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Original article

Age at natural menopause among patients with systemic lupus erythematosus

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Abstract

Objective. The aim of this study was to estimate the age at natural menopause in women with SLE.

Methods. One thousand and thirty-nine consecutive SLE patients <60 years of age were surveyed. Demographic and clinical data were queried by a single investigator. SLE characteristics and co-morbidities were retrieved from their medical records. Natural menopause was defined as amenorrhoea ⩾12 months in the absence of previous hysterectomy, CYC exposure and severe chronic kidney disease (SCKD). Pregnant women and those with menses during the 12 months prior to interview were considered premenopausal. Median age at menopause was estimated by both logit and survival analyses. In addition, mean age at menopause was calculated for patients aged ⩾40 years. Factors associated with age at natural menopause were assessed by Cox regression analysis.

Results. A total of 961 SLE women were analysed. At interview, most patients (81.6%) were premenopausal, 7.9% had natural menopause, 6.3% were postmenopausal previously exposed to CYC, 4.1% had undergone hysterectomy before menopause and 0.1% presented with SCKD and amenorrhoea. The mean age at interview was 35.2 years (S.D. 10.1), the mean age at SLE diagnosis was 26.9 years (S.D. 8.6) and the mean duration of disease was 8.2 years (S.D. 7.1). The mean recalled age at menopause was 46.4 years (S.D. 4.7). Median age at menopause estimated by logit and survival analyses were 50.7 and 50.8 years, respectively. Only the age at SLE diagnosis was associated with age at natural menopause.

Conclusion. Median age at natural menopause in women with lupus is 50 years. This is consistent with the age at menopause reported in the general population.

Key words: systemic lupus erythematosus, age at menopause, risk factors, women's health.

CLINICAL SCIENCE

Introduction

Natural menopause is defined as the permanent cessation of menstruation caused by the loss of ovarian follicular activity. It corresponds to the last menstrual period (LMP) and is recognized to have occurred after 12 consecutive months of amenorrhoea for which there is no other obvious pathological or physiological cause [1]. The age at natural menopause seems to be determined primarily by genetic factors, but some variability should be observed [2]. Indeed, a number of studies have reported differences in the timing of menopause experienced by samples of women of different socio-economic, racial/ethnic and lifestyle backgrounds [3–5]. Moreover, it has long been believed that the menopause is presented at a younger age in women suffering from autoimmune diseases, including SLE [6].

As is well known, SLE is an autoimmune disease that predominantly affects women, and although it generally emerges during the reproductive ages, an increasing number of patients are now reaching the age at which natural menopause occurs [7, 8]. A few small studies have suggested that the age at menopause in lupus patients is lower than that observed in the general

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population; however, whether the occurrence of menopause at a younger age in lupus patients results from the gonadotoxic effects of CYC treatment or from an autoimmune-mediated ovarian injury is still being debated [9].

Besides its reproductive implications, the timing of menopause is important since it is thought that it correlates with the risk of cardiovascular disease, some gynaecological cancers, bone health and overall mortality. In women with lupus, the increased risk of cardiovascular disease and osteoporosis after menopause adds to the risk associated with chronic inflammatory conditions [10]. On the other hand, menopause has been related to both lower lupus activity [11, 12] and greater damage accrual of organs affected by individual flares [13]. Hence a better understanding of the timing of natural menopause and its determinant factors in the SLE population is relevant, not only for improving counselling and health care quality, but also to advance our knowledge regarding the effects that SLE itself may exert on the ovaries. This study is aimed at providing estimates of the mean and median age at menopause in women with SLE, to show the effects of methodological choices on these age estimates and to explore factors associated with the age at menopause among SLE women.

