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Ovarian reserve assessment in crohn patients of reproductive age

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ABSTRACT

Objectives: Crohn's disease (CD) is a repeating bowel disease characterized by remission and exacerbation periods. The disease mostly affects adults of reproductive age. Women with desires to conceive are concerned about the effects of CD on their fertility. To demonstrate the relationship between ovarian reserve and CD anti-Müllerian hormone (AMH) levels, antral follicle count (AFC) and ovarian volüme were evaluated.

Material and methods: The prospective case-controlled study was conducted at a tertiary referral center in Istanbul between March–August 2019**.** Ovarian functions were evaluated in 50 patients with CD and in 95 healthy women. Serum gonadotropin and AMH levels were determined. AFCs and ovarian volumes were calculated for all subjects.

Results: AMH levels were significantly lower in CD patients (2.1 ± 0.8) compared to the control group (3.3 ± 0.9) (P = 0.001). Serum AMH levels were significantly lower in patients with active CD (2.1 ± 0.6) than the CD patients in remission (2.6 ± 0.8) (p = 0.002). Ovarian volumes and AFC values were significantly lower in both ovaries in CD patients compared to the controls (p < 0.05).

Conclusions: AMH levels, ovarian volume and AFC counts, and thus ovarian reserve was shown to be decreased in CD patients of reproductive age compared to healthy control subjects. Because possible effects of inflammatory damage may be seen in newly diagnosed female CD patients who desire to have a child, we believe that CD patients should be comprehensively assessed for ovarian reserve.

Key words: anti-mullerian hormone; crohn disease; inflammatory bowel disease; ovarian reserve

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INTRODUCTION

Crohn's disease (CD) is a repeating bowel disease characterized by remission and exacerbation periods [1]. The disease mostly affects adults of reproductive age. Young women with desire of conception usually are concerned about the potential effects of CD on fertility and pregnancy [2].

According to the latest consensus of the European Crohn's and Colitis Organisation (ECCO), a decrease in fertility is seen especially in women with active CD [3]. CD may reduce fertility directly through inflammation observed in the fallopian tubes and in the ovaries, or indirectly following surgical treatments which can lead to tubal adhesions. There are a number of data about pregnancy outcomes in young women with CD [4]. However, the results of the studies investigating fertility and fecundity in women with CD are controversial [5, 6]. Some authors advocate a relationship between CD and subfertility [5], while others report the same rate of infertility in these patients with that of the general population [6, 7].

Ovarian reserve is an indicator of female fertility and it can be evaluated with age, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, inhibin B, anti-Müllerian hormone (AMH) concentrations, ovarian volume, antral follicle count (AFC) and ovarian biopsy [8].

In this study, we aimed to evaluate the effects of CD on ovarian reserve, and to demonstrate CD's effect on ovarian ageing by comparing serum AMH, steroids, and gon-

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adotropin levels of female CD patients with the results of healthy, and fertile reference population.

MATERIAL AND METHODS

This prospective case-controlled study was conducted at a tertiary referral center in Istanbul province between March 2019 and August 2019. The study protocol was approved by the institution's Ethics Committee (KAEK/2019.03.40) and registered to ClinicalTrials.gov (NCT03897400). According to the G-Power analysis, the number of subjects in the study group was 50 with 5% error and 80% power. Ninety-five patients were recruited to the control group with a case control ratio of 1:2.

After receiving ethics approval, 62 female patients, aged between 18–40 years, diagnosed with CD who were consulted to our outpatient clinic for gynecological examination and who gave written informed consent were included in the study. Inclusion criteria were as follows: regular menstrual periods, no gynecological pathologies detected by gynecological or ultrasound examination, and no history of infertility. Tweleve CD patients aged over 40 years, who had previously undergone ovarian resection, who had polycystic ovary syndrome, renal failure (serum creatinine levels > 1.2 mg/dL), suspected malignancy, hereditary or acquired hematologic disease, who were pregnant or during lactation period, who had severe comorbid chronic diseases, abnormal thyroid function tests, known serious psychological problems or alcohol abuse were excluded from the study. In addition, women with first degree relatives diagnosed with inflammatory bowel disease (IBD), with positive surgical histories and currently under medical treatment were excluded from the study. The control group consisted of women without any known disease and blood transfusion.

Finally the study included 50 women of reproductive age with the diagnosis of CD confirmed with endoscopic, radiologic and histopathological findings, and a volunteer group of 95 healthy women as the control group. Demographic features, history of surgical and medical treatments, gravidity, parity, menstrual cycle, history of smoking, age of CD diagnosis, duration of CD, history of CD related surgery and medication were recorded. Body weight and height were measured in all women using electronic digital scales and light clothes, and body mass index (BMI) was calculated.

