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SECULAR TREND AND INTRAPOPULATIONAL VARIATION IN AGE AT MENOPAUSE IN SPANISH WOMEN

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Summary. Menopause is associated with the general ageing process and marks the end of follicular depletion, a process that begins in the intrauterine stage and lasts throughout the lifetime of women until their reproductive senescence. Controversy persists about whether the age at menopause is sensitive to the ecological determinants prevailing during the lifecycle or whether it has a predominantly genetic component that would allow groups of women to be characterized with respect to particular menstrual characteristics manifested throughout their fertile life. By contrast, there is a definite secular trend in age at menarche in populations that have registered improvements in their environment: sexual maturation is closely associated with the general processes of growth and development. These aspects were analysed in a sample of Spanish women, mothers and daughters, born between 1883 and 1941. The results show (a) indications – although not conclusive – of a secular trend in the age at menopause, (b) a possible association between the age at menopause of mothers and their daughters, and (c) an association at the individual level between age at menarche, particular characteristics of ovarian function (fetal loss) and age at menopause. The reproductive ageing process therefore seems to result from the expression of the influence of ecological conditions in which the lifecycle of the women develops and of a degree of heritability that affects not only the age at menopause but also a range of characteristics of ovarian function.

Introduction

Menarche and menopause signal the beginning and the end of fertile life, as well as biological indicators of physiological age: the first establishes, within women of identical chronological age, their degree of maturation; the second is a general indicator of ageing. The chronological ages at which both processes take place and

the manner in which they occur depend largely on the ecological conditions in which the lifecycle of individuals develops.

However, although there is unquestionably a secular trend in age at menarche – first detected by Tanner (1962) in northern European populations – controversy persists over whether the age at menopause is also sensitive to environmental conditions.

The sensitivity of age at menopause to ecological factors or other biological variables – such as age at menarche – could be detected by evaluating its temporal change over successive generations of a population subjected to environmental change, as well as by comparing intrapopulational differences among groups living in markedly different socioeconomic conditions. Age at menopause is very variable among populations (Gray, 1976; Gage *et al.*, 1989; Wood, 1994) and at the intrapopulational level its variance is greater than that in age at menarche (Treolar, 1974). Studies carried out in Western and developing countries have shown these populational differences to be a function of distinct lifestyle factors, in particular the nutritional state of women (MacMahon & Worcester, 1966; Scragg, 1973; Karim, Chowdhury & Kabir, 1985; Stanford *et al.*, 1987; Boldsen & Jeune, 1990), although this association has not been confirmed by other analyses (McKinlay, Jefferys & Thompson, 1972); in addition, various methodological problems have been identified in previous research (McKinlay & McKinlay, 1978; van Noord *et al.*, 1997a). Flint's (1978) revision suggests that there could have been a secular trend in age at menopause in populations from industrialized countries in the last 100 years. This could be confirmed by longitudinal studies of the type carried by van Noord *et al.* (1997a), who described a small secular trend in a cohort of Dutch women born between 1911 and 1925. This secular trend in menopause may also be reversible, like that in menarche: Cassou *et al.* (1997) described a significant reduction in the age at menopause in French women born between 1938 and 1943 due to the deterioration of living conditions during the Second World War. However, other authors (Gray, 1976; McKinlay, Bifano & McKinlay, 1985) deny that such a secular trend has arisen, thus attributing less influence to environmental factors on the process of reproductive ageing.

This question of a parallel secular trend in the ages of menarche and menopause within a population is linked to the analysis of the relation of both variables at the individual level. In Treolar's (1974) classic study of a large sample of North American middle-class students over a period of 30 years, a secular reduction in the age at menarche was not significantly correlated with age at menopause at the individual level. This relationship was previously demonstrated by the analysis of McKinlay *et al.* (1972), and has since been described by van Noord *et al.* (1997a). Gray (1979) suggests that there may be an inverse relationship between the age at menarche and the age at menopause in poorly nourished populations. However, Leidy (1996) found no association between the age at menarche and the appearance of the symptomatology typically associated with the menopausal transition.

