Journal of Crohn's and Colitis (2013) 7, e29–e34

Available online at www.sciencedirect.com

SciVerse ScienceDirect

Serum anti-Müllerian hormone levels are lower in reproductive-age women with Crohn's disease compared to healthy control women

Ebubekir Şenateş [a,*], Yaşar Çolak [b], Emrullah Düzgün Erdem [a], Atakan Yeşil [a], Ender Coşkunpınar [c], Önder Şahin [c], Mustafa Erhan Altunöz [d], Ilyas Tuncer [e], Ayşe O. Kurdaş Övünç [a]

[a] *Haydarpaşa Numune Education and Research Hospital, Department of Gastroenterology, Turkey*
[b] *Mardin State Hospital, Department of Gastroenterology, Turkey*
[c] *Department of Molecular Medicine, Institute of Experimental Medicine Research, Istanbul University, Turkey*
[d] *Sakarya Education and Research Hospital, Department of Gastroenterology, Turkey*
[e] *Göztepe Education and Research Hospital, Department of Gastroenterology, Turkey*

Received 21 February 2012; received in revised form 28 February 2012; accepted 5 March 2012

KEYWORDS
Crohn's disease;
Anti-Müllerian hormone;
Ovarian reserve

Abstract

Background and aim: Crohn's disease (CD) decreases fertility both directly, by inducing inflammation in the fallopian tubes and ovaries, and indirectly, through the surgical interventions and tubal adhesions associated with disease treatment. Anti-müllerian hormone (AMH) is a reliable indicator of ovarian reserve in women. We aimed to compare serum AMH levels between reproductive-age women with CD and healthy controls.
Methods: Serum AMH levels were measured by ELISA in 35 women with CD and 35 age-matched healthy women controls.
Results: CD patients and controls were similar in terms of age, height, weight and BMI. Mean CD duration was 60 months. CRP, ESR and leukocyte counts were significantly higher in CD patients compared to the controls ($p<0.001$, $p=0.004$ and $p=0.04$, respectively). AMH levels in CD patients (1.02 ± 0.72) were significantly lower compared to the controls (1.89 ± 1.80) ($p=0.009$). Serum AMH levels in CD patients with active disease (0.33 ± 0.25) were significantly lower compared to CD patients who were in remission (1.53 ± 0.49) ($p=0.001$). Serum AMH levels were similar in CD patients with a disease duration of less than 5 years (17 patients) and CD patients with a disease duration of greater than 5 years (18 patients) ($p=0.8$). In CD patients, a negative

* Corresponding author at: Haydarpaşa Numune Education and Research Hospital, Department of Gastroenterology, Tibbiye Cad. No:40 34668 Uskudar, Istanbul, Turkey. Tel.: +90 216 542 32 32-1623, +90 506 688 38 13 (Mobile); fax: +90 216 346 74 63.
E-mail address: ebubekirsenates@yahoo.com (E. Şenateş).

1873-9946/$ - see front matter
doi:10.1016/j.crohns.2012.03.003

correlation between CDAI and serum AMH levels was found ($r=-0.718$, $p<0.001$). Serum AMH levels were similar in CD patients who had (6 patients) and had not undergone (29 patients) surgical treatment ($p=0.2$).
Conclusion: Serum AMH levels of reproductive-age women with CD were significantly lower compared to the controls. CDAI and AMH are inversely correlated.

1. Introduction

Crohn's disease (CD) is a recurrent, chronic inflammatory disease of idiopathic origin that is characterized by periods of remission and flare-ups.

CD is associated with various extraintestinal pathologies in addition to numerous intestinal pathologies. These extraintestinal symptoms often affect the eyes, skin, musculoskeletal, renal, hepatobiliary and hematologic systems.

