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Research article

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The association of fibrocystic breast disease with endometrial histopathological results in abnormal uterine bleeding

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This study was approved by Dr. Sami Ulus Women's Health Education and Research Hospital, Clinical Research Ethics Committee (Number: 2020-KAEK-141/086, Protocol Number: E-21/02-85).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Fibrocystic breast disease (FBD) is the most frequent benign breast disease. Increased estrogen and decreased progesterone concentrations are thought to be involved in the pathogenesis of FBD. But there is insufficient data on benign breast disease and endometrial pathology. This study evaluates the association between FBD and endometrial pathology in women complaining of abnormal uterine bleeding.

Methods: This study was designed as a retrospective case-control study. The medical records of women who had endometrial sampling for abnormal uterine bleeding between 2018 and 2020 were evaluated. Patients with FBD were included in the study group, while the first patients who had endometrial sampling after patients with FBD and without breast disease were recruited as the control group. Demographic, laboratory data, and endometrial histopathological results were obtained from hospital records and compared between the groups.

Results: In total, 250 women (106 women with FBD and 144 without breast disease) were recruited for the study. There was no statistically significant difference in mean age, gravidity, parity, and BMI between FBD and control groups. Endometrial hyperplasia without atypia (19.8% versus 10.5%, respectively, P = 0.037) and endometrial polyp (12.2% versus 4.8%, respectively, P = 0.033) were found to be significantly increased in patients with FBD than women without the disease. There was no statistically significant difference in terms of other histopathological results between the groups.

Conclusion: Evaluation of the endometrium for abnormal uterine bleeding is essential for early diagnosis and treatment of endometrial pathology, especially for endometrial cancer. In this study, we found that women with FBD have an increased risk for endometrial hyperplasia and endometrial polyp. As endometrial hyperplasia is a precursor lesion for endometrial cancer, clinicians should pay attention to and investigate menstrual bleeding abnormalities of women with FBD and should not delay the evaluation of the endometrium.

Keywords: Fibrocystic breast disease, Endometrial pathology, Hyperplasia, Polyp

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Introduction

Benign breast disease represents a spectrum of disorders, and fibrocystic breast disease (FBD), recently termed fibrocystic changes, is the most frequent benign breast disease. The incidence of FBD is approximately 7% in the general population and is mostly seen between 20 and 50 years of age [1]. It has been suggested that the balance of estrogen and progesterone affects the mammary gland [2]. The exact etiology of FBD is unknown. However, an imbalance in steroid ovary hormones with relatively increased estrogen and decreased progesterone concentration during the menstrual cycle may be involved in the etiology of FBD [2, 3].

Abnormal uterine bleeding (AUB) is used for uterine bleeding outside the normal menstruation pattern. It is the most common gynecological complaint and occurs in 9–14% of women, accounting for two-thirds of all hysterectomies [4-5]. Uterine pathologies (myomas, polyps, endometrial hyperplasia or cancer) and ovulatory disorders are common causes of AUB [6]. Endometrial hyperplasia (EH) is a precursor lesion of endometrial adenocarcinoma (EAC), so evaluation of the endometrium for endometrial pathologies and treatment of AUB in women is important. Chronic estrogen stimulation without progesterone is considered a major risk factor for both pathologies [7].

Although an association between gynecological cancers such as ovarian and endometrial cancer with breast cancer is known, there is insufficient data on benign breast disease and endometrial pathology. In the present study, we aimed to investigate if there is an association between FBD and endometrial pathology results in women with AUB.

Materials and methods

This retrospective case-control study was conducted at the Dr. Sami Ulus Women's Health Education and Research Hospital. The medical records of all patients who had endometrial sampling for AUB between 2018 and 2020 were systematically evaluated. Women who had endometrial sampling for AUB with FBD were taken to the study group, and the first patients who had endometrial sampling after patients with FBD and without breast disease were recruited as the control group. Patients with postmenopausal status, malignant disease, women on hormone treatment and women with chronic disease (e.g., diabetes mellitus, hypertension, thyroid disease) were excluded from the study. This clinical study was approved by Dr. Sami Ulus Women's Health Education and Research Hospital, Clinical Research Ethics Committee (Number: 2020-KAEK-141/086, Protocol Number: E-21/02-85).

AUB was defined as bleeding abnormal in frequency, prolonged menstrual bleeding (>8 days), heavy menstrual bleeding (bleeding that affects women's physical and social life), or intermenstrual bleeding.

All women were examined with a speculum for cervical lesions, and a cervical smear was taken from all patients. Serum human chorionic gonadotrophin (hCG) was measured to exclude pregnancy. Serum complete blood count, prolactin (PRL), and thyroid-stimulating hormone (TSH) concentrations were measured for all women. Transvaginal ultrasonography was performed, and endometrial sampling was done with all women. Women with organic pathology (such as myoma, cervical or vaginal lesion) and women using an intrauterine device were excluded from the study. Endometrial pathological results were classified as proliferative endometrium (PE), secretory endometrium (SE), endometrial polyp (EP), chronic endometritis (CE), endometrial hyperplasia (EH) without atypia, endometrial hyperplasia with atypia, and endometrial adenocarcinoma (EAC). FBD was defined as anechoic cystic lesions or the presence of diffuse micronodular or microcytic changes of breast tissue on breast ultrasound or mammography [8, 9]. All women in the study population had breast ultrasound examinations.