These results suggest that the ages at menarche and menopause are not subjected to the same selective or environmental pressures (Gray, 1976; Mayer, 1982), or that their biological bases are independent. Certainly, while the age at menarche is closely linked to the general process of development and is rigidly constrained by biological

(phylogenetic) limits, menopause is the final expression of a process of oocyte and follicular depletion (Gosden, 1985; Richardson, Senikas & Nelson, 1987; Faddy *et al.*, 1992) that, beginning in the fifth month of intrauterine development, lasts for 40–50 years of a woman's life. Given so long a period, it is logical to expect more intrapopulational variability in age at menopause than in age at menarche (Wood, 1994), as has been confirmed in all human populations.

This study tests the hypothesis that the age at menopause and the characteristics of the reproductive ageing process are sensitive to the environmental and constitutional determinants that operate and are manifested throughout the lifecycle, in the same way as occurs with the age at menarche and the maturation process. To this end, the ages at menopause of Spanish women of 45–69 years of age were compared with those of their mothers with the aim of establishing whether there was a secular trend in this marker of reproductive ageing in recent decades. Socioeconomic development over half a century – including intensive migration and urbanization – was considered as a determinant of important changes in the ecological and environmental conditions in which these women lived. Secondly, working within the framework of the lifespan approach, which considers the effect of early menstrual and reproductive events on the process of reproductive ageing, the association between the initial and final stages of the female fertile cycle was analysed considering, amongst other aspects, the age at menarche and the characteristics of the initial cycles. Finally, the relation between particular indicators of reproductive ageing (fecundability) and the age at menopause was analysed.

Materials and methods

The population analysed comprised 1036 women between the ages of 45 and 69 (mean age 52·4 years, SD = 5·4 years), resident in Alcobendas, near Madrid (Ayuntamiento de Alcobendas, 1990), who participated in an on-going population-based uterine and gynaecological cancer screening programme organized by the *Concejalía de Salud* (Health Department) of the town council with the collaboration of the *Comunidad Autónoma de Madrid* (the provincial administration) and the *Universidad Autónoma de Madrid* (UAM). The Biological Anthropology Unit of the UAM specifically developed a research programme concerning reproductive ageing within the framework of this campaign (Bernis *et al.* 1995; Montero *et al.*, 2000). As well as the recording of anthropometrical and physiological measurements and a clinical check-up, women answered a broad-ranging questionnaire concerning (a) socioeconomic status, (b) menstrual and reproductive history, (c) lifestyle habits, (d) diagnosed illness, (e) perceptions of the subject's own health and (f) nutrition; the questionnaire also included questions concerning their mothers, and their age at menopause.

The mean age at menopause of this population – estimated by the current status method – was 51·7 years. Not all women interviewed were postmenopausal and, to avoid bias in the analysis, only those women over 55 years were considered (56 years is the age at which all women were postmenopausal), excluding those who had undergone surgical menopause ($n = 248$). The mean age of this selected group was 59·9 years (SD = 3·0 years).

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Univariate analyses were employed principally, since the study addressed the association of age at menopause with genetic and physiological factors that are expressed early on in the lifecycle. Other reproductive (e.g. fertility or age at last maternity) and morphophysiological (e.g. Body Mass Index) factors, which characterize more advanced stages of the reproductive cycle, were not considered except as covariates. The women analysed all belonged to a traditional group that is highly homogeneous socioeconomically (e.g. with respect to education and employment) and in its habits (e.g. tobacco consumption, exercise and diet). As artificial contraception was legalized in Spain as late as 1976, the majority (77·6%) of the participants had never used oral contraceptives, and those that had taken them did so late on in their reproductive lives (mean age at starting: 35·6 years, SD = 6·5; mean age at cessation: 38·4 years, SD = 6·9), and for a short period (mean duration: 5·9 months, SD = 22·7), from which it may be assumed that the effect of this variable on the age at menopause was slight. As the distributions of most of the continuous variables were not normal, Spearman *rho* coefficients were used to evaluate the association between them. Multiple regression analysis was used to control for the correlation among selected variables. All statistical analyses were performed using SPSS for Windows (release 7·5).

