Reduction of ovarian reserve in adult patients with dermatomyositis

F.H.C. de Souza[1], S.K. Shinjo[1], L.Y.S. Yamakami[2], V.S.T. Viana[1], E.C. Baracat[2], E. Bonfá[1], C.A. Silva[1,3]

[1]Division of Rheumatology, [2]Division of Gynaecology and [3]Paediatric Rheumatology Unit, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Abstract

Objective

To assess ovarian reserve markers and anti-corpus luteum (anti-CoL) antibodies in dermatomyositis (DM) patients.

Methods

Forty female DM patients were invited to participate. Exclusion criteria included hormonal contraceptive use within the last six months, neoplasia associations, overlapped systemic autoimmune diseases, current pregnancy, gynaecological surgery and individual choice not to participate. The final experimental group for this cross-sectional study included 16 DM patients and 23 healthy controls, each of whom was evaluated during the early follicular phase of the menstrual cycle. Values for IgG anti-CoL (via immunoblotting), follicle stimulating hormone (FSH), estradiol, inhibin B, anti-Müllerian hormone (AMH) serum levels (via ELISA) and sonographic antral follicle count (AFC) were determined.

Results

DM patients and controls were of comparable mean age ($p>0.05$). The mean age of DM onset was 29.1±4.7 years, with disease duration of 5.6±3.2 years. Menstrual cycle characteristics, comorbidity and lifestyle were similar amongst patients in both groups ($p>0.05$). AMH values of ≤1ng/mL ($p=0.027$) and AFC values ($p=0.017$) were significantly reduced in DM patients relative to the control group, whereas serum estradiol levels ($p<0.001$) were higher in DM patients compared to controls. In contrast, serum FSH and inhibin B levels, ovarian volumes, and anti-CoL antibody frequency were similar in both groups. Differences in AFC and estradiol were determined to be significant following Bonferroni correction for multiple testing.

Conclusion

We identified a diminished ovarian reserve in DM patients of reproductive age. Further studies are necessary to assess the idiopathic inflammatory myopathy-related factors involved in the ovarian impairment of this patient population.

Key words

idiopathic inflammatory myopathies, anti-Müllerian hormone, antral follicule count, dermatomyositis, ovarian reserve

Fernando H. C. de Souza, MD
Samuel K. Shinjo, PhD
Lucas Y.S. Yamakami, PhD
Vilma S.T. Viana, PhD
Edmund C. Baracat, PhD
Eloisa Bonfá, PhD
Clovis A. Silva, PhD

Please address correspondence to:
Samuel Katsuyuki Shinjo,
Disciplina de Reumatologia,
Faculdade de Medicina da
Universidade de São Paulo,
Av. Dr. Arnaldo, 455,
3º andar, sala 3150,
CEP 01246-903, São Paulo, Brazil.
E-mail: samuel.shinjo@gmail.com

Received on March 8, 2014; accepted in revised form on July 16, 2014.

Funding: this work was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) [2011/15609-5 to S.K. Shinjo and 2011/12471-2 to C.A. Silva]; Federico Foundation to E. Bonfá, C.A. Silva and S.K. Shinjo; Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) [301411/2009-3 to E. Bonfá and 302724/2011-7 to C.A. Silva] and by Núcleo de Apoio à Pesquisa "Saúde da Criança e do Adolescente" da USP (NAP-CriAd-SP) to C.A. Silva.

Competing interests: none declared.

Introduction

Dermatomyositis (DM) is a rare, systemic autoimmune disease characterised by symmetrical proximal muscle weakness and typical skin lesions described as heliotrope and/or Gottron's papules (1). That the DM can affect women of reproductive age has raised concerns about the impact of this autoimmune chronic inflammatory disorder on ovarian reserve and future fertility (2).

In relation to gonadal dysfunction in female patients with systemic autoimmune diseases, there is clear evidence that such patients are more likely to develop menstrual irregularities and amenorrhoea due to several factors, including: disease activity, therapy with corticosteroids and/or immunosuppressive agents and possible autoimmune mechanisms of direct aggression to ovarian tissue (3-5).

For example, juvenile systemic lupus erythematosus (SLE) patients exhibit a higher incidence of sexual dysfunction, delayed menarche and higher frequency of menstrual abnormalities when compared to healthy controls matched for age, gender and ethnicity (3-5).