Patients and methods

The study was approved by the Research Ethics Committee (Comité de Ética en Investigación) of Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, and all patients gave their written informed consent before enrolment in the study in accordance with the Declaration of Helsinki. Enrolment was carried out over a 12-month period at our outpatient rheumatology clinic. Consecutive patients with a diagnosis of SLE according to the ACR criteria [14], <60 years old and attending their scheduled medical visit were asked to participate in the survey. Women who were unable to communicate by themselves were excluded. A face-to-face interview that lasted 5–7 min was undertaken by a single investigator (D.A.-R.) using a standardized validated questionnaire. The questionnaire included demographic characteristics (date of birth, years of education and marital status), history of smoking (current and past) and gynaecological data (age at menarche, presence of menstrual cycles, date of the most recent menstrual period, parity, current pregnancy or breastfeeding, use of contraceptives or menopausal hormone therapy in the 3 months prior to the interview, history of hysterectomy or tubal occlusion and their dates). Additional information regarding treatment with prednisone, CYC, AZA, MTX and antimalarials was also collected. In a second step, each woman's medical record was reviewed to determine the precise date at diagnosis (when four criteria of SLE were met), if SLE criteria presented at any time before the interview, the date of first exposure to CYC and the presence of other chronic diseases. Renal function was assessed by either the Cockcroft–Gault equation [15] or the Modification of Diet in Renal Disease equation [16]. Finally, chronic damage accrual at the time of the interview was estimated by a trained researcher using the SLICC/ACR Damage Index (DI), with scores ranging from 0 to 47 and higher scores corresponding to more severe damage [17]. SLE disease activity was not included in the survey data set because it is not systematically assessed in daily clinical practice. All information was registered in standardized research forms to be entered later into an electronic database.

Definitions used in the study

Premenopausal status was assigned to all women who had regular or irregular menses during the 12 months prior to the study or who were pregnant at the time of the interview. Postmenopausal status was assigned to women who fulfilled the definition of natural menopause. Natural menopause was defined as amenorrhoea $\geqslant$12 months in the absence of previous hysterectomy, CYC exposure or severe chronic kidney disease (SCKD). Premature menopause was natural menopause at $<$40 years of age. Age at menopause was the age in years calculated as the difference between the self-reported LMP date and the patient's birth date. Users of contraceptive or menopausal hormone treatments were considered to be pre- or postmenopausal according to their current menstrual pattern. Hysterectomy meant surgical removal of the uterus, with or without oophorectomy. Age at hysterectomy was the age in years calculated as the difference between the self-reported date of surgery and the patient's birth date. CYC exposure was considered whenever the drug was administered, regardless of its dose and route of administration. Age at first exposure was the age in years calculated as difference between the date of the registered first prescription and the patient's birth date. SCKD was defined as creatinine clearance <30 ml/min/1.73 m^2 in at least two consecutive measurements 6 months apart. Age at SCKD was the age in years calculated as the difference between the second creatinine clearance measurement and the patient's birth date.

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical characteristics.

Time at menopause was identified by both survey techniques: self-recalled age at menopause and status at the interview. Mean age at menopause was calculated with ages obtained by self-recalled date at LMP in women $\geqslant$40 years of age, excluding those who had undergone hysterectomy prior to the menopause, CYC treatment or SCKD.

As described in several studies in the general population, to arrive at the best estimate of age at menopause in SLE women, median ages were calculated by logit and Kaplan–Meier analyses. In the logit analysis the current status approach was used to define age at menopause, considering menopause status as the dependent variable and the age at interview as the independent variable. The median age at menopause was the point at which 50% of women in the study population were postmenopausal

[18, 19]. Patients with amenorrhoea ⩾12 months, who had previously had a hysterectomy, CYC exposure and/or SCKD were excluded. Given that the age distribution of the sampled population affects menopausal age estimations, the analysis was repeated in a subgroup of women ⩾40 years of age (which includes a larger proportion of postmenopausal women).

The self-recalled date at LMP was used to compute the median age at natural menopause by Kaplan–Meier analysis [20]. Amenorrhoeic women with hysterectomy, CYC treatment or SCKD that preceded the menopause were censored by the event that occurred first. Premenopausal women were censored by interview date. The time variable was age at censoring or LMP in natural menopause. A modified Kaplan–Meier survival analysis [21, 22] was also applied to the sample, considering four competing event risks: natural menopause, hysterectomy, menopause with previous CYC exposure and amenorrhoea with SCKD. The competing risk model allows accurate analyses of the distribution of age at menopause accounting for the effects of the other three risks. This analysis was computed using the module cmprsk in R to calculate the adjusted cumulative incidence estimates in the study group [23, 24]. Lastly, the Kaplan–Meier analysis was repeated in a subgroup of patients settled by the principal stratification method [25, 26]. For this stratification analysis we considered age at interview as an exposure with three age groups: (i) <40 years, (ii) ⩾40 to <50 years and (iii) ⩾50 years. The median age at menopause was assessed in the group of women ⩾50 years of age [group (iii)], who had remained free of hysterectomy, CYC exposure and SCKD.