During the early follicular phase (day 3 of the menstrual cycle) early morning venous blood samples were collected in lithium-heparin tubes to determine AMH and hormone levels. AMH levels were determined in batches using enzyme-linked immunosorbent assay (ELISA) (Ansh Labs, Webster, USA). AMH correlates with AFC with a sensitive measurement range of 0.405–6.96 ng/mL [9]. In addition, serum acute phase reactants (human C reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelet count and albumin) were measured in all participants.

The Crohn's Disease Activity Index (CDAI) is used to evaluate disease severity. A score ranging from 0 to over 600 is given to the patients according to their symptoms which they record in a diary for seven days along with other measurements such as the patient's weight, CDAI, range of bowel involvement and drug use. Patients with a CDAI score of < 150 were considered to be in remission, while patients with scores higher than 150 were accepted to have active disease. All patients received a transvaginal ultrasonographic (TVUS) examination with a 8.5 MHz transvaginal transducer (ATL 5000 HDI, Philips, Netherlands) performed by a trained physician for the measurements of AFC and ovarian volume. AFC was calculated by counting the follicles of 2–10 mm diameter in both ovaries with a standard systemic approach. Ovarian volume was calcuted using the following formula: Length (L) × Width (W) × Thickness (T) × 0.523 [10].

Statistical analysis was performed with SPSS Statistics v. 20 for Macintosh package software. Normality of the continuous variables was tested using Kolmogorov-Smirnov test. Continuous variables are expressed as mean ± standard deviation and nominal variables as number of cases (n) and percentage (%). Significance of the differences between the groups in terms of the mean values was studied using Student's t test. Nominal valuables were evaluated using Chi-square test. Correlation between CDAI and serum AMH levels in CD patients was investigated with Pearson's correlation analysis. A p value of < 0.05 was considered statistically significant.

RESULTS

A total of 157 women matched for demographic features including age, gender and BMI were included in the study. Among these, 12 CD patients were excluded according to the exclusion criteria. The groups consisted of 50 CD patients and 95 healthy control subjects. Clinical and demographic data of CD patients and healthy controls are shown in Table 1. Median follow-up duration was 68 months for CD patients. Median CDAI was 128 in these patients.

Among acute phase reactants, ESR was significantly higher in CD patients compared to the healthy controls ($p < 0.05$). There were no significant differences between either group in terms of albumin levels, CRP and leukocyte counts ($p > 0.05$). Both groups were statistically similar in terms of estradiol (E2), FSH, LH, prolactin (PRL), hemoglobin (g/dL), platelet count ($\times 10^3$), ferritin (ug/L), creatinine (mg/dl) levels. Results of the serum AMH levels, ovarian volumes, and AFC are given in Table 2. Serum AMH levels were significantly lower in CD patients ($p < 0.05$) (Tab. 3).

Table 1. Demographic ve clinical characteristics of the crohn disease patients and controls

Variables	CD patients (n: 50)	Control group (n: 95)	p value
Age [years]*	29.6 ± 6.2	30.6 ± 6.4	0.239
BMI [kg/m^2]*	26.5 ± 5.6	25.5 ± 5.3	0.517
Gravidity [n]*	1.6 ± 1.4	1.5 ± 1.1	0.198
Parity [n]*	1.3 ± 1.1	1.2 ± 0.9	0.543
Abortions [n]*	0.1 ± 0.07	0.1 ± 0.05	0.659
Alive [n]*	1.2 ± 0.3	1.1 ± 0.2	0.987
Age at CD onset [years]*	29.6 ± 6.2	–	–
Age at CD diagnosis [years]*	21.3 ± 5.1	–	–
Disease duration [years]*	5.3 ± 4.1	–	–
Intestinal resection, n (%)** Ileal Colonic Ileocolonic	8 (16%) 3 (6%) 2 (4%) 3 (6%)	–	–
Treatment, n (%)** Azathioprine Methotrexate Infliximab	40 (80%) 12 (24%) 8 (16%) 20 (40%)	–	–

*Student's t- test; ** Chi-square test; CD — crohn disease; BMI — body mass index; Values are presented as mean (standard deviation) for continuous variables and number (percent) for categorical variables

Table 2. Anti-Müllerian hormone levels, ovarian volumes, and antral follicle numbers of the groups