First, to verify whether there had been a secular trend in menopause, mean ages of matched pairs of mothers–daughters over 55 ($n = 80$) were compared, and the association between age at menopause and date of birth were investigated. Mothers were born between 1883 and 1922, and their daughters between 1927 and 1941.

Secondly, the association between ages at menarche and menopause and certain characteristics of ovarian function were evaluated: whether initial cycles were painful and irregular, and if either symptom persisted in subsequent stages of the fertile life. The mean ages at menarche and menopause in postmenopausal over-55 women ($n = 248$) were 13·6 (SD = 1·8) and 49·9 years (SD = 3·8), respectively; as in other populations, variance in age at menopause was greater than that in age at menarche. Upper and lower quartiles of age at menarche and menopause were taken to establish the groups of early maturing (≤ 12 years, $n = 64$) and late maturing (≥ 15 years, $n = 71$), and premature (<48 years, $n = 57$) and delayed (≥ 53 years, $n = 69$) reproductive ageing women.

Thirdly, the variation in age at menopause was evaluated as a function of the first birth interval (values greater than 8 months) and of the number of fetal losses. Both variables were used as indicators of fecundability and of premature ovarian failure, and thereby as possible predictive variables of reproductive ageing and age at menopause.

Results

Secular trend in age at menopause: age at menopause and family history

The mean age of menopause of daughters over 55 was 50·4 years (SD = 3·9, $n = 80$) and that of their mothers 49·3 (SD = 5·5, $n = 80$). Although this difference of more than a year in mean age of menopause of mother–daughter pairs was not significant, there is an indication of a secular trend in age at menopause between generations: a

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Table 1. Mean age of maternal menopause by daughters' age group and menstrual state (entire sample, Alcobendas, Madrid)

	Age of maternal menopause: mean (standard deviation), *n*	
	Age group 45–49	Age group 50–54
Premenopausal women	49·6	50·5
	(4·9)	(4·3)
	165	55
Postmenopausal women	46·1	47·6
	(4·6)	(4·9)
	34	75
F	3·841	3·507
df	197	128
p	0·000	0·001

significant increase in the age at menopause with year of birth, considering together mothers and daughters over 55 years (Spearman correlation coefficient: 0·093, $p = 0·01$, $n = 668$). It is also interesting to note that age at menopause was less variable in the daughters than in their mothers, a phenomenon that characterizes the process of temporal change in other biosocial variables.

Independently of an effective temporal change, ages at natural menopause of mothers and daughters were highly positively correlated (Spearman correlation coefficient: 0·290, $p = 0·01$, $n = 80$). This association was persistent. First, as shown in Table 1, the age of menopause of the mothers of non-menopausal daughters (those whose last cycle had taken place less than 3 months before the study) in both the 45–49 and 50–55 year age groups, was significantly later than that of the mothers of already postmenopausal daughters (no cycle in the year before the study). Secondly, among the postmenopausal women, those with early and late age at menopause differed significantly in the age of menopause of their mothers: 45·4 (SD = 7·4, $n = 23$) and 50·2 (SD = 6·5, $n = 29$) years, respectively ($F = 6·162$, df = 1, $p = 0·01$). Family history appears to be a predictor of risk of early menopause.

Age at menopause, sexual maturation and ovarian function

It was not possible to differentiate the early ($\leq$12 years) and late ($\geq$15 years) maturing groups on the basis of the symptomatology of their initial cycles, whether or not they were painful and irregular, and the process of normalization of these with the disappearance of both symptoms. Neither did they show significant differences in the mean number of fetal losses experienced during their fertile life. Likewise, women of early (<48 years) and late ($\geq$53 years) menopausal age did not differ significantly in the symptomatology of their first cycles, nor in the percentage of those who

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Table 2. Distribution of age groups of women of early and late menarche and menopause (women >55 years, natural menopause, Alcobendas, Madrid)

	Percentage (*n*)	
	Early menarche group (≤12)	Late menarche group (≥15)
Early menopause group (≤47)	62·2 (23)	37·8 (14)
Late menopause group (≥53)	38·9 (14)	61·1 (22)
χ^2		3·954
df		1
p		0·04

stopped experiencing them in more advanced stages of their lifecycle and those who did not.