Cox regression analysis was used to explore causal relationships between variables present before menopause that do not change with time (age at menarche, parity, tubal occlusion and age at SLE diagnosis) and the age at menopause. Other collected covariates were not used for this analysis because they were ascertained only at the time of interview (i.e. smoking, education level, marital status, SLICC/ACR DI and BMI). SPSS 21.0 (SPSS, Chicago, IL, USA), STATA 11.0 (StataCorp, College Station, TX, USA) and R 3.0.1 (R Foundation for Statistical Computing) were used for the analyses.

Results

Of the 1039 patients who were interviewed, 78 were excluded because they did not meet SLE diagnostic criteria ($n = 19$), SLE ensued after they became postmenopausal, underwent hysterectomy or were diagnosed with SCKD ($n = 54$) or data were incomplete ($n = 5$), leaving 961 to be analysed.

Tables 1 and 2 summarize the principal demographic and clinical characteristics of the study population. The average age at interview was 35.2 years (S.D. 10.1) and at SLE diagnosis was 26.9 years (S.D. 8.6). The mean duration of disease was 8.2 years (S.D. 7.1). The mean SLICC/ACR DI score in the study population was 0.9 (S.D. 1.4) and 42% of patients had a SLICC/ACR DI score ⩾1. Nearly one-third [$n = 303$ (31.5%)] of the

Table 1 Demographic features and gynaecological characteristics of women with SLE at interview

	SLE women ($n = 961$)
Demographic features	
Age, mean (S.D.), years	35.2 (10.1)
Education, mean (S.D.), years	12.6 (3.9)
Marital status, *n* (%)	
Never married	459 (48)
Married/living as married	434 (45)
Divorced/separated/widowed	68 (7)
Current smoking, *n* (%)	95 (10)
Past smoking, *n* (%)	122 (13)
BMI, mean (S.D.), kg/m^2	25.9 (5.0)
Gynaecological characteristics	
Age at menarche, mean (S.D.), years	12.6 (1.5)
Number of pregnancies, mean (S.D.)	1.4 (1.6)
Current pregnancy, *n* (%)	17 (2)
Menses during the previous 12 months, *n* (%)	
Present	784 (82)
Absent	177 (18)
Contraceptive method use, *n* (%)	169 (18)
Menopausal hormone therapy use, *n* (%)	24 (3)
History of tubal occlusion, *n* (%)	196 (20)
History of hysterectomy, *n* (%)	47 (5)

Table 2 Disease characteristics of women with SLE at interview

	SLE women ($n = 961$)
Age at SLE diagnosis, mean (S.D.), years	26.9 (8.6)
Disease duration, mean (S.D.), years	8.2 (7.1)
Current prednisone treatment, *n* (%)	549 (57)
Prednisone dose, mean (S.D.), mg	12.9 (12.6)
CYC treatment ever, *n* (%)	303 (32)
Past CYC treatment, *n* (%)	259 (27)
Current oral CYC, *n* (%)	19 (2)
Current i.v. CYC, *n* (%)	25 (3)
SLICC/ACR DI score, mean (S.D.)	0.9 (1.4)
SLICC/ACR DI score ⩾1, *n* (%)	406 (42)
SLICC/ACR DI score[a], mean (S.D.)	2.1 (1)
SCKD, *n* (%)	43 (5)
SLE criteria over time, *n* (%)	
Malar rash	642 (67)
Discoid rash	112 (12)
Photosensitivity	530 (55)
Oral ulcers	569 (59)
Arthritis	841 (88)
Serositis	337 (35)
Renal disorder	436 (45)
Neurological disorder	132 (14)
Haematological disorder	865 (90)
Immunological disorder	884 (92)
Abnormal ANAs	833 (87)