Variables	CD patients (n: 50)	Control group (n: 95)	p value
AMH [pg/mL, Mean ± SD]	2.1 ± 0.8	3.3 ± 0.9	0.001
Right ovarian volume [cm^3]	7.1 ± 4.3	8.8 ± 5.2	0.001
Left ovarian volume [cm^3]	7.2 ± 4.1	8.7 ± 4.3	0.002
Right ovarian AFC [n]	4.1 ± 2.1	5.8 ± 2.3	0.002
Left ovarian AFC [n]	3.2 ± 0.8	5.3 ± 2.9	0.001

CD — Crohn disease; SD — standard deviation; AMH — Anti-Müllerian hormone (pg/mL); AFC — antral follicle count

Table 3. Comparison of serum anti-Müllerian hormone levels between crohn disease (CD) patients and controls and various subgroups of CD patients

		Serum AMH levels [ng/mL]	p value
All participants	CD patients (n = 50) Controls (n = 95)	2.1 ± 0.8 3.3 ± 0.9	0.001
Disease activity	Active CD (n = 21) In-remission (n = 29)	2.1 ± 0.6 2.6 ± 0.8	0.002
Disease duration	Less than 5 years (n = 23) More than 5 years (n = 27)	2.7 ± 0.6 2.2 ± 0.4	0.000
History of CD- related surgery	Yes (n = 8) No (n = 42)	2.3 ± 0.7 2.5 ± 0.8	0.237
History of medical treatment	Yes (n = 40) No (n = 10)	2.6 ± 0.4 2.4 ± 0.8	0.904

CD — crohn disease; AMH — Anti-Müllerian hormone (pg/mL)

When CD patients were divided into groups according to CDAI results; 21 (42%) CD patients were evaluated as having active disease and 29 (48%) as in remission. Serum AMH levels were significantly lower in CD patients with active disease compared to those in remission ($p < 0.05$). Only 8 (16%) CD patients had a history of surgical treatment. Among these, 3 underwent ileal, 2 colonic and 3 ileocolonic operations. There was no significant difference between these patients and CD patients without a history of resection in terms of serum AMH levels ($p = 0.237$) (Tab. 3). Serum AMH levels were lower in smoker CD patients compared to non-smoker CD patients, but the difference was not significant ($p > 0.05$). Among CD patients; 12 received azathioprine, 8 received methotrexate, and 20 were treated only by infliximab in monotherapy. None of the patients received corticosteroids or 5-ASA (5-aminosalicylic acid) (Tab. 3). There was no significant difference between the patients who received medical therapy and those who did not receive in terms of serum AMH levels ($p > 0.05$).

We performed a correlation analysis between CDAI scores and serum AMH levels, disease duration, and ovarian volume. There was a significant negative correlation between CDAI and serum AMH levels in CD patients ($r = –0.317$, $p < 0.001$). Again, there was a significant negative correlation between disease duration and serum AHM levels in CD patients ($r = –0.618$, $p = 0.000$). A significant positive correlation was observed between ovarian volume and serum AMH levels in CD patients ($r = 0.243$, $p = 0.001$).

DISCUSSION

Gynecological diseases are common in women with CD. Therefore, abdominopelvic pain, menstrual irregularities, pelvic inflammatory diseases may be related to gynecological pathologies such as endometriosis or ovarian pathologies. This may interfere with earlier diagnosis of inflammatory bowel disease due to similar symptoms [5, 11, 12]. Women with CD in general are in their reproductive ages with a fertility wish. Therefore, they are concerned about the harmful effects of the disease on their fertility potential. CD has an inflammatory effect on the fallopian tubes and ovaries especially during the active phase of the disease leading to decreased fertility [5, 6, 12, 13]. AMH seems an early, reliable and direct indicator of decreased ovarian function. In IVF studies, a serum AMH level > 1.32 ng/mL indicated a good ovarian reserve, while a serum AMH level < 1.32 ng/mL has been accepted as an indicator of decreased ovarian pool [14]. Therefore, serum AMH levels can be used in the evaluation of ovarian reserve [15]. In the first study evaluating ovarian reserve using AMH levels, it was demonstrated that female CD patients of 30–40 years of age had significantly lower AMH levels compared to healthy controls [16]. However, this study was retrospectively designed. To our knowledge our study was the first prospective study evaluating ovarian reserve in female CD patients.

