

Concise report

Ovarian reserve alterations in premenopausal women with chronic inflammatory rheumatic diseases: impact of rheumatoid arthritis, Behçet's disease and spondyloarthritis on anti-Müllerian hormone levels

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Abstract

Objective. Recent publications have shown a negative influence of SLE on female ovarian reserve. Other authors have not found a significant impact of Crohn's disease or early RA on anti-Müllerian hormone (AMH) levels. This study aimed to investigate the potential effect of Behçet's disease (BD), RA and SpA on ovarian reserve as reflected by serum AMH levels.

Methods. Serum samples from 33 RA, 32 SpA and 30 BD patients without previous cytotoxic treatment were analysed and compared with age-matched, healthy controls. AMH was quantified using a standard ELISA with a standard value of 1–8 ng/ml; values <1 ng/ml defined a reduced ovarian reserve.

Results. Median age was 26, 28.5 and 33 years and median disease duration was 6, 5.9 and 7 years for RA, SpA and BD patients, respectively. Compared with healthy controls, patients had significantly reduced AMH levels, with a median value for RA of 1.8 ng/ml (control 2.4 ng/ml; $P=0.009$), for SpA of 1.5 ng/ml (control 2.3 ng/ml; $P=0.013$) and for BD of 1.1 ng/ml (control 1.9 ng/ml; $P=0.007$). HLA-B27 had a negative influence on ovarian reserve in SpA patients, whereas other serological parameters did not in the other diseases.

Conclusion. This is the first study to show a reduced ovarian reserve in patients with RA, SpA or BD. Together with our findings in SLE, we conclude a negative influence of chronic rheumatic diseases on ovarian reserve.

Key words: ovarian reserve, fertility, AMH, spondyloarthritis, rheumatoid arthritis, Behçet's disease.

Rheumatology key messages

- SpA, RA and Behçet's disease all have a negative influence on ovarian reserve.
- Pregnancy in patients with rheumatic diseases should be encouraged while patients are in their twenties.
- Ovary protection before and during cytotoxic treatment is important in young patients with rheumatic diseases.

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Submitted 30 November 2014; revised version accepted 19 March 2015

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Introduction

Anti-Müllerian hormone (AMH) is secreted by granulosa cells during a woman's fertile years. It reflects the remaining follicle pool and is therefore used as a marker for ovarian reserve. Its advantage over other fertility serum markers, such as follicle stimulating hormone or luteal hormone, is its low variability throughout the menstrual cycle [1–3].

Patients with inflammatory joint diseases such as RA or SpA as well as patients with collagenous diseases such as

SLE have a reduced number of children [4–6]. Several factors may contribute to this. Personal choice, age, uncertainty of patients and consulting doctors as well as impaired sexual function due to pain or fatigue may play a role. Some of the frequently used medications, including NSAIDs or alkylating agents such as CYC, have a negative influence on conception and fertility [7].

Recent studies have found reduced AMH levels or antral follicle counts in patients with SLE, Takayasu arteritis, Behçet's disease (BD) and primary APS [8–12], whereas other groups were unable to demonstrate a reduction in ovarian reserve measured by AMH in patients with early RA or Crohn's disease [13, 14].

The objective of this study was to examine the impact of pathogenically different rheumatic autoimmune diseases on ovarian reserve measured by serum AMH levels. The potential influence of genetic and serological factors as well as disease duration were also analysed.

Methods

We analysed serum samples from 33 RA, 32 SpA and 30 BD patients and compared them with a similar number of age-matched healthy controls (HCs). All patients were recruited from our rheumatology outpatient clinic at the University Hospital Tuebingen. The study was approved by the ethics committee of the University Hospital Tuebingen and all patients and HCs gave written informed consent. Patients who had received previous systemic cytotoxic treatment, especially CYC, as well as patients who had undergone ovarian surgery or radiation, were excluded. Medication without known negative influence on ovarian reserve (e.g. glucocorticosteroids, NSAIDs, colchicine, antimalarials, SSZ, MTX, LEF, AZA, MMF, CSA, IFN- α , TNF antagonists, rituximab, tocilizumab and abatacept) were permitted.

AMH was quantified using a standard ELISA (AMH Gen II, Beckmann Coulter, Brea, CA, USA; normal range 1–8 ng/ml) in duplicate samples. Values <1 ng/ml were regarded as reduced values, according to the manufacturer's suggestion. All patients filled out a questionnaire on menstrual irregularities, lifestyle, obstetric data and contraception.

AMH levels were correlated with disease-specific laboratory parameters: HLA-B27 for SpA, HLA-B51 for BD and RF and anti-CCP for RA. Furthermore, the influence of disease duration on AMH was examined; early disease was defined as disease duration <2 years, whereas late disease was defined as ≥ 2 years.

For statistical analysis, SPSS 22.0 (IBM, Armonk, NY, USA) was used and the results are presented as median and range. Student's *t*, Mann-Whitney *U* and Wilcoxon tests were used to compare data from patients and HCs. *P*-values <0.05 were considered statistically significant.