SLICC/ACR DI: SLICC/ACR Damage Index (score range 0–47) [17]. Severe chronic kidney disease is defined as creatinine clearance <30 ml/min/1.73 m^2. [a]Mean SLICC/ACR DI score among patients with a score ⩾1.

patients had ever been exposed to CYC and 549 (57.1%) were under prednisone treatment. At the time of interview most patients were still menstruating [784 (81.6%)], whereas 177 (18.4%) were amenorrhoeic. Among amenorrhoeic women, 76 (7.9%) had experienced menstrual cessation via natural menopause (17 before the age of 40 years), 39 (4.1%) by hysterectomy, 61 (6.3%) after CYC exposure and 1 (0.1%) due to SCKD.

Age at natural menopause

Table 3 summarizes the results of the estimations of age at natural menopause. The mean recalled age at menopause was 46.4 years (S.D. 4.7). The median age at menopause computed by logit analysis was 50.7 years, quite similar to the age of 50.5 years that resulted from the analysis restricted to women $\geqslant 40$ years of age ($n = 309$). The median age calculated by the Kaplan–Meier survival analysis was 50.8 years (S.E. 0.7); this figure was consistent with that obtained by logit analysis. In survival analyses, 101 patients with amenorrhoea who did not fulfil the criteria of natural menopause were censored: 39 by age at hysterectomy, 61 by age at first exposure to CYC and 1 by age at diagnosis of SCKD. Premenopausal patients ($n = 784$) were censored by age at interview. When competing risks were considered in the Kaplan–Meier analysis, the median age at natural menopause was 2.45 years later: 53.3 years (S.E. 0.1). At age 50 years the adjusted cumulative incidence was 0.32, therefore the cumulative survival proportion by each age year was higher across the analysis.

In the principal stratification analysis, the number of patients corresponding to the groups (i) <40 years, (ii) $\geqslant 40$ to <50 years and (iii) $\geqslant 50$ years were 652 (67.8%), 226 (23.5%) and 83 (8.7%), respectively. In group (iii) there were 57 (69%) patients who remained free of events such as hysterectomy, CYC exposure and SCKD. Forty-five of these 57 women had undergone natural menopause. The causal effect of age group (ii) *vs* age group (i) was $[(27/57) - (4/57)] = 0.40$ [the difference between the risk of natural menopause in age group (ii) and age group (i)]. Similarly, the causal effect of age group (iii) *vs* age group (ii) was $[(14/57) - (27/57)] = -0.22$. The median age at menopause among the patients free of events from group (iii) was 49.7 years (S.E. 0.5). Fig. 1 depicts in a boxplot the distributions of menopause ages by Kaplan–Meier survival analysis with censoring, with competing risk and in the group of women $\geqslant 50$ years of age from principal stratification analysis free of events.

Factors associated with age at menopause among SLE women

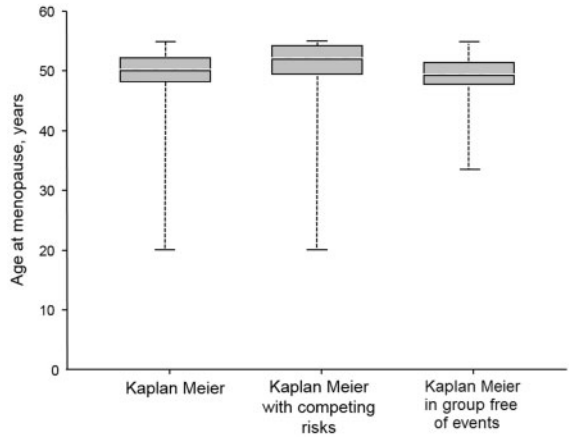
Only age at SLE diagnosis was significantly associated with age at natural menopause, with a relative risk of 0.97 (95% CI 0.94, 0.99), suggesting that older age at SLE diagnosis is associated with a lower risk of menopause. Parity, age at menarche and history of tubal occlusion were not significantly associated with the age at natural menopause.