It has been shown that patients with SLE (6, 7) and juvenile DM (8) have an increased incidence of ovarian dysfunction. Some conditions such as autoimmune oophoritis associated with the production of anti-corpus luteum (anti-CoL) antibody (9) as well as use of immunosuppressive therapy (particularly intravenous cyclophosphamide) are recognised as potential causes of diminished ovarian reserve (9-12).

Despite the significance of a possible ovarian involvement in DM, there is currently no literature assessing ovarian reserves in adult patients with DM. Therefore, this study was conducted to investigate ovarian reserves in adult female DM patients by evaluating levels of ovarian hormone markers and their possible association with DM-related demographic, clinical, gynaecological, laboratory and treatment features.

Materials and methods

Patients and healthy individuals

Forty female patients with DM, with aged 18–42, followed at the Myopathy Clinic of the Rheumatology Division of our tertiary centre, from March 2011 to December 2012. All patients fulfilled the Bohan and Peter classification criteria for the disease (13).

Exclusion criteria were hormonal contraceptive use within the last six months (n=13), neoplasia associations (n=3), current pregnancy (n=2), gynaecological surgery (n=1), other autoimmune diseases (n=3) and individual choice not to participate (n=2). A total of 16 DM patients and 23 healthy volunteer age-matched women were enrolled in the study.

The local ethics committee of our tertiary service approved the study and informed consent was obtained from all participants.

General clinical features of female DM patients

All of the participants underwent an initial clinical evaluation that included a standardised interview and extensive review of electronic medical charts. The following data were collected at study entry:

a) Demographic data: current age, ethnicity, household income status (socio-economic status, according to "Associação Brasileira dos Institutos de Pesquisa de Mercados") (14) and body mass index [BMI: weight / height^2 (kg / m^2)]
b) Clinical and laboratory data: age at disease onset, disease duration, creatine phosphokinase (CPK: normal range: 24–173 IU/L) and aldolase (normal range: 1.0–7.5 IU/L) by using a kinetic automated method;
c) Disease status: patient disease status was evaluated through the application of questionnaires and Medical Research Council scoring (grade 0: no muscle contraction; grade I: signs of mild muscle contraction; grade II: normal range of motion, but inability to move against gravity; grade III: normal range of motion against gravity; grade IV: integral mobility against gravity and against a certain degree of resistance; grade V: complete mobility against marked resistance and against gravity) (15). Kendall Manual Muscle Testing (0-10 scale) was utilised on 8 different muscle groups: deltoid middle, biceps brachii, wrist

extensors, quadriceps femoris, ankle dorsiflexors, neck flexors, gluteus medius and gluteus maximus (MMT) (16). Finally health assessment quality (HAQ) (17) and global assessment of the disease by the physician and the patient through the visual analogue scale (VAS) was performed;

d) Pharmacological therapy: previous and current use of immunosuppressive agents and corticosteroids;
e) Comorbidities and habits: type 2 diabetes mellitus and tobacco use;
g) Gynaecological characteristics: menarche, gynaecologic age (time between current age and menarche) and menstrual cycles (flow duration and cycle length).

Autoantibodies analysis

The presence of anti-Jo-1 (histidyl-) and anti-Mi-2 autoantibodies was investigated in all patients with DM at study entry using a commercially available line blot test kit (Myositis Profile Euroline Blot test kit, Euroimmun, Lübeck, Germany) according to the manufacturer's protocol. The results were arbitrarily defined as negative (0/+++), and weakly (+/+++), moderately (++/+++), or strongly (+++/+++) reactive by two independent researchers who had no prior knowledge of clinical data. In the present study, only sera with moderate or strong reactivity were considered to be positive.

Ovarian reserve tests

Ovarian function was assessed by determining serum hormone levels during the early follicular phase of the menstrual cycle or randomly for those with defined amenorrhoea, and was blinded to the other parameters of ovarian function. FSH (reference levels: 3.5-12.5 IU/L) and estradiol were measured by radioimmunoassay using commercial kits (Cobas®, Roche, Mannheim, Germany). Intra- and inter-assay coefficients of variation were recommended by the manufacturer and were limited to 5.7 and 3.6%, respectively. The serum levels of FSH and estradiol were considered elevated when measured at ≥10 IU/L and ≥60 pg/mL, respectively. Anti-Müllerian hormone (AMH) was measured by using two different kits: i) by enzyme-linked immunosorbent assay (AMH Gen II ELISA, Beckman Coulter Inc., Brea, CA, USA) in duplicated samples, and ii) by ultrasensitive AMH / Müllerian inhibiting substance enzyme linked chemiluminescent immunoassay (CLIA) kit (US AMH/MIS AnshLabs ELISA). AMH levels of ≤1.0 ng/mL were considered reduced.