After Dr Crohn's first report on CD and fertility, who thought that fertility was not impaired by CD, following reports concluded contrary results [5, 6]. These studies demonstrated that fertility rate might be lower in women with CD compared to the general European and Australian populations. The etiology is unclear. However, most authors suggested that lower fertility rate in women with CD was due to the postponement of conception or lack of desire to have a child [17]. The lack of desire for conception is based on the heritability of CD, the increased risk of congenital abnormalities, and teratogenicity of CD medications. This underlines the need for a thorough medical communication on reproduction with CD patients [2, 18]. Postponement of conception expose women with CD to age related change in ovarian reserve and associated infertility.

Epidemiologic studies have demonstrated that female fertility decreseases significantly after 30 years of age especially due to loss of ovarian follicles [19]. This follicular loss is physiological in some women, although it can be accelerated, resulting in premature ovarian reserve changes [16]. In a recent study, age older than 25 years and an active CD were both found to be independently associated with low ovarian reserve. Currently AMH is considered as the most accurate marker in the evaluation of ovarian reserve. In the above-mentioned study, decreased AMH levels i CD patients older than 25 years of age were reported. On the other hand serum AMH levels of patients younger than 25 were similar to that of the controls [20].

It has been demonstrated that the levels of serum AHM secreted by the antral follicles reflect ovarian follicle pool, and can be used as one of the hormonal markers associated with ovarian reserve in the diagnosis of ovarian insufficiency [21]. There is a lifelong decrease in the number and quality of oocytes in normal women [19]. AMH can be successfully used in order to evaluate damage to the ovary caused by pathologies or therapeutic agents [22]. It is possible to use AMH for the evaluation of fertility potential in women with CD who are at a higher risk, similarly as used among the healthy population [16, 23]. In our study, we discussed the effects of AMH levels on fertility potential in women with CD.

In a study by Senates et al. [23], CD patients were divided into two groups according to their disease status. When these groups were compared with each other, serum AMH levels were found to be significantly lower in patients with active CD. The mean serum AMH level was reported as 0.33 ± 0.25 ng/mL, which was lower than the accepted cut-off value (0.5 ng/mL) for normal ovarian reserve. This result supports other studies showing that fertility is

very low in female CD patients even in the absence of any structural pathology in the genital system [23]. In our study, we observed differences in the medical histories, various exacerbation frequencies and medication protocols of CD patients. This enabled us to evaluate the study population also in terms of inflammation and disease activity. Serum AMH levels were significantly lower in patients with active disease.

Intestinal and extra-intestinal complications in CD patients tend to increase as the duration of the disease is prolonged [24]. We also evaluated serum AMH levels on the basis of disease duration. When CD patients were divided into groups according to disease duration and AMH levels; serum AMH levels were found to be higher in patients with a disease of duration less than five years.

Furthermore, pelvic surgery may cause damage to reproductive organs, namely ovaries and tubas especially following ileal pouch-anal anastomosis [25]. Previous studies have suggested an association between surgical intervention and decreased fertility in women with CD [26]. In the present study, no significant difference was found in serum AMH levels between women operated due to CD and those without a history of surgery.

In our study, along with the other factors that may damage reproduction performance, smoking status was also recorded in women with CD. In a study by Van der Heide et al. [25], patients known to have CD were mostly smokers. In that study, smoking in CD patients was associated with longer exacerbation periods, more complications, more need for steroids and postoperative relapse [27]. Detrimental effects of tobacco on ovarian physiology has been subject to debate for a long time, and some newer studies have demonstrated decreased ovarian reserve in smokers [28]. In our study, AMH levels were higher in non-smoker CD patients than in smoker ones, but the difference between smokers and non-smokers was not statistically significant.

Although our study has the power for evaluating serum AMH levels between patient and control groups, our relatively small number of patients could limit generalization of our results. Since this study was conducted with Turkish-origin individuals, it could be insufficient in evaluation of individuals from different ethnic origins. One of the limitations of our study is; Even if the number of patients receiving immunosuppressive agents is low, it is not possible to distinguish whether the cause of low ovarian reserve is caused by Crohn disease or medical treatment used for the disease. However, being the first prospective study about ovarian reserve among Crohn's disease patients, and using additional parameters such as AFC, ovarian volume and FSH in addition to AHM are strengths of our study.

CONCLUSIONS

This study demostrated that CD causes a significant decrease in serum AMH levels of women within the reproductive ages compared to healthy women. This effect is most prominent in active disease periods. In the light of these data, we believe that CD patients' awareness of their reproductive potential could be increased by ovarian reserve evaluation to be performed in an early period, and making conception plans in this direction could be helpful for these patients.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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