Results

Median age was 26 years (range 19–38) for RA, 28.5 years (20–40) for SpA and 33 years (18–40) for BD patients and

we used age-matched HCs with the same median age for each disease group. Median disease duration was 6.0 years (range 0.3–3) for RA, 5.9 years (0.5–22) for SpA and 7.0 years (0.3–30) for BD. Median age at menarche was 13 years (range 10–16) for RA, 11 years (9–15) for SpA and 13 years (9–16) for BD patients. From the disease group, 54.5% (*n* = 18) of the RA, 71.9% (*n* = 23) of the SpA and 86.7% (*n* = 26) of the BD patients stated that they were in a durable relationship and 15.5% (*n* = 5) of RA, 6.3% (*n* = 2) of SpA and 20% (*n* = 6) of BD patients had an unfulfilled desire for a child. The mean number of children was 0.4 (0–3) for RA, 0.5 (0–3) for SpA and 0.8 (0–4) for BD patients, whereas for HCs it was 0.9 (0–3) children. The median age at the time of first pregnancy was 27 years (range 18–30) in RA, 22.5 years (20–26) in SpA and 26.5 years (14–32) in BD patients.

Compared with HCs, all patients had significantly reduced AMH levels, with a median value for RA of 1.8 ng/ml [range 0.0–11.3; control 2.4 (0.3–13.2); *P* = 0.009], for SpA of 1.5 [0.1–7.4; control 2.3 (0.05–13.2); *P* = 0.013] and for BD of 1.1 [0–6.1; control 1.9 (0.1–13.2); *P* = 0.007].

Several of the patients had severely reduced AMH levels, with 50% of BD patients having reduced (<1 ng/ml) AMH levels, but also in RA and SpA patients, with 30.0% and 37.5% having reduced, compared with HCs with 16.7, 9 and 15.6%, respectively.

Fig. 1 illustrates the influence of different laboratory markers. Regarding HLA status, there was a statistically significant difference between HLA-B27⁺ (*n* = 21; 67.7%) and HLA-B27[−] (*n* = 10; 31.3%) SpA patients, with a median of 0.8 ng/ml (range 0.0–7.4) for HLA-B27⁺ and 2.4 (1.1–4.6) for HLA-B27[−] patients (*P* = 0.003).

HLA-B51 in BD patients was not associated with reduced AMH levels. HLA-B51⁺ patients (*n* = 15; 50%) had a median AMH level of 1.6 ng/ml (range 0.0–6.1) and HLA-B51[−] patients had a median of 0.9 (0.0–3.1) (*P* = 0.3).

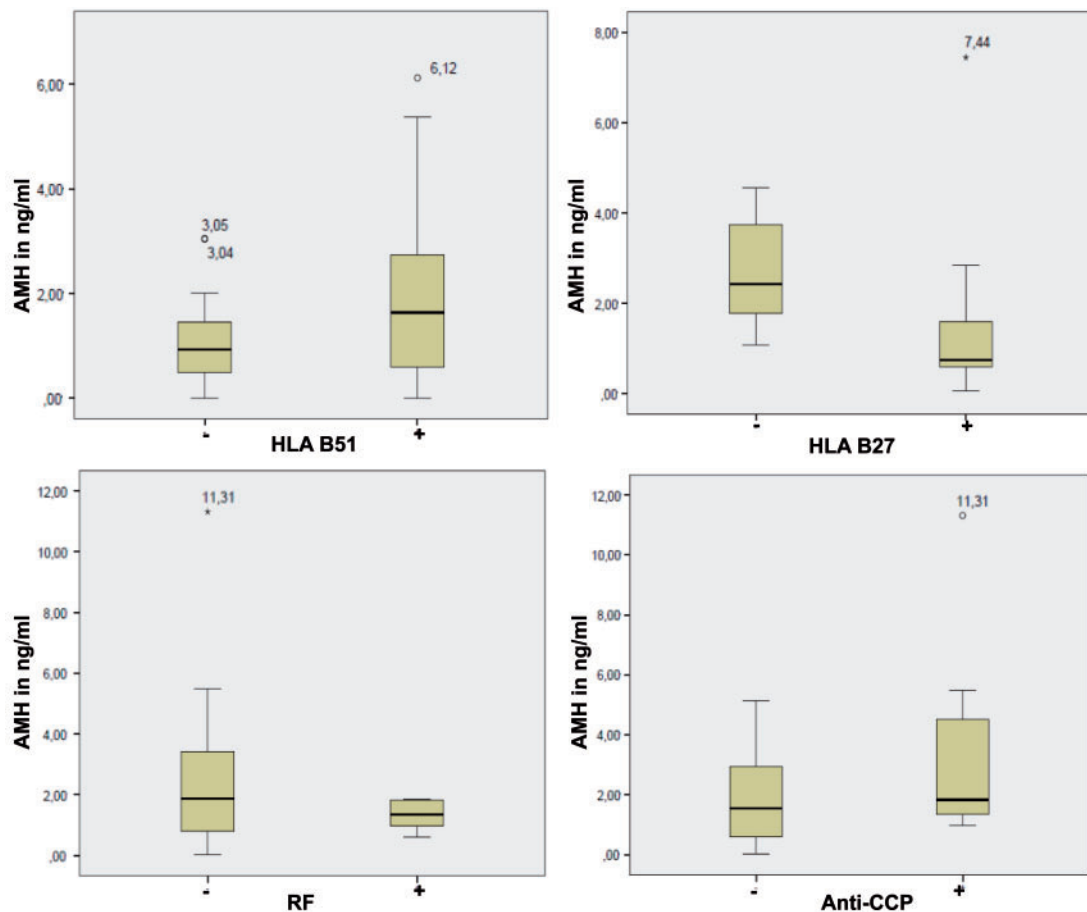
For RA patients, we analysed the potential influence of RF and anti-CCP antibodies. Both parameters had no significant influence on AMH level (Fig. 1). The 6 (20%) RF⁺ patients had a median AMH level of 1.4 ng/ml (range 0.6–1.9) and the 25 RF[−] patients had a median of 1.9 (0.0–11.3) (*P* = 0.296). The 22 (73.3%) anti-CCP[−] patients had a median AMH level of 1.6 ng/ml (range 0.0–5.1) vs 1.8 (1.0–11.3) for the 8 (26.7%) anti-CCP⁺ patients (*P* = 0.159).