Women with CD have fewer children compared to healthy women.[1] The underlying reason for this difference is hypothesized to be related to a decreased desire to have children by women with CD rather than being caused by the disease itself.[2] However, the most recent consensus report, published by the European Crohn's and Colitis Organisation (ECCO), documents decreased fertility in women with CD, especially in patients with active disease.[2] CD is a chronic inflammatory disease that decreases fertility both directly, through the induction of inflammation in the fallopian tubes and ovaries, and indirectly, through the surgical interventions and tubal adhesions that are associated with disease treatment.[3–15]

Objective indicators that reflect ovarian reserve, an indicator of fertility in reproductive-age women, include estradiol, follicle-stimulating hormone (FSH) and anti-Müllerian hormone (AMH); additionally, the clomiphene citrate challenge test (CCCT), the exogenous FSH ovarian reserve test (EFORT) or an ultrasound assessment of the antral follicle count or ovarian volume can be performed to assess fertility.[16] Tests involving estradiol and FSH require sample collection on a particular day of the menstrual cycle (day 3), and the collection of more than one sample is often needed.[16] The CCCT, EFORT and ultrasound assessment of antral follicle count or ovarian volume have limitations in their methodologies and value for predicting fertility. However, because AMH levels vary only slightly during the menstrual cycle, an analysis can be conducted on a single sample collected at any point during the patient's menstrual cycle. Therefore, AMH testing has replaced these other fertility tests over time, especially in the context of in vitro fertilization (IVF) studies.[17–19]

In recent studies,[16,20–22] AMH levels have been reported to be a good indicator of ovarian reserve in women. AMH is a member of the transforming growth factor-β (TGF-β) family and is secreted by small (<8 mm) preantral and early antral follicles.[16] AMH levels reflect the size of the primordial follicle pool. In mature women, AMH levels decrease over time due to the reduction in the primordial follicle pool that occurs with advancing age.[23] Consistent with this phenomenon, AMH levels decrease during menopause and eventually become undetectable.[24] AMH levels appear to be an early, reliable, direct indicator of reduced ovarian function. Serum AMH levels exceeding 0.5 ng/mL are indicative of a good ovarian reserve, whereas serum levels below 0.5 ng/mL are indicative of a reduced ovarian pool. Serum AMH levels below 0.15 ng/mL indicate that the patient will respond poorly to IVF.[25,26] Thus, AMH measurements can play an important role in the diagnosis of patients with low ovarian reserve.[27]

The aim of this study was to compare serum AMH levels between female reproductive-age patients with CD and healthy, age-matched women.

2. Materials and methods

In total, 35 reproductive-age female patients who had a definitive clinical CD diagnosis that was confirmed through endoscopic, radiologic and histopathologic findings were included in the study. The women were treated and subsequently followed at the Haydarpasa Numune Education and Research Hospital between 2004 and 2010. Additionally, 35 healthy, age-matched women were included in the study as controls.

Exclusion criteria for CD patients were as follows: age greater than 40 years, having a previous ovarian resection, renal failure (serum creatinine levels >1.2 mg/dL), a diagnosis or suspicion of malignancy, the presence of hereditary or acquired hematologic disease, pregnancy, current lactation, the presence of a serious comorbid chronic illness, chronic liver disease-induced cirrhosis, abnormal thyroid function tests, the presence of a known serious psychological problem, alcoholism and male gender. The control group was selected from women with no known diseases and who had never received any drug or transfusion treatment. In addition, women must have had no inflammatory bowel disease diagnoses in any of their first-degree relatives, no surgical history and not be taking any current medications.

At the beginning of the study, demographic data such as age, height, weight and body mass index (BMI) were recorded for all study participants. Additionally, serum levels of acute phase reactants (CRP, ESR, platelet count and albumin) were determined, and complete blood work analyses were performed for all subjects. For CD patients, the CD activity index (CDAI), sites of intestinal disease involvement and any medications used were recorded. CD patients with a CDAI below 150 were considered to be in remission, whereas CD patients with a CDAI over 150 were considered to have active CD.

Patients and healthy controls were compared in terms of demographics, serum biochemical parameters and serum AMH levels. Next, CD patients were divided into patients with active disease and patients in remission, and the groups were compared in terms of their serum AMH levels. In CD patients, the existence of a correlation between CDAI and serum AMH levels was investigated using a Pearson correlation analysis. Finally, serum AMH levels in CD patients who had

Table 1 Clinical and demographic data of the CD patients and controls.