By contrast, early maturers reached menopause significantly earlier (48·9 years, SD = 4·3, $n = 64$) than late maturers (50·2 years, SD = 3·7, $n = 71$): $t = -2·004$, df = 133, $p = 0·05$. The contingency table of groups of early and late menarche and menopause also reveals this link between sexual maturation and reproductive ageing ($\chi^2 = 3·954$, df = 1, $p = 0·04$: Table 2), an association confirmed by the moderately significant value of the Spearman correlation coefficient between both variables (0·127, $p = 0·04$, $n = 246$).

Age at menopause and fecundability

The process of reproductive ageing in women who reached menopause early was more premature and/or rapid and its consequences might thus be revealed by a decrease in their fecundability. The first birth interval is a variable that allows any differences in fecundability to be detected, especially in a population like the one studied here that is characterized by delayed ages of marriage and first maternity (24·5 years, SD = 3·3, and 25·6 years, SD = 3·6, respectively: Varea & Bernis, 1998); the mean value of this variable for the analysed group was 22·8 months (SD = 23·3, $n = 174$). However, the first-birth interval did not correlate significantly with age at menopause, nor did the mean values of this variable differ significantly between early and late maturing women.

In addition, the incidence of intrauterine mortality may suggest premature ovarian failure and predicts early age at menopause. The mean number of fetal losses in the group was 0·4 (SD = 0·7, $n = 248$); 69·8% of women suffered no loss, and 23·0% and 7·2% had experienced one, or two or more losses, respectively. There seems to be a definite relation between increased intrauterine mortality and reproductive ageing. First, women who had two or more fetal losses reached menopause significantly earlier (Table 3), and secondly, the percentage of those who had experienced two or more losses was higher in early than in late maturers (14·0% and 2·9%, respectively) ($\chi^2 = 6·426$, df = 2, $p = 0·04$). In contrast, there was no difference in the final fertility of women with early and late menopause.

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Table 3. Mean age at menopause classified by number of fetal losses (women >55, natural menopause, Alcobendas, Madrid)

Number of fetal losses	Mean age at menopause (standard deviation)	*n*
0	50·0 (3·7)	173
1	50·5 (3·6)	57
2 or more	47·6 (4·9)	19
F	57·396	
df	2	
p	0·021	

A linear regression analysis was conducted to estimate the amount of variance in age at natural menopause explained by the variables correlated independently with it. Age, age at menarche, number of fetal losses and age at menopause of mothers were included in the analysis as predictor variables on age at menopause. Variables included in the model were age at menopause of mothers ($\beta = 0{\cdot}339$, $t = 3{\cdot}408$, $p = 0{\cdot}001$), age at menarche ($\beta = 0{\cdot}209$, $t = 2{\cdot}065$, $p = 0{\cdot}04$); number of fetal losses and age were excluded. The overall model was statistically significant ($F = 3{\cdot}967$, df = 4, $p = 0{\cdot}005$) but with a low percentage of variance explained in age at menopause by the combined variables ($R^2 = 0{\cdot}15$), although this percentage falls within the range of those obtained in another studies (van Noord *et al.*, 1997a).

Discussion

The results confirm the complex inter-relationship and, as yet, not fully clarified influence of two sets of factors on reproductive ageing and menopause: that of environment and lifestyle, and a family historical/genetic component that may determine other characteristics of ovarian function throughout female reproductive life. First, there was some indication of a slight secular trend in the age at menopause, whereby later cohorts reached menopause later. Secondly, there was an association between the ages of menopause of mothers and their daughters, which might indicate a degree of heritability of the trait, although this interpretation requires more direct confirmation. Thirdly, at the individual level there was an association between age at menarche and several characteristics of ovarian function and age at menopause, by which early maturers and those who registered a higher incidence of intrauterine mortality had a greater propensity towards early menopause.