TABLE 3 Age at natural menopause in 961 patients with SLE estimated by different statistical methods

Statistical method	Study group	Observations[a]	Number of women analysed	Age at menopause, years
Descriptive statistics	Women aged $\geqslant 40$ years ($n = 309$)	Excluded: premenopausal ($n = 167$), hysterectomy ($n = 34$), CYC exposure ($n = 47$), SCKD ($n = 0$)	61	Mean 46.4 (S.D. 4.7) (range 34.2–54.1)
Logit analysis	All women ($n = 961$)	Excluded: hysterectomy ($n = 39$), CYC exposure ($n = 61$), SCKD ($n = 1$)	860	Median 50.7 (95% CI 50.6, 53.3)
	Women $\geqslant 40$ years of age ($n = 309$)	Excluded: hysterectomy ($n = 34$), CYC exposure ($n = 47$), SCKD ($n = 0$)	228	Median 50.5 (95% CI 49.1, 52.2)
Kaplan–Meier analysis with censoring	All women ($n = 961$)	Censored: premenopausal ($n = 784$), hysterectomy ($n = 39$), CYC exposure ($n = 61$), SCKD ($n = 1$)	961	Median 50.8 (S.E. 0.74) (95% CI 49.3, 52.2)
Kaplan–Meier analysis with competing risks	All women ($n = 961$)	Competitive risks: natural menopause, hysterectomy, CYC exposure, SCKD	961	Median 53.3 (S.E. 0.05) (95% CI 53.2, 53.3)
Kaplan–Meier analysis after principal stratification analysis	Women >50 years of age [group (iii)] ($n = 57$)	Censored: premenopausal ($n = 12$)	45	Median 49.7 (S.E. 0.45) (95% CI 48.8, 50.6)

[a]Excluded or censored patients are those who had had a hysterectomy, CYC exposure or SCKD before menopause. SCKD: severe chronic kidney disease.

FIG. 1 Distribution of age at natural menopause among women with SLE



Boxplot shows median age at menopause estimated by different survival analyses: with censoring, with competing risks and in the group of women who reached the age of 50 years without having had hysterectomy, CYC exposure or severe chronic kidney disease (from the principal stratification analysis). The median age is depicted by the centre line of the box and the interquartile range (distance from the 25th to 75th percentiles) by the length of the box. The dotted lines extending from the top and bottom of the box represent the extreme values of the data.

Discussion

Herein we report on the results of a survey to estimate the age at natural menopause among women with SLE and to examine the factors associated with that. Since it has been claimed that variations in the reported age at menopause might depend on the procedure utilized for measurement as well as on the age distribution of the sample, we examined the age at menopause in patients with lupus by applying different methodologies.

The mean recalled age at menopause in our study group, 46.4 years, was within the range of those previously reported in SLE women [13, 20, 27–29]; however, valid comparisons cannot be made across studies due to existing differences in patients' conditions, protocol designs and data analysis methods. Like in most studies carried out in either clinic or population-based samples, we used the median to better estimate the age at menopause in women with lupus. To our knowledge this measurement has not been made in samples of lupus patients; therefore our study provides pioneering information on this issue. Median age at menopause obtained by either logit or survival analysis in our SLE population was similar and in line with that obtained in the subgroup of patients who had reached the age of 50 years remaining free of hysterectomy, CYC exposure and SCKD (50.8, 50.7 and 49.6 years, respectively). Only when competing event risks were taken into account did the median estimation shift to 53.5 years, which means 2.5 years later than the median calculated by the survival analysis with censoring. This finding might reflect the influence that hysterectomy, CYC exposure and SCKD exert on the hazard of natural menopause in SLE patients.

Our results cannot be compared with others because no similar studies in lupus patients are available in the literature. Neither can they be compared with estimations of the age at menopause in the general population because a control group was not included in the study design. However, it should be noted that our findings are consistent with results of previous research on the age at menopause in samples of Mexican women without lupus. Indeed, utilizing logit or probit analysis, the median age at menopause found in a number of Mexican studies ranged from 48.2 to 49.7 years [30–33]. On the other hand, the median age at menopause computed by survival analysis among women participating as controls in a multinational study by the World Health Organization was 51 years [34] and that found in the population-based investigation carried out in Puebla, Mexico, was 50 years [32].