Characteristic	CD (n = 35)	Control (n = 35)	p
Age (year)	34 ± 5	33 ± 5	0.3
Gender (F)	35	35	1
Oral contraceptive drug use (yes)	6	10	0.3
Patients with children (n)	23	28	0.2
Patients with miscarriage (n)	5	3	0.7
Clinical disease			
Active (CDAI >150)	15 (43%)	NA	
Remission (CDAI <150)	20 (57%)		
Height (cm)	161 ± 6	160 ± 5	0.6
Weight (kg)	63 ± 12	68 ± 13	0.2
BMI (kg/m^2)	26.6 ± 5.3	24.5 ± 4.2	0.1
Disease duration (months)	60 (min, 9; max, 163)	NA	
CDAI	134 (min, 44; max, 492)	NA	
Surgery (yes)	6/35	NA	
Site of involvement (for CD)		NA	
Ileal	12 (34%)		
Ileocolonic	13 (37%)		
Colonic	10 (29%)		

NA: Not applicable.

undergone surgery due to CD complications were compared to CD patients who had not undergone surgery.

2.1. Serum collection and analysis

All blood samples were collected from the antecubital fossa vein between 8:00 and 9:00 in the morning after a 12-hour fast. Venous blood samples were deposited into polypropylene tubes containing sodium EDTA. The serum samples were then immediately centrifuged for 15 min at 4 °C at 3000 *g*, transferred to Eppendorf tubes and stored at −80 °C for further analysis.

Serum AMH levels were measured using a commercially available ACTIVE MIS/AMH Enzyme-Linked Immunosorbent Assay (ELISA) Kit (Diagnostic Systems Laboratories, Inc., Webster, TX, USA). The limit of detection for this kit is 0.006 ng/mL for 90% accuracy.

2.2. Statistical evaluation

SPSS v. 15.0 software (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. A sample size of 35 patients per group was determined to be sufficient to detect, with 80% power, a 25% difference between patients and controls. For the comparison of categorical variables, Pearson's chi-square test was used. For the comparison of numerical variables with a normal distribution, a Student's *t* test was used. For the comparison of numerical variables without a normal distribution, a Mann–Whitney *U*-test was used. To compare more than 2 numerical variables between groups, a Kruskal–Wallis test was used. To assess the relationship between 2 variables, a Pearson correlation analysis was performed. A two tailed p-value <0.05 was considered to be significant.

3. Results

A total of 70 women, 35 with CD and 35 healthy controls with equivalent demographic characteristics in terms of age, gender, height, weight and BMI, were included in the study. The clinical and demographic data of the CD patients and healthy controls are shown in Table 1.

There were no significant differences between the CD patients and healthy controls in terms of age, height, weight or BMI (Table 1). The median follow-up period of the CD patients was 60 months (min, 9; max, 163). For the CD patients, the median CDAI was 134 (min, 44; max, 492). Of the CD patients, 15 (43%) were considered to have active disease, while 20 (57%) were considered to be in remission. Only 6 (17.1%) CD patients had a history of surgical treatment.

The results for the serum biochemical parameters assessed in the two groups are shown in Table 2. While levels of the acute phase reactants ESR and CRP and leukocyte

Table 2 Serum biochemical parameters of the CD patients and controls included in the study.

Parameter	CD (n = 35)	Control (n = 35)	p
ESR	34 ± 24	17 ± 10	<0.001
CRP	1.91 ± 3.02	0.38 ± 0.28	0.004
White blood cells	7354 ± 2569	6277 ± 1424	0.04
Hemoglobin	11.8 ± 1.4	12 ± 1.1	0.5
Platelet count	304,314 ± 123,146	271,142 ± 72,939	0.2
Albumin	4.06 ± 0.45	4.35 ± 0.30	0.002
Thyroid-stimulating hormone	1.3410 ± 0.59842	1.7734 ± 1.10190	0.06
Ferritin	11 (min, 3; max, 384)	32 (min, 3; max, 95)	0.9
FBG	89 ± 12	85 ± 10	0.1
Creatinine	0.68 ± 0.12	0.75 ± 0.14	0.3
ALT	20 ± 7	17 ± 8	0.2
AST	17 ± 9	20 ± 9	0.3

Abbreviations: ESR; erythrocyte sedimentation rate, CRP; C reactive protein, FGB; Fasting Blood Glucose, ALT; alanine aminotransferase, and AST; aspartate aminotransferase.

numbers were significantly higher in CD patients compared to healthy controls ($p<0.001$, $p=0.004$ and $p=0.04$, respectively), the level of the negative acute phase reactant albumin was significantly lower in CD patients than in healthy controls ($p=0.002$). No significant differences were detected between the two groups in terms of their serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting blood sugar (FBS) and thyroid-stimulating hormone (TSH) (Table 2).