Inhibin B levels were measured in serum samples obtained from patients during the follicular phase of the menstrual cycle (between the 1st and 3rd days) by ELISA (Diagnostic Systems Laboratories, Inc., Webster, Texas, USA). The inter-assay coefficient of variability for inhibin B was limited to 3.5–5.6% (reference levels: 10–320 pg/mL).

All serum samples were tested for the presence of IgG anti-CoL antibodies by immunoblotting using extract of bovine corpus luteum as substrate, as previously described (9).

Transvaginal ultrasound was performed in all sexually active DM patients and controls using a 6.5 MHz endovaginal transducer (HD3, Philips Ultrasound, Bothell, WA, USA), by an expert sonographer (L.Y.S.Y.) who was blinded to other parameters of gonadal function. Ovaries were scanned in the axial and longitudinal planes, and at least two measurements of length (L), width (W) and thickness (T) were obtained to calculate the mean ovarian volumes (L x W x T x πumber/6) (18). The antral follicle counts (AFC) included all identifiable follicles measuring between 2 and 10 mm in diameter (19) and followed a clinically suitable classification of ≤10 = low, and ≤5 = very low follicle numbers.

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the distribution of each parameter. The results were expressed as the mean ± standard deviation (SD) or median (25^{th} – 75^{th} percentiles) for continuous variables, and as a percentage (%) for categorical variables. Comparisons between patients *vs*. control group were performed using Student's *t*-test or the Mann-Whitney U-test for continuous variables. The Spearman rank correlation coefficient (r_s) was used for correlations between AMH Gen II ELISA and US AMH / MIS Ansh Labs ELISA kits in DM patients and healthy controls. $p \leq 0.05$ was considered significant. The STATA computer programme, version 7 (STATA, College Station, TX USA), was used for statistical analysis. Bonferroni correction for multiple comparisons was performed, adjusting the significance level to $p \leq 0.017$ and included the three most relevant screening test variables of ovarian reserve: FSH, AMH and AFC (20).

Results

Mean age (33.4±4.9 *vs*. 31.4±6.8 years), ethnicity and socioeconomic class were similar between DM patients and controls ($p>0.05$). Gynaecological characteristics, comorbidity and lifestyle were also comparable between groups (Table I). The average age of DM onset was 29.1±4.7 years, and disease duration lasted for 5.6±3.2 years.

The average number of previous pregnancies was 81.3 *vs*. 47.8% in DM patients and controls, respectively ($p=0.05$), whereas the live birth rate was 27/16 *vs*. 19/23, and the rate of abortion was 18.8 *vs*. 13.0% ($p=0.674$).

At the time of study, 68.8% of DM patients were using corticosteroids, with a median dose of 6.3 mg/day (0-18.8 mg/day), and 75.0% were using at least one immunosuppressant (azathioprine, methotrexate, cyclosporine, antimalarial or rituximab). Previous treatments with corticosteroids and immunosuppressive agents are included in Table I

The laboratory features and disease status of DM patients at study entry are shown in Table I. AMH values of ≤1 ng/mL ($p=0.027$), measured by two different AMH kits, were significantly reduced in DM patients when compared to control groups (Table II), but this association was not significant after Bonferroni correction for multiple testing. AFC values ($p=0.017$) were significantly reduced in DM patients compared to control groups (Table II), and this association remained significant after Bonferroni correction for multiple testing. A positive correlation was observed between AMH Gen II ELISA and US AMH / MIS Ansh Labs ELISA kits in DM patients ($p<0.001$, $r_s = 0.916$) and in healthy controls ($p<0.001$, $r_s = 0.926$).

Table I. General features of patients with dermatomyositis (DM) and control individuals at study entry.

