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Assessment of ovarian function with anti-Müllerian hormone in systemic lupus erythematosus patients undergoing hematopoietic stem cell transplant

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Abstract

In this small pilot study, anti-Müllerian hormone (AMH) levels in women undergoing chemotherapy and hematopoietic stem cell transplantation facilitated earlier identification of impaired ovarian reserve compared with FSH and the resumption of menses. Larger studies are needed to accurately assess the clinical significance of AMH levels in the prediction of long-term reproductive outcomes in reproductive-age transplant patients with our current conditioning regimen.

Keywords

Stem cell transplant; ovarian reserve; anti-Müllerian hormone

Iatrogenic ovarian failure and infertility is an increasingly significant issue for women undergoing immunosuppressive therapy for systemic lupus erythematosus. Women with refractory disease, unresponsive to cyclophosphamide therapy, often benefit from hematopoietic stem cell transplantation (HSCT) (1). Although HSCT can result in sustained complete remission, the lymphoablative dosages of chemotherapy used for the conditioning regimens are responsible for many of the late complications, including reproductive failure because of gonadal damage.

The increased use of HSCT in this group of young women has increased the need for methods to preserve ovarian function, and to identify more sensitive measures of ovarian function. Recently, anti-Müllerian hormone (AMH) has shown great promise as a possible marker of ovarian function. Anti-Müllerian hormone is expressed in granulosa cells of growing follicles, and reflects the size of the primordial follicle pool (2). It is expressed in the perinatal period, and begins to decline during reproductive life (3), but serum levels vary little during the menstrual cycle. An association between the number of ovarian follicles and AMH has been observed in both fertile (4) and infertile women (5,6), and it has been used to predict ovarian responsiveness to controlled ovarian stimulation during assisted reproduction (7,8). Studies

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have suggested that AMH may be an early indicator of waning ovarian function in chemotherapy patients, and may be superior to current markers of ovarian reserve (9).

In this pilot study, we examined FSH, estradiol, and AMH in an effort to assess ovarian function in patients with systemic lupus erythematous (SLE) undergoing HSCT. Our objective was to determine whether AMH levels might detect impaired ovarian function in this group before other markers of ovarian function, such as FSH.

MATERIALS AND METHODS

This was a retrospective analysis from a phase II study of six SLE patients, four with World Health Organization Class IV lupus nephritis and two with central nervous system (CNS) lupus, with refractory disease. Patients were evaluated at the National Institutes of Health as part of a nonmyeloablative, autologous HSCT protocol between January 2004 and October 2006. Patients were considered to have treatment-resistant disease if they had active lupus after at least 6 months (for nephritis) or 3 months (for pulmonary and CNS disease) of cytoxan therapy, and recalcitrant disease if they had more than two flares after receiving adequate therapy. Before the transplantation, all subjects received a regimen of methylprednisolone, cyclophosphamide, fludarabine, and rituximab.

At enrollment in the cohort, women were between the ages of 16 and 36 years. One patient died shortly after her transplant, and one was lost to follow-up. All women had an intact uterus and at least one ovary. Records were reviewed and information was abstracted for menstrual and reproductive history, and the use of hormonal medications before, during, and after treatment. Two menopausal patients and one premenarchal patient did not receive hormonal treatment. Measures of ovarian function included resumption of menses, AMH, and random FSH and estradiol levels measured at baseline, 4, and 6 to 9 months after treatment. The study was approved by the institutional review board and written informed consent was obtained.

Hormone Assays

Serum levels of FSH and estradiol were performed at the NIH Clinical Research Center. Serum FSH measurements were obtained using a microparticle enzyme immunoassay (Abbott AxSYM System, Abbott Diagnostics, Abbott Park, IL). Serum estradiol levels were measured using a chemiluminescence immunoassay (Siemens Immulite 2500). The FSH and estradiol intraassay and interassay coefficients were 3.3% and 6.2%, and 4.0% and 7.9%, respectively. Plasma AMH concentrations were measured in duplicate using an ELISA (Esoterix Laboratory Services, Calabasas, CA). The range of the assay was 0.0–6.9 ng/mL. The intra- and interassay coefficients for AMH determination were 5.3 and 8.7%, respectively.

Statistical Analysis

Descriptive statistics were performed for each variable. The results are presented as mean ± SEM. Student's *t* test was used for statistical analysis, performed with Microsoft Office Excel software. A value of $P<.05$ was considered statistically significant.