Natural premature menopause was identified in ~1.7% of surveyed patients. Elucidation of the mechanisms underlying the premature cessation of ovarian function in these individuals is beyond the scope of this study and deserves future investigation. In our patient sample, only older age at SLE diagnosis was associated with a lower risk of menopause. Parity, age at menarche and a history of tubal occlusion have not been clearly described as factors associated with age at natural menopause in the general population either [3–5].

We should recognize several limitations and strengths of our investigation. The principal limitation relies on the cross-sectional design, since it is agreed that better assessments of the age at menopause and its related factors can be obtained with a longitudinal design. As in other studies, a methodological concern is that amenorrhoea >12 months was taken as synonymous with menopause. Thus patients with reversible amenorrhoea, unrelated to ovarian failure, could have been misclassified. Such is the case of women receiving progestin-only contraceptives, danazol and perhaps high doses of prednisone; however, all these scenarios would shift the median age at menopause towards a lower rather than a higher estimate. On the other hand, patients receiving either combined contraceptives or menopausal hormone treatment could also be misclassified. Oestrogen-containing formulations induce endometrial bleeding or menstruation that can mask natural menopause. In these cases the median age at menopause would be shifted towards a higher estimate. We did not attempt to identify patients with natural menopause under hormonal treatment because the collected data referred only to the use of unspecified hormonal treatments over the 3 months prior to the interview. In this survey it was not possible to gather useful information about SLE activity and chronic damage accrual prior to menopause. Hence inferences on how disease activity and the severity of chronic damage may impact the age at menopause cannot be made. Repeated measures of

SLE activity within a longitudinal design would be necessary to explore these important relationships. Lastly, the lack of a control group precludes valid comparisons of the age at menopause between SLE patients and women in the general population.

Among the strengths are that all patients belonged to similar racial/ethnic groups, were studied and treated in the same institution (under uniform criteria) and were interviewed by a single investigator. All definitions employed in the survey were previously defined and are widely accepted. Since both CYC treatment and SCKD are known causes of amenorrhoea [35–37], non-menstruating patients who had been exposed to these before natural menopause were excluded or censored in the analyses. On the other hand, menstruating patients ever exposed to CYC or SCKD remained in the study and were analysed. Even though our study population reflects a wide spectrum of lupus, our data may not be generalized to other lupus patient populations because ethnic and sociocultural conditions have been associated with variations in the age at menopause.

In conclusion, the median age at menopause among women with SLE is estimated at ~50 years. This is consistent with the age at menopause reported in the general population and suggests that the physiological mechanisms responsible for ovarian ageing seem to be preserved in most SLE women.

Rheumatology key messages

- This study provides pioneering information on age at natural menopause in women with SLE.
- Applying strict methodology, age at natural menopause in SLE is consistent with that reported in the general population.
- This research suggests that the physiological mechanisms responsible for ovarian ageing are preserved in most SLE patients.

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References

1 World Health Organization. Research on the Menopause in the 1990s. WHO Technical Report Series No. 866. Geneva, Switzerland: World Health Organization, 1996.

2 Murabito JM, Yang Q, Fox C *et al*. Heritability of age at natural menopause in the Framingham Heart Study. J Clin Endocrinol Metab 2005;90:3427–30.

3 Gold EB, Bromberger J, Crawford S *et al*. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol 2001;153:865–74.

4 Gold EB. The timing of the age at which natural menopause occurs. Obstet Gynecol Clin North Am 2011;38:425–40.

5 Gold EB, Crawford SL, Avis NE *et al*. Factors related to age at natural menopause: longitudinal analyses from SWAN. Am J Epidemiol 2013;178:70–83.

6 Bove R. Autoimmune diseases and reproductive aging. Clin Immunol 2013;149:251–64.

7 Sánchez-Guerrero J, González-Perez M, Durand-Carbajal M *et al*. Menopause hormonal therapy in women with systemic lupus erythematosus. Arthritis Rheum 2007;56:3070–9.

8 Feldman CH, Hiraki LT, Liu J *et al*. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000–2004. Arthritis Rheum 2013;65:753–63.

9 Sammaritano LR. Menopause in patients with autoimmune diseases. Autoimmun Rev 2012;11:A430–6.

10 Romero-Díaz J, Vargas-Vóracková F, Kimura-Hayama E *et al*. Systemic lupus erythematosus risk factors for coronary artery calcifications. Rheumatology 2012;51:110–9.