A comparison of serum AMH levels in CD patients and healthy controls is shown in Table 3. Serum AMH levels were significantly lower in CD patients than in healthy controls (Table 3).

After the CD patients were divided into groups according to their CDAI results, we compared CD patients with active disease to CD patients who were in remission in terms of their serum AMH levels (Table 3). Serum AMH levels were significantly lower in patients with active CD than in CD patients who were in remission ($p<0.001$) (Table 3). To analyze the relationship between serum AMH levels and disease duration, CD patients were divided into two groups based on whether they had been diagnosed with CD for less than 5 years or greater than 5 years; a comparison of AMH levels between these groups is shown in Table 3.

Serum AMH levels in patients who had a disease duration of more than 5 years were lower compared to patients who had a disease duration of less than 5 years; however, this difference was not statistically significant ($p=0.8$).

Fertility is known to be decreased in patients with active CD. Therefore, we investigated whether a correlation exists between CDAI scores and serum AMH levels. To test this possibility, we performed correlation analysis between serum AMH levels and CDAI scores (Table 4).

In CD patients, a negative correlation between CDAI and serum AMH levels was observed ($r=-0.718$, $p<0.001$). A diagram of the correlation between CDAI and serum AMH levels in CD patients is shown in Fig. 1. In total, 6 CD patients (17%) had undergone surgical treatment. When we compared the serum AMH levels of these patients to those of CD patients with no history of resection, no significant differences were detected ($p=0.2$) (Table 3).

Table 3 Comparison of serum AMH levels between CD patients and controls and various subgroups of CD patients.

Feature		Serum AMH levels (ng/mL)	p
All participants	CD patients (n=35)	1.02±0.72	0.009
	Controls (n=35)	1.89±1.80	
Disease activity	Active CD (n=15)	0.33±0.25	<0.001
	In-remission (n=20)	1.53±0.49	
Disease duration	Less than 5 years (n=17)	1.07±0.79	0.8
	More than 5 years (n=18)		
History of CD-related surgery	Yes (n=6)	1.33±0.49	0.2
	No (n=29)	0.95±0.75	

Table 4 Correlation analysis of CDAI and serum AMH levels.

Pearson correlation test		AMH	CDAI
Serum AMH (ng/mL)	Correlation coefficient	1.000	−0.718**
	Significance (2-tailed)	–	<0.001
	N	35	35

** Significant at $p<0.01$.

4. Discussion

In this observational, cross-sectional case–control study, we investigated whether CD, a chronic, systemic inflammatory disease, affects serum AMH levels in female patients, which are an early, reliable, direct indicator of ovarian reserve.

CD decreases fertility, especially during active disease episodes, by inducing inflammation in the fallopian tubes and ovaries, causing dyspareunia in the presence of perianal disease and through indirect mechanisms, such as the surgical resections that are often required for treatment.[3–15] Serum AMH levels in female CD patients were significantly lower compared to healthy controls (1.02±0.72 ng/mL vs. 1.89±1.80 ng/mL, $p=0.009$) (Table 3). In women who are diagnosed with CD, markedly lower serum AMH levels indicate that fertility is decreased as a result of direct defects in ovarian function.

When we divided female CD patients into 2 groups based on their disease status and compared these groups in terms of their serum AMH levels, we found that serum AMH levels were significantly lower in CD patients who had active disease (15/35 patients) than in CD patients who were in remission ($p<0.001$). This finding is consistent with the findings of previous studies. Serum AMH levels in CD patients who had active disease were 0.33±0.25 ng/mL, which is below the level of 0.5 ng/mL that is accepted as an indicator of a

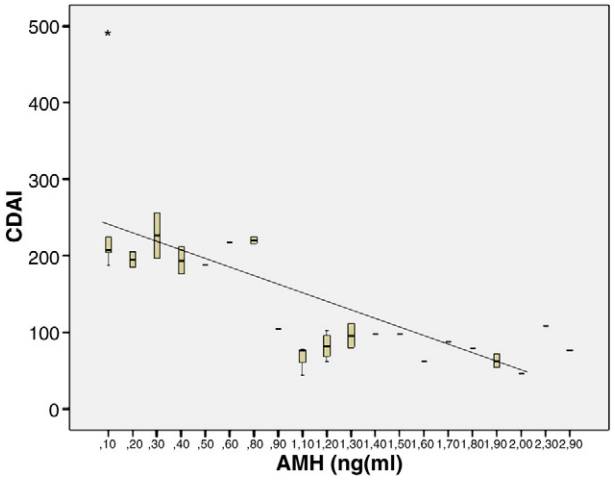

Figure 1 Correlation graph between CDAI and serum AMH levels in CD patients.CD: Crohn's disease, CDAI: Crohn's disease activity index, and AMH: anti-Müllerian hormone.

