects, and pseudo-decidualization develops, particularly with copper IUDs [20]. Enzymatic and proliferative activities change and cytotoxic inflammatory responses increase [22]. Ammälä et al. [2] detected that interleukin 1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) levels were high in the late secretory phase and IL-6 levels were high in the proliferative early secretory phase in IUD-subjected endometrial samples. The expression of IL-1, IL-6, and TNF-α was found to be associated with the pathophysiology of uterine fibroids [15].

Faerstein et al. [23] concluded in his study that there was a fivefold increased risk of fibroids in cases where IUD use was reported to be discontinued due to infection. Stewart et al. [24] suggested intrauterine injury as a source of fibroid formation, as it causes inflammation and an infectious agent may have a role in this injury, especially for submucosal fibroids. In our study, the rate of IUD use in women with fibroids (55.5%) was found to be statistically and significantly higher than those without fibroids (43.4%) ($P = 0.001$; $P < 0.05$). However, unlike Stewart et al. we did not find a statistical difference in the use of IUDs between patients with submucosal, intramural, and subserosal fibroids. Furthermore,

we found that having fibroids was statistically significantly related to age, number of abortions, smoking, and duration of IUD use.

Estrogen and progesterone hormones were reported to affect fibroid development. Obesity and early menarche may cause fibroids by increasing exposure to estrogen. Also, exercise and increased parity were reported to be protective against fibroids by decreasing exposure [5]. Also, an inverse association was reported between depot medroxyprogesterone acetate use and fibroids [25]. Parity and smoking are suggested to decrease uterine fibroid growth [5–7, 25]. In our study, we did not detect any significant correlation between fibroid size and parity. Monleon *et al.* [26] did not indicate any association between parity and uterine fibroid volume, similar to our study. In a review, spontaneous abortions were not found to be a risk factor [25]. However, having fibroids was found to be significantly associated with number of abortions in our study.

Parazzini [27] concluded that since OC users are followed by physicians more frequently, they may have more fibroid diagnoses than nonusers; however, there are conflicting results in the literature. Chiaffarino *et al.* [28] indicated that the incidence of uterine fibroids is less in OC users, and it was negatively correlated with duration of use. In their meta-analysis, Qin *et al.* [29] concluded that uterine fibroid risk decreased by 17% with five years of OC use. In our study, we did not detect a significant association between having fibroids and OC use. Moreover, a weak, negative, statistically insignificant association was found between fibroid size and duration of OC use.

A pro-inflammatory environment may also increase estrogen production [30]. Samadi *et al.* [7] found that smoking reduces the risk of fibroids by decreasing endogenous estrogens. Nevertheless, the relationship between fibroid formation and smoking is inconsistent. Wise *et al.* [31] suggested that smoking and caffeine consumption are unrelated to fibroid risk. We detected a statistically significant association between having fibroids and smoking using multiple logistic regression analysis. In women who had fibroids, the mean fibroid size was found to be smaller in smokers compared to non-smokers (29.00 ± 17.83 mm vs 31.75 ± 18.99 mm). We detected no statistically significant difference between the participants who had submucosal, intramural, and subserosal fibroids regarding smoking status.

This study has potential limitations. Medical records of women were checked for confirming OC and IUD durations. Since the nature of the study was cross-sectional and retrospective, prospective data and bigger studies are needed to identify a clear association between inflammation, Cu IUDs, and fibroid formation. Although cases and controls were selected from the same population, IUD users could come to control more frequent and this could increase likelihood of fibroid diagnosis.

5. Conclusions

This study points to an association between Cu IUDs, inflammation, and fibroids, which can be a steppingstone for new studies evaluating this hypothesis. Exploring alternative etiologic hypotheses can be assessed to identify modifiable risk factors for fibroid formation. If inflammation is the preliminary event, and Cu IUDs cause inflammation, preventive health strategies could be implemented with this association in mind.

Author contributions

SAA: Project development, data analysis, writing manuscript. HS: Project development, data collection. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Haydarpasa Numune Training and Research Hospital (Date: January 2019, approval number: HNEAH/2019/11).

Conflict of interest

The authors declare no conflicts of interest.

References

[1] Stewart EA, Laughlin-Tommaso SK, Catherino WH, Lalitkumar S, Gupta D, Vollenhoven B. Uterine fibroids. Nature Reviews Disease Primers. 2016; 2: 16043.

[2] Ämmälä M, Nyman T, Strengell L, Rutanen E M. Effect of intrauterine contraceptive devices on cytokine messenger ribonucleic acid expression in the human endometrium. Fertility and Sterility. 1995; 63: 773–778.

[3] Stein K, Ascher-Walsh C. A comprehensive approach to the treatment of uterine leiomyomata. The Mount Sinai Journal of Medicine. 2009; 76: 546–556.

[4] Hensley ML, Ishill N, Soslow R, Larkin J, Abu-Rustum N, Sabbatini P, *et al.* Adjuvant gemcitabine plus docetaxel for completely resected stages I–IV high grade uterine leiomyosarcoma: results of a prospective study. Gynecologic Oncology. 2009; 112: 563–567.