Variables	Controls (n=23)	DM (n=16)	*p*-value
Demographic features			
Age (years)	31.4 ± 6.8	33.4 ± 4.9	0.337
Ethnicity (white)	14 (60.9)	13 (81.2)	0.175
Socio-economic class C or D	13 (43.5)	12 (75.0)	0.317
Age at disease onset (years)	-	9.1 ± 4.7	-
Disease duration (years)	-	5.6 ± 3.2	-
Current smoking	1 (4.3)	0	0.255
Diabetes mellitus	0	1 (6.3)	0.398
Laboratory features			
Antinuclear antibody	-	14 (87.5)	-
Anti-Jo-1 antibody	-	5 (31.3)	-
Anti-Mi-2 antibody	-	2 (12.5)	-
Creatine phosphokinase (U/L)	-	117 (82-209)	-
Aldolase (U/L)		5.3 (4.2-6.5)	
Disease status			
Medical Research Council			
Grade V	-	15 (93.7)	-
Grade IV	-	1 (6.3)	-
MMT (0-80)	-	80 (79-80)	-
HAQ score (0.0-3.0)	-	0 (0.0-1.2)	-
Patient VAS (0-10 cm)	-	1.5 (0.0-3.0)	-
Physician VAS (0-10 cm)	-	1.5 (0.2-3.5)	-
Gynaecological features			
Menarche (years)	12 (12-13)	11.5 (11-13)	0.343
Gynaecologic age (years)	19 (14-24)	20 (17-24)	0.200
Menstrual cycle			
Flow duration (days)	5 (2-10)	4 (3-10)	0.223
Cycle length (days)	30 (15-35)	30 (15-40)	0.639
Previous drug therapy			
Corticosteroids	-	16 (100)	-
Azathioprine	-	14 (87.5)	-
Antimalarial	-	11 (68.8)	-
Methotrexate	-	9 (56.3)	-
Cyclosporine	-	8 (50.0)	-
Intravenous human immunoglobulin	-	4 (25.0)	-
Rituximab (anti-CD-20)	-	4 (25.0)	-
Leflunomide	-	1 (6.3)	-

Values expressed in n (%), mean ± standard deviation (SD) or median (interquartile). MMT manual muscle testing, HAQ: health quality assessment (HAQ); VAS: visual analogue score.

Median serum estradiol levels were significantly higher in DM *versus* control patients ($p<0.001$) (Table II). This association remained significant after Bonferroni correction for multiple testing.

In contrast, serum levels of FSH and inhibin B, ovarian volumes, and anti-CoL antibody frequency were similar in both groups (Table II).

Discussion

To our knowledge, this is the first study to identify that DM patients have a subclinical impaired ovarian reserve at reproductive age.

Our work presents a complete and careful assessment of ovarian reserve in post-pubertal DM and control patients, evaluating the best currently available ovarian-linked parameters. An accurate estimation of ovarian follicle populations was obtained during the early follicular phase of patient menstrual cycles, a period when serum concentrations of FSH, LH, estradiol and AMH, as well as the CFA, have less variability (21, 22). In addition, we evaluated the regional and functional anatomy of 8 different muscle groups based on MMT scoring, which provided a more detailed account of weakness (16) as compared to Medical Research Council assessment (15). Based on these findings, a majority of our DM patients were considered to have inactive disease.

The rigorous selection criteria of our patients and controls, which included women under 42 years of age, recent gynaecologic surgeries, pregnancy or associated neoplasia, are relevant as these conditions may interfere with the ovarian reserve assessment tests (8, 22). Moreover, as recent studies have reported that decreased AMH levels can be observed in women using hormonal contraceptives (23, 24), the ovarian hormonal profile described herein was determined without the effect of any exogenous hormone for a period of at least six months to avoid this possible *bias*. To overcome any potential discrepancy among the values measured by AMH Gen II ELISA (as has been recently reported) (25), our analysis included the use of two different kits, which both measured reduced AMH with similar frequency. Similar results were also observed in two recent studies of ovarian reserve in rheumatic disease patients (26, 27).

Currently, the best static screening tests for ovarian reserve are AMH testing and ultrasonographic AFC (20, 28). Our findings of lower AFC numbers in adult DM patients reinforced the diagnosis of premature reduced ovarian reserve. The clinical utility of AFC to assess ovarian reserve has high specificity, as opposed to the low sensitivity obtained when measuring AMH (20). Of note, the frequency of this alteration was higher than previously reported by our group in juvenile SLE (3) and DM (8).

Additionally, the current literature does not consider inhibin B to be a reliable measure of ovarian reserve, as the levels of this hormone rise with GnRH or FSH stimulation with high intra- and inter-cycle variability (20). Likewise, basal estradiol also has poor inter- and intra-cycle reliability. The majority of current research has observed that estradiol levels are similar between women with and without diminished ovarian reserve (20).

Ovarian reserve in autoimmune rheumatic diseases may be influenced by age, smoking and overall disease status (8, 19, 21). Regarding the latter, in adult

Table II. Ovarian reserve markers and ovarian antibodies in dermatomyositis (DM) patients and control individuals at study entry.