Demographic data were recorded from patients' files, including all patients' age, parity, BMI, and laboratory data. Endometrial histopathological results were obtained from the patient hospital records. The patients in the study population were classified into two groups: Group 1, patients with FBD (n = 106) and Group 2, patients without breast disease (n = 144). Endometrial histopathological results were compared between the two groups.

Statistical analysis

Statistical Package for Social Sciences, Windows version 20.0 (SPSS, Chicago, IL, USA), was used for study data analyses. Mean, and standard deviation (SD) were used for descriptive data. Normality of the data distribution and variance homogeneity were evaluated with the Kolmogorov-Smirnov test. The student's t-test was used to compare groups with normal distribution. The Chi-square test was used to compare categorical variables. Non-parametric tests, such as Mann–the Whitney U test or Fisher Exact test, were used to compare parameters with non-normal distribution. *P*-values < 0.05 was considered statistically significant.

Results

Two-hundred-fifty patients were included in the study. The mean age of the study population was 46.1 (4.7). The predominant histopathological result was PE+SE in 144 (57.6%) patients. DPP was reported in 11 (4.4%), EH without atypia was reported in 36 (1.4%), and EH with atypia was reported in 18 (7.2%) women. One patient had a diagnosis of endometrial adenocarcinoma. The endometrial histopathological results of the study population are presented in Table 1.

Table 1: Endometrial histopathological results of the study population

Variable	Study population (n = 250) n (%)
Proliferative endometrium + Secretory endometrium	144 (57.6%)
Disordered proliferative pattern	11 (4.4%)
Endometrial polyp	20 (8%)
Chronic endometritis	20 (8%)
Endometrial hyperplasia without atypia	36 (14.4%)
Endometrial hyperplasia with atypia	18 (7.2%)
Endometrial adenocarcinoma	1 (0.4%)
Total	250 (100%)

Mean age, gravidity, parity, and BMI values were similar between FBD and control groups. In terms of laboratory characteristics, serum TG levels were significantly higher in the FBD group than in the control group (146.1 [73.9] vs. 120.7 [40.5] respectively; *P* = 0.03), while there was no difference in other parameters. The demographic and laboratory data of the study are presented in Table 2.

Endometrial hyperplasia without atypia (19.8% vs 10.5%, respectively, P = 0.037) and endometrial polyp (12.2% vs 4.8%, respectively, P = 0.033) were significantly more frequent in patients with FBD than women without the disease. Proliferative endometrium+secretory endometrium was significantly less reported in the FBD group than the control group (47.2% versus 65.3 %, respectively, P = 0.004). Other histopathological results were similar between the groups. A comparison of endometrial histopathological results of the FBD and control groups is presented in Table 3.

Table 2: Comparison of demographic and laboratory findings of FBD and control groups

Variable	FBD group (n = 106)	Control group (n = 144)	*P*-value
Age (year)	46.1 (4.5)	46.08 (5.1)	0.90
Gravidity	2.7 (1.4)	2.5 (1.2)	0.29
Parity	2.3 (1.2)	2.08 (1.04)	0.09
BMI (kg/m^2)	30.3 (3.8)	30.4(3.5)	0.90
Hemoglobin(gr/dL)	11.9 (1.3)	11.7 (1.4)	0.80
Glucose (mg/dL)	99.7 (19.7)	103.5 (34.9)	0.37
ALT (U/L)	14.2 (7.2)	15.1 (4.1)	0.80
AST (U/L)	16.7 (8.1)	18.2 (5.6)	0.60
TC (mg/dL)	219.8 (41.3)	211.0 (41.4)	0.27
TG (mg/dL)	146.1 (73.9)	120.7 (40.5)	0.03*
LDL (mg/dL)	137.6 (36.8)	133.7 (38.7)	0.60
HDL (mg/dL)	53.1 (10.6)	56.0 (22.7)	0.37
HT (n, %)	26 (24.5%)	29 (20.1%)	0.40
DM (n,%)	10 (9.4%)	15 (10.4%)	0.79

BMI: Body Mass Index, WBC: White Blood Cell, Plt: Platelet, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, TC: Total Cholesterol, TG: Triglyceride, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, HT: Hypertension, DM, Diabetes Mellitus. Data are expressed as mean (standard deviation), * indicates statistical significance

Table 3: Comparison of endometrial histopathological results of FBD and control groups

Variable	FBD group (n = 106)	Control group (n = 144)	*P*-value
Proliferative endometrium + Secretory endometrium	50 (47.2%)	94 (65.3%)	0.004
Disordered proliferative pattern	4 (3.8%)	7 (4.8%)	0.76
Endometrial polyp	13 (12.2%)	7 (4.8%)	0.033*
Chronic endometritis	7(6.7%)	13 (9.1%)	0.48
Endometrial hyperplasia without atypia	21 (19.8%)	15 (10.5%)	0.037*
Endometrial hyperplasia with atypia	10 (9.4%)	8 (5.5%)	0.24
Endometrial adenocarcinoma	1 (0.9%)	0	-
Total	106 (100%)	144 (100%)	

Data are given as n (%), FBD; Fibrocystic Breast Disease, * indicates statistical significance

Discussion

In this study, we found that endometrial hyperplasia without atypia and endometrial polyp were more frequently observed in women who complained of AUB with FBD than those without breast disease. To our knowledge, our study is the first clinical study to report a relationship between endometrial histopathological findings and FBD in women with AUB.