RESULTS

The clinical and hormonal characteristics of the patients are summarized in Table 1. The mean AMH levels for all women who resumed menses or were amenorrheic post-HSCT was 0.4 and 0.1 ng/mL, respectively. The mean number of cycles of IV cyclophosphamide before HSCT was 14. All women ≥31 years of age had FSH levels in the menopausal range before HSCT. Three patients received hormonal therapy before and during treatment, and two continued hormonal therapy after treatment. Patients #1 and #6 were excluded from the final analysis,

because they continued hormonal therapy after transplant. Patient #3 was also excluded from the final analysis because she died shortly after her transplant. Patient #5, who was amenorrheic, had AMH levels similar to those reported in women treated for Hodgkin's lymphoma during childhood (2), and in women entering the menopausal transition (4). Patient #1 continued hormonal therapy after HSCT and had persistently normal FSH levels in the setting of decreasing AMH levels. The one premenarchal patient (Patient #4) began her menses after transplant, and had higher AMH levels compared with those who were amenorrheic. Patients who had spontaneous menses after treatment had normal FSH levels, but demonstrated a reduction in AMH levels from baseline.

DISCUSSION

This is the first study to examine AMH levels in women with SLE undergoing HSCT. As expected, patients with menses after chemotherapy had higher AMH levels compared with patients who were amenorrheic. Two patients with menses after treatment had normal FSH levels but demonstrated marked falls in their AMH levels from baseline. The reduction in AMH levels after treatment that occurred before increases in FSH suggests that AMH may be a more sensitive indicator of impaired ovarian function.

It is a challenging problem to assess ovarian reserve in women who have undergone treatment with chemotherapeutic agents that are toxic to the ovary. Despite regular menstrual cycles and normal FSH (10), young women who continue to menstruate after chemotherapy may erroneously presume that their fertility is unaffected (11). In fact, studies of ovarian function following cancer therapy demonstrated smaller ovarian volumes, reduced antral follicle counts AFC (12) and inhibin-B levels (13) when compared with age-matched controls. Thus, FSH measurement and menstruation are not sufficient measures to detect impaired ovarian reserve after cytotoxic therapy.

Anti-Müllerian hormone has emerged as a more sensitive indicator of impaired ovarian function. Van Rooij et al. (4) showed that AMH and AFC were highly correlated with age during the perimenopause, whereas substantial changes in FSH and inhibin B levels occurred only in women >40 years of age. The investigators (4) concluded that serum AMH represented the more sensitive endocrine marker to assess the age-related decline of reproductive capacity.

Furthermore, studies (2,14) of women treated for cancer during childhood in whom ovarian function was maintained, have shown that a reduction in AMH levels occurred before changes were seen in other markers of ovarian function. Anderson et al. (9) postulated that the earlier changes in AMH levels after chemotherapy may be due to of the cytotoxic effects on different follicle sizes. The fall in AMH levels may reflect primordial and preantral follicles as the primary site of toxicity with larger follicles being less affected (producing predominately inhibin B and estradiol). With continued production of inhibin and estradiol by growing follicles, FSH concentration remains unchanged (9) and later reflects depletion of the primordial follicle pool.

Anti-Müllerian hormone may be a marker of interest in predicting the risk of premature ovarian failure after high-dose chemotherapy therapy in SLE patients, and, by extension, might be important in other reproductive-age transplant patients. We propose this as a novel concept, especially because our current conditioning regimens are of low intensity and we have very little data about the prediction of long-term reproductive outcomes. Having a sensitive and specific test, such as AMH, to determine ovarian reserve would be an invaluable patient counseling tool.

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TABLE 1

Clinical and hormonal characteristics of SLE patients with refractory disease undergoing HSCT.

Patients	Age at Dx	Age at transplant	Menstrual history post-HSCT	Baseline FSH (U/L)/ E2 (pg/mL)	4 months FSH (U/L)/ E2 (pg/mL)	6–9 Months FSH (U/L)/E_2 (pg/mL)	Baseline AMH (ng/mL)	4 Months AMH (ng/ mL)	6–9 Months AMH (ng/ mL)
1	19[a]	19	Amenorrheic on Depot Provera	2/<20	8/33.7	6/35.9	0.6	0.4	0.15
2	14[b]	20	Menses post-HSCT (but no further information available)	4/28.3	8/33.8	7/37.1	0.5	<0.1	[e] ND
3	32[c,d]	38	Amenorrheic	71/46.4	49/30.3	53/34.4	<0.1	[e] ND	[e] ND
4	14	16	Irregular Menses post-HSCT	3/23.7	7/57.6	[e] ND/94.3	1.0	0.6	0.5
5	26[c]	32	Amenorrheic	110/31	96/<20	129/<20	<0.1	<0.1	<0.1
6	20[b,a]	30	Amenorrheic on Depot Provera	14/<20	49/31.5	40/37.4	<0.1	<0.1	<0.1

Note: HSCT = hematopoietic stem cell transplantation; AMH = anti-Müllerian hormone.

[a] Depot Provera.

[b] GnRHa.

[c] Menopausal prior to HSCT.

[d] Deceased.

[e] ND = not done.