Variables	Controls (n=23)	DM (n=16)	*p*-value
Ovarian reserve markers			
FSH (IU/L)	6.6±3.8	6.2±2.0	0.617
Elevated levels (≥10 IU/L)	2 (8.7)	2 (8.7)	0.778
Estradiol (pg/mL)	34.0 (24-128)	45.0 (29-126)	<0.001
AMH Gen 2 (ng/mL)	2.7 (0.1-6.6)	1.3 (0.2-6.6)	0.200
Decreased levels (≤1 ng/mL)	3 (13.0)	8 (50.0)	0.027
AMH Ansh Labs (ng/mL)	2.3 (0.2-6.6)	1.5 (0.3-6.6)	0.202
Decreased levels (≤1 ng/mL)	3 (13.0)	8 (50.0)	0.027
Inhibin B (pg/mL)	45.2±29.0	49.8±31.5	0.616
AFC (n)	17.3±10.7	10.5±5.6	0.017
Low AFC (≤10)	3 (14.3)	5 (38.5)	0.078
Very low (≤5)	2 (9.5)	2 (15.4)	0.540
Ovarian volumes (mm^3)	5.5 (1.4-15.8)	6.2 (4.7-8.2)	0.214
Ovarian antibodies			
Anti-CoL antibody (%)	0	1 (6.3)	0.398

Values expressed in n (%), mean ± standard deviation (SD) or median (interquartile). AFC: antral follicle count; AMH: anti-Müllerian hormone; anti-CoL: anti-corpus luteum antibody; FSH: follicle stimulating hormone; LH: luteinising hormone.

and adolescent SLE (11), amenorrhea was particularly associated with disease activity and damage. In contrast, analysis of the clinical and laboratorial disease status of DM patients evaluated herein revealed a mild and controlled disease, as demonstrated by mean values of muscle enzymes, muscle strength tests and activity indices within the normal range. In addition, the possible effects of age and smoking on measured variables were minimised by the fact that the patients and controls had comparable ages and that the frequency of smoking was very low and comparable in both groups.

The reduced follicle quantity and/or quality may also be caused by autoimmune oophoritis (9, 28). Anti-CoL antibodies did not influence the low ovarian reserve observed herein, contrasting with our previous report of an association of this antibody in female SLE patients (9).

Regarding treatment, immunosuppressive agents, particularly intravenous cyclophosphamide, may alter menstrual cycles and ovarian reserve in female SLE and juvenile DM patients (8, 12, 21, 22). The cumulative dose of methotrexate was associated with reduced levels of AMH and high doses of immunosuppressive drugs, and may be correlated with follicular atresia (26). In the present study, the possible role of treatment cannot be completely excluded, as all patients had long-term exposure to multiple immunosuppressive agents and over half have made use of methotrexate, though none were treated with cyclophosphamide.

The small sample size is the major limitation of this cross-sectional study, which is due to our rigorous selection criteria of patients with a relatively rare disease (1). Additionally, the inclusion of patients solely from a tertiary care centre may not represent the full DM spectrum, which could result in an overestimation of the disease or drug complications observed with a more severe disease phenotype.

In conclusion, the present work is the first to identify a high frequency of diminished ovarian reserve in DM patients at reproductive age. Further studies are necessary to assess the DM-related factors by which this idiopathic inflammatory myopathy causes ovarian impairment.

Acknowledgements

We thank Elaine Pires Leon for technical support.