good ovarian reserve. This result supports other studies that found that, even in the absence of any structural pathology in the genital system, fertility is very low in female CD patients, especially during periods of active disease.

In CD, intestinal and extraintestinal complications tend to increase as the duration of the disease increases.[28] Therefore, we evaluated serum AMH levels in women with CD in our study in terms of disease duration. When the CD patients were divided into groups based on their disease duration and AMH levels were compared, we detected no significant difference in serum AMH levels between patients who had a disease duration of less than 5 years and those who had a disease duration of greater than 5 years (1.07 ± 0.79 ng/mL vs. 0.97 ± 0.67 ng/mL, p = 0.8).

In accordance with the literature cited above, we found that serum AMH levels were decreased in female CD patients, especially during periods of active disease. In addition, we found a significant negative correlation between serum AMH levels and CDAI in female CD patients ($r = -0.718$, $p < 0.001$) (Table 4, Fig. 1). As shown in Fig. 1, as CDAI increase, serum AMH levels decrease.

In CD patients who were treated with surgical resection, fertility decreases due to inflammation in the fallopian tubes following resection and adhesions that occur due to surgery. In our patients, we detected no significant difference in terms of serum AMH levels between patients who were treated with resection (6 patients, 17.1%) and patients who were not (29 patients, 82.9%) (1.33 ± 0.49 ng/mL vs. 0.95 ± 0.75 ng/mL, p = 0.2). Although this result appears to be in contrast to findings from other studies, genital tract examinations for signs of infertility after resection were not performed in these patients. We compared serum AMH levels, which are an early, reliable, direct indicator of ovarian reserve. Importantly, serum AMH levels represent an ovarian reserve indicator that is not affected by surgery.

We believe that the results obtained from this study will be helpful in clinical practice, especially in the treatment of recently diagnosed female CD patients who are of reproductive age and want to or plan to have children.

Most of the studies assessing the role of serum AMH levels regarding the ovarian reserve are reported in the patients with malignancy which treated with chemotherapeutics. Recently there are two recent studies assessing the role of serum AMH levels in, systemic lupus erythematosus (SLE), another chronic systemic inflammatory disease.[35,36] In the retrospective study of Brown et al.[35] they measured plasma AMH levels in six females with SLE undergoing chemotherapy and hematopoietic stem cell transplantation. They found that serum AMH levels facilitated earlier identification of impaired ovarian reserve compared with FSH and the resumption of menses. In another study reported by Lawrenz et al.[36] serum AMH levels of 33 premenopausal SLE patients without previous cyclophosphamide treatment and 33 age-adjusted healthy females were compared. They also reported the number of children and miscarriages. They found that, the AMH values in the SLE group were significantly lower than in the healthy control group. However there were no significant differences between the groups regarding number of children and miscarriages were noted and no correlation between the AMH value and the duration of illness or the SLE disease activity index. They also found that despite mild disease activity, SLE patients had a significantly lower ovarian reserve than age-matched healthy women. These findings are similar to our findings.

Azathioprine and 5-ASA compounds have no effect on fertility in women. By contrast, sulfasalazine causes a reversible reduction in sperm motility and sperm count in men but this effect is dose-dependent and is not responsive to folic acid treatment.[29–34] Although the direct effects of infliximab (IFX) on female fertility are not known, no congenital malformations have been reported in women who were impregnated by men being treated with infliximab (IFX). However, miscarriage was reported in 1 out of every 10 women.[2] For this reason, an evaluation of medications used for CD was not made in this study.

Several study limitations must be addressed. First, this is an observational, cross-sectional case study; to better define the relationship between AMH and actual fertility in CD patients, long-term prospective studies are needed. Second, although our study has the power to evaluate the differences in serum AMH levels between patients and controls, the relatively small sample size might limit the generalization of our results. Third, because this study was conducted with individuals of Turkish origin, it cannot be applied to individuals with different ethnic backgrounds.