[5] Parker WH. Etiology, symptomatology, and diagnosis of uterine myomas. Fertility and Sterility. 2007; 87: 725–736.

[6] Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. American Journal of Obstetrics and Gynecology. 2003; 188: 100–107.

[7] Samadi AR, Lee NC, Flanders WD, Boring JR, Parris EB. Risk factors for self-reported uterine fibroids: a case-control study. American Journal of Public Health. 1996; 86: 858–862.

[8] Stewart EA. Uterine fibroids. The Lancet. 2001; 357: 293–298.

[9] Abdinasab M, Dehghani Firouzabadi R, Farajkhoda T, Abdoli AM. Lack of association between Cu T-380a intrauterine device and secondary infertility in Iran. International Journal of Fertility & Sterility. 2017; 10: 343–349.

[10] World Health Organization. Family planning: a global hand book for providers. 3rd edition. 2018.

[11] Buhling KJ, Zite NB, Lotke P, Black K. Worldwide use of intrauterine contraception: a review. Contraception. 2014; 89: 162–173.

[12] Protic O, Toti P, Islam MS, Occhini R, Giannubilo SR, Catherino WH, *et al.* Possible involvement of inflammatory/reparative processes in the development of uterine fibroids. Cell and Tissue Research. 2016; 364: 415–427.

[13] Wegienka G. Are uterine leiomyoma a consequence of a chronically inflammatory immune system? Medical Hypotheses. 2012; 79: 226–231.

[14] Munro MG, Critchley HOD, Fraser IS. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. International Journal of Gynaecology and Obstetrics. 2018; 143: 393–408.

[15] Chegini N. Proinflammatory and profibrotic mediators: principal effectors of leiomyoma development as a fibrotic disorder. Seminars in Reproductive Medicine. 2010; 28: 180–203.

[16] Malik M, Norian J, McCarthy-Keith D, Britten J, Catherino WH. Why leiomyomas are called fibroids: the central role of extracellular matrix in symptomatic women. Seminars in Reproductive Medicine. 2010; 28: 169–179.

[17] Commandeur AE, Styer AK, Teixeira JM. Epidemiological and genetic clues for molecular mechanisms involved in uterine leiomyoma development and growth. Human Reproduction Update. 2015; 21: 593–615.

[18] Weiss G, Goldsmith LT, Taylor RN, Bellet D, Taylor HS. Inflammation in reproductive disorders. Reproductive Sciences. 2009; 16: 216–229.

[19] Sozen I, Arici A. Cellular biology of myomas: interaction of sex steroids with cytokines and growth factors. Obstetrics and Gynecology Clinics of North America. 2006; 33: 41–58.

[20] Buckley CH. The pathology of intra-uterine contraceptive devices. Current Topics in Pathology. 1994; 86: 307–330.

[21] Johnson MJ, Morgan KW. Intrauterine contraception benefits extend beyond birth control. The Nurse Practitioner. 2005; 30: 50–55.

[22] Johannisson E. Mechanism of action of intrauterine devices: Biochemical changes. Contraception. 1987; 36: 11–22.

[23] Faerstein E, Szklo M, Rosenshein NB. Risk factors for uterine leiomyoma: a practice-based case-control study. II. Atherogenic risk factors and potential sources of uterine irritation. American Journal of Epidemiology. 2001; 153: 11–19.

[24] Stewart EA, Nowak RA. New concepts in the treatment of uterine leiomyomas. Obstetrics & Gynecology. 1998; 92: 624–627.

[25] Wise LA, Laughlin-Tommaso SK. Epidemiology of uterine fibroids: from menarche to menopause. Clinical Obstetrics and Gynecology. 2016; 59: 2–24.

[26] Monleón J, Cañete ML, Caballero V, Del Campo M, Doménech A, Losada MÁ, *et al.* Epidemiology of uterine myomas and clinical practice in Spain: an observational study. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2018; 226: 59–65.

[27] Parazzini F, Negri E, La Vecchia C, Fedele L, Rabaiotti M, Luchini L. Oral contraceptive use and risk of uterine fibroids. Obstetrics and Gynecology. 1992; 79: 430–433.

[28] Chiaffarino F, Parazzini F, La Vecchia C, Marsico S, Surace M, Ricci E. Use of oral contraceptives and uterine fibroids: results from a case-control study. British Journal of Obstetrics and Gynaecology. 1999; 106: 857–860.

[29] Qin J, Yang T, Kong F, Zhou Q. Oral contraceptive use and uterine leiomyoma risk: a meta-analysis based on cohort and case-control studies. Archives of Gynecology and Obstetrics. 2013; 288: 139–148.

[30] Modugno F, Ness RB, Chen C, Weiss NS. Inflammation and endometrial cancer: a hypothesis. Cancer Epidemiology, Biomarkers & Prevention 2005; 14: 2840–2847.

[31] Wise LA, Palmer JR, Harlow BL, Spiegelmane D, Stewart EA, Adams-Campbell LL, *et al.* Risk of uterine leiomyomata in relation to tobacco, alcohol and caffeine consumption in the Black Women's Health Study. Human reproduction. 2004; 19: 1746–1754.