Hormones play a critical role in the function of the breast and gynecological tissues, and most of the pathologies, including cancer in these organs, are related to excess exposure or relative imbalance in the levels of these hormones. FBD is the most common benign breast disease, and its incidence is approximately 7% in the general population. It is a hormone-dependent disease with lobular and diffuse increases in glandular tissue [10, 11]. Small cysts, large cysts, and diffuse micronodules may be seen, and pain, tension, and tender nodes in the breast are the most common complaints in women with FBD [12].

The balance between estrogen and progesterone is significant in the growth of the mammary gland, and hyperestrogenism and anovulation are suggested to be involved in the pathogenesis of FBD [2]. Inappropriate estrogen stimulation causes proliferation in the breast tissue and is thought to be responsible for the pathogenesis of FBD [13]. Mauvais-Jarvis et al. also verified this hypothesis [14]. Furthermore, in their study, Marchesoni et al. [15] showed that luteal phase progesterone levels were significantly lower in women with mastodynia and breast micronodularity than in women without breast disease. Wypych et al. [16] showed decreased progesterone levels in women with gross breast cysts and suggested that decreased progesterone activity can be a hormonal reason for the pathogenesis of benign breast disease. Some studies have also found a statistically significant relationship between polycystic ovary syndrome (PCOS) and FBD [17, 18]. Ozkaya et al. [19] found that FBD risk is increased in women with anovulation, and PCOS patients with hyperandrogenemia had a decreased risk of FBD when compared with anovulatory and normoandrogenemic PCOS patients. In their study, they found that hyperandrogenemia is protective for FBD.

Abnormal proliferation of endometrial glands causes EH, and its incidence is approximately 133 per 100,000 women-years [20]. Endometrial cancer (EC) is the most common gynecological malignancy affecting women in developed countries [21]. Chronic stimulation of the endometrium by estrogens unopposed by a progestin is responsible for both EH and EAC, so the risk factors are similar for both diseases. EH is a precursor lesion of EC, and the presence of cytological atypia is the main histological finding for its malignant potential, so early diagnosis and treatment of EH are important [7, 21].

Breast cancer (BC) is the most common malignancy and the first common cause of cancer death in women worldwide, and benign breast disease is also known to be a risk factor for BC [22]. Probably due to common risk factors (such as age, obesity, high endogenous estrogen levels, and higher insulin levels, and reproductive factors (such as earlier menarche or later menopause, nulliparity, and infertility), breast cancer patients have an increased risk of endometrial pathology [23]. The association between endometrium cancer and breast cancer is clear in the literature. However, the relationship between benign breast disease and endometrial pathology is unknown. Our study found that endometrial hyperplasia without aypia was significantly higher in women with FBD than in women without breast disease. There was no difference in endometrial hyperplasia with atypia between groups, and one patient was diagnosed with endometrial adenocarcinoma in the FBD group.

Endometrial polyp is one of the most common pathologies of abnormal genital bleeding in both premenopausal and postmenopausal women [24]. Hyperplastic overgrowth of the endometrial gland and stroma causes the formation of endometrial polyps. Endometrial polyps have estrogen and progesterone receptors, as in normal endometrial tissue, and progesterone has an antiproliferative role in the pathogenesis of endometrial polyps [25]. Age, obesity, postmenopausal hormone therapy, and tamoxifen treatment are known risk factors for the disease [25, 26]. Although the prevalence of endometrial polyp is not known exactly, in one study, it was found to be 23.8% among symptomatic women undergoing endometrial biopsy [27]. In their study of asymptomatic gynecological patients with breast cancer, Lopez et al. found a hysteroscopic diagnosis of endometrial polyp in 28.5% of all patients in their study group [28]. To our knowledge, this study is the first to investigate the prevalence of endometrial polyp in women with benign breast disease. In our study, we found that 12.2% of women with FBD and 4.8% of women without the disease had a diagnosis of

endometrial polyp, and the difference reached statistical significance. The histopathological results of CE and DPP were similar between the groups.

Limitations

Our study's limitations include its retrospective design and the low number of cases of endometrial carcinoma. Prospective large-scale studies are needed to better define the association between FBD and endometrial pathologies.

Conclusions

According to our knowledge, our study is the first preliminary study to report the association of FBD and endometrial pathology in women with abnormal bleeding. We showed that endometrial hyperplasia without atypia and endometrial polyps were more often diagnosed in women with FBD than without the disease. As endometrial hyperplasia is a precursor lesion for endometrial carcinoma, clinicians should pay attention to menstrual bleeding abnormalities in women with FBD and should not delay evaluation of the endometrium.

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