In conclusion, CD causes a significant decrease in the serum AMH levels of women of reproductive age compared to healthy women with similar age and demographic properties; this effect is most pronounced during periods of active disease. Moreover, a significant negative correlation between CDAI and serum AMH levels was observed in female CD patients. We believe that these data will be helpful for the treatment of recently diagnosed female CD patients who want to or plan to have children.

Conflict of interest

The authors declare that they have no conflict of interest related to the publication of this manuscript.

References

1. Baird DD, Narendranathan M, Sandler RS. Increased risk of preterm birth for women with inflammatory bowel disease. *Gastroenterology* 1990;**99**(4):987–94.
2. Van Assche G, Dignass A, Reinisch W, van der Woude CJ, Sturm A, De Vos M, et al. European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. *J Crohns Colitis* 2010;**4**(1):63–101.
3. Woolfson K, Cohen Z, McLeod RS. Crohn's disease and pregnancy. *Dis Colon Rectum* 1990;**33**(10):869–73.
4. Fonager K, Sørensen HT, Olsen J, Dahlerup JF, Rasmussen SN. Pregnancy outcome for women with Crohn's disease: a follow-up study based on linkage between national registries. *Am J Gastroenterol* 1998;**93**(12):2426–30.
5. Baiocco PJ, Korelitz BI. The influence of inflammatory bowel disease and its treatment on pregnancy and fetal outcome. *J Clin Gastroenterol* 1984;**6**(3):211–6.
6. Mayberry JF, Weterman IT. European survey of fertility and pregnancy in women with Crohn's disease: a case control study by European collaborative group. *Gut* 1986;**27**(7):821–5.
7. Hudson M, Flett G, Sinclair TS, Brunt PW, Templeton A, Mowat NA. Fertility and pregnancy in inflammatory bowel disease. *Int J Gynaecol Obstet* 1997;**58**(2):229–37.