References

1. FELDMAN BM, RIDER LG, REED AM, PACHMAN LM: Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. *Lancet* 2008; 28: 371: 2201-12.
2. GREENBER SA: Inflammatory myopathies: evaluation and management. *Semin Neurol* 2008; 28: 241-9.
3. SILVA CA, LEAL MM, LEONE C *et al*.: Gonadal function in adolescents and young women with juvenile systemic lupus erythematosus. *Lupus* 2002; 11: 419-25.
4. MEDEIROS P, FEBRONIO M, BONFÁ E, BORBA E, TAKIUTI A, SILVA C: Menstrual and hormonal alterations in juvenile systemic lupus erythematosus. *Lupus* 2009; 18: 38-43.
5. FEBRONIO MV, PEREIRA RM, BONFÁ E, TAKIUTI AD, PEREIRA EA, SILVA CA: Inflammatory cervicovaginal cytology is associated with disease activity in juvenile systemic lupus erythematosus. *Lupus* 2007; 16: 430-5.
6. GHALEB RM, FAHMY KA: Anti-Müllerian hormone: A marker for ovarian function in systemic lupus erythematosus patients treated with cyclophosphamide. *Joint Bone Spine* 2013; 80: 434-5.
7. APPENZELLER S, BLATYTA PF, COSTALLAT LTL: Ovarian failure in SLE patients using pulse cyclophosphamide: comparison of different regimes. *Rheumatology Int* 2008; 28: 567-71.
8. AIKAWA NE, SALLUM AM, LEAL MM, BONFÁ E, PEREIRA RM, SILVA CA: Menstrual and hormonal alterations in juvenile dermatomyositis. *Clin Exp Rheumatol* 2010; 28: 571-5.
9. PASOTO SG, VIANA VS, MENDONÇA BB, YOSHINARI NH, BONFÁ E: Anti-corpus luteum antibody: a novel serological marker for ovarian dysfunction in systemic lupus erythematosus? *J Rheumatol* 1999; 26: 1087-93.
10. OSTENSEN M, BRUCATO A, CARP H *et al*.: Pregnancy and reproduction in autoimmune rheumatic diseases. *Rheumatology* (Oxford) 2011; 50: 657-64.
11. SILVA CA, HILÁRIO MO, FEBRÔNIO MV *et al*.: Risk factors for amenorrhea in juvenile systemic lupus erythematosus (JSLE): a Brazilian multicentre cohort study. *Lupus* 2007; 16: 531-6.
12. AIKAWA NE, SALLUM AM, PEREIRA RM *et al*.: Subclinical impairment of ovarian reserve in juvenile systemic lupus erythematosus after cyclophosphamide therapy. *Clin Exp Rheumatol* 2012; 30: 445-9.
13. BOHAN A, PETER JB: Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975; 292: 344-7.
14. ALMEIDA PM, WICKERHAUSER W: Critério de classe econômica da Associação Brasileira de Anunciantes (ABA) e Associação Brasileira dos Institutos de Pesquisa de Mercado (ABIPEME). In: ALMEIDA PM, WICKERHAUSER W (Eds). O Critério ABA / ABIPEME, ABIPEME (São Paulo); 1991. p. 1-29.
15. MEDICAL RESEARCH COUNCIL: Aids to the investigation of peripheral nerve injuries. 2th ed. London: Her Majesty's Stationery Office; 1943. (War Memorandun No 7).
16. LEGG AT, MERRIL JB: Physical therapy in infantile paralysis. *In*: *Principles and practice of physical therapy*. Hagerstown: Mock Pemberton and Coulter; 1932.
17. BRUCE B, FRIES JF: The Stanford Health Assessment Questionnaire: dimensions and practical applications. *Health Qual Life Outcomes* 2003; 1: 20.
18. HENDRIKS DJ, MOL BW, BANCSI LF, TE VEL-

DE ER, BROEKMANS FJ: Antral follicle count in the prediction of poor ovarian response and pregnancy after *in vitro* fertilization: a meta-analysis and comparison with basal follicle-stimulating hormone level. *Fertil Steril* 2005; 83: 291-301.

19. KERR GS, HALLAHAN CW, GIORDANO J *et al*.: Takayasu arteritis. *Ann Intern Med* 1994; 120: 919-29.
20. SILVA CA, BRUNNER HI: Gonadal functioning and preservation of reproductive fitness with juvenile systemic lupus erythematosus. *Lupus* 2007; 16: 593-9.
21. SILVA CA, BONFÁ E, OSTENSEN M: Maintenance of fertility in patients with rheumatic diseases needing anti-inflammatory and immunosuppressive drugs. *Arthritis Care Res* (Hoboken) 2010; 62: 1682-90.
22. SATWIK R, KOCHHAR M, GUPTA SM, MAJUMDAR A: Anti-müllerian hormone cut-off values for predicting poor ovarian response to exogenous ovarian stimulation in in-vitro fertilization. *J Hum Reprod Sci* 2012; 5: 206-12.
23. KALLIO S, PURUNEN J, RUOKONEN A *et al*.: Anti-müllerian hormone levels decrease in women using combined contraception independently of administration route. *Fertil Steril* 2013; 99: 1305-10.
24. SILVA CA, YAMAKAMI LY, AIKAWA NE, ARAUJO DB, CARVALHO JF, BONFÁ E: Autoimmune primary ovarian insufficiency. *Autoimmun Rev* 2014 (in press).