11 Sánchez-Guerrero J, Villegas A, Mendoza-Fuentes A *et al*. Disease activity during the premenopausal and postmenopausal periods in women with systemic lupus erythematosus. Am J Med 2001;111:464–8.

12 Mok CC, Lau CS, Ho CT *et al*. Do flares of systemic lupus erythematosus decline after menopause? Scand J Rheumatol 1999;28:357–62.

13 Urowitz MB, Ibañez D, Jerome D *et al*. The effect of menopause on disease activity in systemic lupus erythematosus. J Rheumatol 2006;33:2192–8.

14 Tan EM, Cohen AS, Fries JF *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.

15 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.

16 Levey AS, Bosch JP, Lewis JB *et al*. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–70.

17 Gladman D, Ginzler E, Goldsmith C *et al*. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.

18 McKinlay SM, Bifano NL, McKinlay JB. Smoking and age at menopause in women. Ann Intern Med 1985;103:350–6.

19 Cramer DW, Xu H. Predicting age at menopause. Maturitas 1996;23:319–26.

20 Luoto R, Kaprio J, Uutela A. Age at natural menopause and sociodemographic status in Finland. Am J Epidemiol 1994;139:64–76.

21 Krailo MD, Pike MC. Estimation of the distribution of age at natural menopause from prevalence data. Am J Epidemiol 1983;117:356–61.

22 Shinberg DS. An event history analysis of age at last menstrual period: correlates of natural and surgical menopause among midlife Wisconsin women. Soc Sci Med 1998;46:1381–96.

23 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999; 94:496–509.

24 Gray B. Harvard. Subdistribution Analysis of Competing Risks. http://cran.r-project.org/web/packages/cmprsk/cmprsk.pdf (22 April 2014, date last accessed).

25 Frangakis CE, Rubin D. Principal stratification in causal inference. Biometrics 2002;58:21–9.

26 Seuc AH, Peregoudov A, Betran AP *et al*. Intermediate outcomes in randomized clinical trial: an introduction. Trials 2013;14:78.

27 Lee C, Almagor O, Dunlop DD *et al*. Disease damage and low bone mineral density: an analysis of women with systemic lupus erythematosus ever and never receiving corticosteroids. Rheumatology 2006;45:53–60.

28 Mok CC, Mak A, Ma KM. Bone mineral density in postmenopausal Chinese patients with systemic lupus erythematosus. Lupus 2005;14:106–12.

29 Cravioto MD, Durand-Carbajal M, Jiménez-Santana L *et al*. Efficacy of estrogen plus progestin on menopausal symptoms in women with systemic lupus erythematosus: a randomized, double-blind, controlled trial. Arthritis Care Res 2011;63:1654–63.

30 García Vela A, Nava LE, Malacara JM. The age of menopause in the urban population of the city of León, Guanajuato. Rev Invest Clin 1987;39:329–32.

31 Velasco E, Malacara JM, Cervantes F *et al*. Gonadotropins and prolactin serum levels during the perimenopausal period: correlation with diverse factors. Fertil Steril 1990; 53:56–60.

32 Sievert LL, Hautaniemi SI. Age at menopause in Puebla, Mexico. Hum Biol 2003;75:205–26.

33 Castelo-Branco C, Blumel JE, Chedraui P *et al*. Age at menopause in Latin America. Menopause 2006;13: 706–12.

34 Morabia A, Costanza MC. International variability in ages at menarche, first livebirth, and menopause. World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. Am J Epidemiol 1998;148: 1195–205.

35 Lim VS, Henriquez C, Sievertsen G *et al*. Ovarian function in chronic renal failure: evidence suggesting hypothalamic anovulation. Ann Intern Med 1980;93: 21–7.

36 Doumouchtsis KK, Perrea DN, Doumouchtsis SK. The impact of sex hormone changes on bone mineral deficit in chronic renal failure. Endocr Res 2009;34:90–9.

37 Katsifis GE, Tzioufas AG. Ovarian failure in systemic lupus erythematosus patients treated with pulsed intravenous cyclophosphamide. Lupus 2004;13:673–8.