8. Ørding Olsen K, Juul S, Berndtsson I, Oresland T, Laurberg S. Ulcerative colitis: female fecundity before diagnosis, during disease, and after surgery compared with a population sample. *Gastroenterology* 2002;**122**(1):15–9.
9. Olsen KO, Joelsson M, Laurberg S, Oresland T. Fertility after ileal pouch-anal anastomosis in women with ulcerative colitis. *Br J Surg* 1999;**86**(4):493–5.
10. Oresland T, Palmblad S, Ellström M, Berndtsson I, Crona N, Hultén L. Gynaecological and sexual function related to anatomical changes in the female pelvis after restorative proctocolectomy. *Int J Colorectal Dis* 1994;**9**(2):77–81.
11. Ravid A, Richard CS, Spencer LM, O'Connor BI, Kennedy ED, MacRae HM, et al. Pregnancy, delivery, and pouch function after ileal pouch-anal anastomosis for ulcerative colitis. *Dis Colon Rectum* 2002;**45**(10):1283–8.
12. Tiainen J, Matikainen M, Hiltunen KM. Ileal J-pouch-anal anastomosis, sexual dysfunction, and fertility. *Scand J Gastroenterol* 1999;**34**(2):185–8.
13. Juhasz ES, Fozard B, Dozois RR, Ilstrup DM, Nelson H. Ileal pouch-anal anastomosis function following childbirth. An extended evaluation. *Dis Colon Rectum* 1995;**38**(2):159–65.
14. Damgaard B, Wettergren A, Kirkegaard P. Social and sexual function following ileal pouch-anal anastomosis. *Dis Colon Rectum* 1995;**38**(3):286–9.
15. Johnson E, Carlsen E, Nazir M, Nygaard K. Morbidity and functional outcome after restorative proctocolectomy for ulcerative colitis. *Eur J Surg* 2001;**167**(1):40–5.
16. Broer SL, Mol BW, Hendriks D, Broekmans FJ. The role of anti-mullerian hormone in prediction of outcome after IVF: comparison with the antral follicle count. *Fertil Steril* 2009;**91**(3):705–14.
17. Hehenkamp WJ, Looman CW, Themmen AP, de Jong FH, Te Velde ER, Broekmans FJ. Anti-mullerian hormone levels in the spontaneous menstrual cycle do not show substantial fluctuation. *J Clin Endocrinol Metab* 2006;**91**(10):4057–63.
18. La Marca A, Giulini S, Tirelli A, Bertucci E, Marsella T, Xella S, et al. Anti-Müllerian hormone measurement on any day of the menstrual cycle strongly predicts ovarian response in assisted reproductive technology. *Hum Reprod* 2007;**22**(3):766–71.
19. Cook CL, Siow Y, Taylor S, Fallat ME. Serum mullerian-inhibiting substance levels during normal menstrual cycles. *Fertil Steril* 2000;**73**(4):859–61.
20. La Marca A, Giulini S, Tirelli A, Bertucci E, Marsella T, Xella S, et al. Anti-Müllerian hormone measurement on any day of the menstrual cycle strongly predicts ovarian response in assisted reproductive technology. *Hum Reprod* 2007;**22**(3):766–71.
21. Hazout A, Bouchard P, Seifer DB, Aussage P, Junca AM, Cohen-Bacrie P. Serum antimüllerian hormone/müllerian-inhibiting substance appears to be a more discriminatory marker of assisted reproductive technology outcome than follicle-stimulating hormone, inhibin B, or estradiol. *Fertil Steril* 2004;**82**(5):1323–9.
22. Fadini R, Comi R, Mignini Renzini M, Coticchio G, Crippa M, De Ponti E, et al. Anti-mullerian hormone as a predictive marker for the selection of women for oocyte in vitro maturation treatment. *J Assist Reprod Genet* 2011;**28**(6):501–8.
23. Seifer DB, Baker VL, Leader B. Age-specific serum anti-Müllerian hormone values for 17,120 women presenting to fertility centers within the United States. *Fertil Steril* 2011;**95**(2):747–50 (Epub 2010 Nov 13).
24. de Vet A, Laven JS, de Jong FH, Themmen AP, Fauser BC. Anti-müllerian hormone serum levels: a putative marker for ovarian aging. *Fertil Steril* 2002;**77**(2):357–62.
25. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. *Hum Reprod Update* 2006;**12**(6):685–718.
26. Gnoth C, Schuring AN, Friol K, Tigges J, Mallmann P, Godehardt E. Relevance of anti-Mullerian hormone measurement in a routine IVF program. *Hum Reprod* 2008;**23**(6):1359–65.
27. Lutchman Singh K, Muttukrishna S, Stein RC, McGarrigle HH, Patel A, Parikh B, et al. Predictors of ovarian reserve in young women with breast cancer. *Br J Cancer* 2007;**96**(12):1808–16.
28. Peyrin-Biroulet L, Loftus Jr EV, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010;**105**(2):289–97.
29. Levi AJ, Fisher AM, Hughes L, Hendry WF. Male infertility due to sulphasalazine. *Lancet* 1979;**11;2**(8137):276–8.
30. Birnie GG, McLeod TI, Watkinson G. Incidence of sulphasalazine induced male infertility. *Gut* 1981;**22**(6):452–5.
31. O'Moráin C, Smethurst P, Doré CJ, Levi AJ. Reversible male infertility due to sulphasalazine: studies in man and rat. *Gut* 1984;**25**(10):1078–84.
32. Toth A. Reversible toxic effect of salicylazosulfapyridine on semen quality. *Fertil Steril* 1979;**31**(5):538–40.
33. Dejaco C, Mittermaier C, Reinisch W, Gasche C, Waldhoer T, Strohmer H, et al. Azathioprine treatment and male fertility in inflammatory bowel disease. *Gastroenterology* 2001;**121**(5):1048–53.
34. Narendranathan M, Sandler RS, Suchindran CM, Savitz DA. Male infertility in inflammatory bowel disease. *J Clin Gastroenterol* 1989;**11**(4):403–6.
35. Browne H, Armstrong A, Decherney A, Babb R, Illei G, Segars J, et al. Assessment of ovarian function with anti-Müllerian hormone in systemic lupus erythematosus patients undergoing hematopoietic stem cell transplant. *Fertil Steril* 2009;**91**(4 Suppl):1529–32.
36. Lawrenz B, Henes J, Henes M, Neunhoeffer E, Schmalzing M, Fehm T, et al. Impact of systemic lupus erythematosus on ovarian reserve in premenopausal women: evaluation by using anti-Muellerian hormone. *Lupus* 2011;**20**(11):1193–7.