Comparing those patients with early (<2 years' disease duration) vs late (≥ 2 years) disease, there was no significant difference in the three disease cohorts, with 1.9 vs 1.7 ng/ml (*P* = 0.405) in RA, 1.1 vs 1.6 (*P* = 0.646) in SpA and 0.9 vs 1.4 (*P* = 0.173) in BD.

Discussion

To the best of our knowledge this is the first study showing significantly reduced AMH levels in RA, SpA and BD patients compared with HCs. We chose these patient cohorts as all these autoimmune diseases commonly affect young women during their reproductive years and are, on the other side, different with regard to their pathogenesis, epidemiology and organ involvement. Together with our

Fig. 1 Boxplot analysis of subgroups: HLA-B27 positivity had a significant negative influence on AMH levels in SpA patients, whereas HLA-B51, RF and anti-CCP did not



work on AMH in SLE patients—where we found significantly reduced AMH levels in SLE patients as well [8]—and the work of colleagues in Brazil on APS, Takayasu arteritis and BD [10–12], we herein cover the most important and most prevalent rheumatic diseases for younger women. In all these diseases a significant reduction in ovarian reserve measured by AMH level was demonstrated. We therefore strongly assume a negative influence on ovarian reserve from these chronic rheumatic disorders.

A recent article by Brouwer *et al.* [14] analysed AMH levels in early RA patients and could not find a significant difference in AMH level at the time of diagnosis, and even during their first 6 months of treatment. There are aspects we can confirm in our RA patients, especially that there is no additional negative influence of RF, anti-CCP antibodies or disease duration >2 years. Nevertheless, in our RA patients there was a significantly reduced ovarian reserve compared with HCs, which is in line with the earlier menopause in RA patients described by Del Junco *et al.* [6].

The role of the genetic impact on ovarian reserve—reflected by HLA-B27 in SpA or -B51 in BD—remains

unclear; in SpA, HLA-B27 positivity was associated with a significant reduction in AMH levels, but not in HLA-B51+ patients in BD.

Several patients had AMH levels <1 ng/ml, with the highest proportion found in BD patients. This might be reflected in the 20% of BD patients with an unfulfilled desire to have children, although most of them were engaged/married. On the other hand, BD patients had more children compared with RA and SpA patients, a fact that cannot be explained by younger age at the time of their first pregnancy, but may be explained by socio-economic or cultural aspects. Mont'Alverne *et al.* [11] found similar data in their analysis of ovarian reserve in BD patients. Although only 10 patients were compared with HCs in their article, we can confirm their findings on reduced AMH levels <1 ng/ml in 50% of their patients in our larger cohort.

Our study has some limitations, especially the relatively small number of patients and the use of only one ovarian reserve parameter. In addition, there are factors that influence ovarian reserve that have not been examined in this study, especially the role of additional medication other

than cytotoxic agents. Nevertheless, since AMH is not influenced by hormonal contraception, parity or recurrent genital infections, which are more common in patients with a rheumatic disease and immunosuppressive treatment, this serological marker is an excellent tool to compare ovarian reserves in different cohorts. Recent studies have reported on some instabilities with the Beckmann Coulter AMH Gen II ELISA [15], but Mont'Alverne *et al.* [10] ruled this out by using two different kits and obtaining similar results.

In summary, we found additional evidence for a negative influence of chronic rheumatic disease on ovarian reserve measured by AMH levels. Family planning is an important issue for patients with rheumatic diseases. As far as their disease course and medication allows pregnancy, these patients should not wait too long to become pregnant. Especially with the knowledge of reduced ovarian reserve, patients with rheumatic diseases should be advised to consider pregnancy preferably during their 20s. In young patients where cytotoxic treatment is necessary, which can be the case, for example, in SLE or BD patients with renal or neurological involvement, ovary protection before and during treatment is important and should be offered [16].

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

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