Separate studies have shown that within populations different ages of sexual maturation determine different patterns of ovarian function during the initial years after menarche or throughout the fertile life with respect to the regularization of the menstrual cycle, the duration and adjustment of the follicular and luteal phases and the overall ovulatory character (Apter, Viinkka & Vihko, 1978, 1987; Apter & Vihko, 1983; Gadner, 1983; Lenton, Landgren & Sexton, 1984; Venturoli *et al.*, 1987;

Bernis *et al.*, 1995). Also, women with extreme ages at menarche experience a greater frequency of fetal losses throughout their fertile period (Liestol, 1980; Wyshak, 1983; Madrigal, 1991). The characteristics of ovarian function throughout the fertile cycle may also be associated with the age at menopause and the characteristics of menopausal transition. Thus, Cramer & Xu (1996) showed that women with early menarche and whose cycles were short were more likely to reach menopause early, while Stanford *et al.* (1987) and Bromberger (1997) also demonstrated an association between irregular and anovulatory cycles in the first stage of the fertile life and earlier menopause.

In the sample of women from Alcobendas, early menarche was associated with early menopause. This positive correlation is remarkable in that it is seemingly the opposite of a possible secular trend in age at menopause. Certainly, at the populational level and as an indicator of improvements in the environmental conditions, a secular trend in reproductive ageing should yield a negative association between the ages at menarche and menopause, bringing forward the former and delaying the latter. But, at the individual level, the positive association between both ages is consistent with the hypothesis of ovarian function as a comprehensive process throughout the entire fertile lifecycle, a hypothesis that the above literature review and other results of this analysis appear to confirm. Thus, although no significant differences were found in age at menopause or menarche in this population in terms of the characteristics of the menstrual cycle (pain or irregularity), the association between enhanced intrauterine mortality and precocious menopause is nevertheless significant. This result is of considerable interest, especially given that, on the other hand, there is no association between age at menarche and subsequent intrauterine mortality. In the majority of cases, fetal losses resulted from chromosomal abnormalities, which could be associated with premature ovarian failure and could consequently be an indicator of a more rapid process of reproductive ageing in those women with greater intrauterine mortality. This hypothesis is supported by the observation that, in the sample from Alcobendas, although women with earlier menopause and two or more fetal losses married and had their first child at an age that was not significantly different from that of the other women, they had tended to have abortions younger (e.g. mean age of first abortion was 24·3 years compared with 27·7 years in those women who had only had one fetal loss).

The age at menopause and menopausal status of the daughters at the time of interview seems to be related to the age at menopause of their mothers, an association that might indicate a heritable component of the trait and reinforce the former hypothesis. However, this association might simply be due to a bias introduced into the data of mothers' age at menopause due to the manner of its collection: there may have been a tendency for each woman to identify her own menstrual experience with that of her mother. Nevertheless, other studies evaluating mothers' menopause on the basis of their daughters' reports (Torgerson *et al.*, 1994; Cramer, Xu & Harlow, 1995; Cramer & Xu, 1996) have also shown that women with family histories of early menopause have a greater probability of early menopause; recent studies, such as that of van Noord *et al.* (1997b) of mono- and dizygotic twin sisters, appear to confirm that there is a genetic component.

Therefore, the process of reproductive ageing appears to reflect the complex interaction of different groups of factors. As the indications of a secular trend in age at menopause bear out, ecological, reproductive and lifestyle factors may have a significant, albeit small, influence; additionally, there may be a genetic component that ought not only to affect the age at menopause but also the characteristics of ovarian function throughout the distinct phases of women's lifecycles, which are ultimately the result of individual hormonal profiles (Ellison, 1991, 1996). As van Noord *et al.* (1997a) showed, the total number of oocytes might be genetically determined, while the velocity of follicular atresia throughout the entire female lifecycle depends on a wide range of distinct factors. Thus, studies of menopause have the double responsibility to describe the hierarchy of this range of genetic, ecological and behavioural factors, and to reveal clearly the biological foundation that underlies the process of reproductive ageing and its relation to the process of general ageing in our species.

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