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Season of birth influences the timing of menopause

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BACKGROUND: Seasons may influence prenatal growth and future fertility. This study investigated whether season and month of birth influenced the timing of menopause in a group of women attending three Italian menopause clinics. METHODS and RESULTS: Age at menopause of 2822 post-menopausal women (>12 months of amenorrhoea) was stratified by month and season of birth. Mean age at menopause was 49.42 years (SEM: 0.78 years). Menopause occurred earlier for women born in the spring (age 49.04 ± 0.15 years) than in the autumn (49.97 ± 0.14 years). The earliest menopause was found in women born in March (48.9 ± 0.25 years) and the latest in women born in October (50.3 ± 0.25 years). The effect of season of birth on age at menopause remained even when considering factors that in our analysis were capable of significantly interfering with the timing of menopause, such as age at menarche, body mass index, smoking habit, level of education and type of job. CONCLUSIONS: Taking into consideration the retrospective design of the study, and a possible recall bias, the present data seem to suggest that environmental factors linked to seasons are capable of interfering with the timing of a woman's ovarian exhaustion by an action exerted in the prenatal period.

Key words: menopause/season/rhythms/fertility/environment

Introduction

A woman's fertility is limited by the amount of oocytes formed during prenatal life and by the rate of their degeneration (Adashi, 1991). Accordingly, the final number of primordial cells may be influenced by many factors including those capable of influencing embryo–fetal development. Environmental and/or social factors linked to seasons, by an action exerted in prenatal life, were reported to influence fetal growth (Rantakallio, 1971; Selvin and Janerich, 1971; Bantje, 1987; Weber *et al.*, 1998; Matsuda *et al.*, 1993, 1995; Murray *et al.*, 2000), human lifespan (Gavrilov and Gavrilova, 1999; Doblhammer and Vaupel, 2001) and fertility of both men (Francois *et al.*, 1997; Huber *et al.*, 2004a) and women (Smits *et al.*, 1997; Lummaa and Tremblay, 2003; Huber *et al.*, 2004b). This study investigates whether environmental factors linked to seasons may also influence the timing of ovarian exhaustion.

Materials and methods

A retrospective study was performed as a part of the goals of the Group Emiliano-Romagnolo for the menopause (GOERM). Four university hospitals (Bologna, Ferrara, Modena and Parma) and one hospital division (Cattolica) use an identical electronic database for their daily clinical management of peri- and post-menopausal women. Women seeking advice and/or treatment of peri- and post-menopausal disturbances at the menopause centres of the above hospitals are interviewed and examined. Their data are entered into an electronic database, from which they are retrieved at each following examination. New information is added to each woman's file whenever she is evaluated. When necessary, data of interest are extracted from the database of each single centre, combined with those of the other centres, and then analysed. In this case, for patients visiting between January 1997 and December 2001, the following parameters were extracted from the databases of Ferrara, Modena and Parma: patient number (but not patient name), date of evaluation, month and year of birth, age at menarche, number of pregnancies (including miscarriages and stillbirth), date of last spontaneous menstrual period, menopausal status at evaluation, use of estrogens, progestins or hormonal contraception during the menopausal transition, weight, body mass index (BMI; kg/m^2), education, present/past type of job, and smoking habit. Education was divided into low (primary school) and high (high school and university). On the basis of the type of job, women were divided into housewives, workers (skilled or unskilled) and employers/officials. On the basis of their smoking habit, women were considered as ever or never smokers. Data of 14 320 women were retrieved (Figure 1). Of these, 1000 women were excluded because they had undergone surgical menopause or had suffered from diseases or received medicine capable of interfering with the timing of menopause. Another 6200 women in the perimenopausal transition were also excluded. In 4298 of the remaining 7120 women, the timing of the menopause

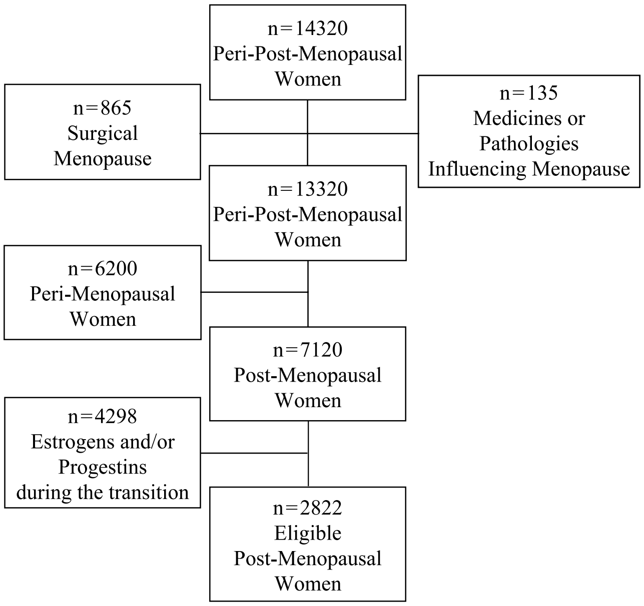

Figure 1. Flow chart of the selection process.

was not clearly identifiable since they had received oral contraceptives or estrogen and/or progestin therapies during the menopausal transition. Accordingly, the analysis was performed in the remaining 2822 women in which physiological menopause, i.e. amenorrhoea for >12 months, was identifiable during the medical interview. The excluded and included women did not differ by season of birth, as evaluated by the χ^2 goodness of fit application. Of the women included in the final analysis, 1142 were from the database of Ferrara, 963 from the database of Modena and 717 from the database of Parma.

Statistical analysis was performed by the StatView 5.0.1 (1998; SAS Institute, NC) statistical package. Multiple regression analysis was performed to evaluate factors capable of independently determining the timing of menopause. Linear regression models were constructed with age at menopause as dependent variable and age at menarche, number of pregnancies, BMI, smoking habit, education, present/past type of job and season of birth as predictor variables. Seasons (e.g. spring from March 21 to June 21) were entered into the analysis as three dummy variables, present/past type of job was entered into the analysis as two dummy variables, and ever/never smokers or high/low education were entered as single dummy variable. Contingency tables were used to compare proportions of early (≤40 years) and late (≥55 years) menopause among women born in the different seasons (Jongbloet *et al.*, 1994). For all analyses, P-values <0.05 were used to reject the null hypothesis. All results are reported as the mean and SEM.

Results

No difference was observed among women from the different centres. Women had a mean age of 53.0 (±0.1) years, and BMI of 25.2 kg/m^2 (±0.1). Women experienced menopause at 49.42 (±0.78 years) and had been in menopause for 3.0 (±0.02 years).

Multiple regression analysis showed that age at menopause was not related to number of pregnancies. Accordingly, this estimate was removed from the multiple regression model. Age at menopause was determined positively by age at menarche, BMI and high education, and negatively by ever smoking, and workers/employers versus housewives (Table I). Independently of these determinants, age at menopause was conditioned by season of birth (Table I).

Table I. Linear regression model: dependent variable age at menopause

Variable	Regression coefficient (SEM)	95% CI	P-value
Age at menarche (years)	0.224 (0.113)	0.001 to 0.446	0.049
BMI (kg/m^2)	0.084 (0.019)	0.046 to 0.122	0.0001
Ever smokers[a]	−0.516 (0.222)	−0.945 to −0.081	0.02
High education[b]	0.889 (0.407)	0.088 to 1.689	0.029
Workers[c]	−1.088 (0.469)	−2.010 to −0.167	0.021
Employees[c]	−1.286 (0.425)	−2.120 to −0.452	0.003
Winter[d]	−0.493 (0.224)	−0.933 to −0.053	0.028
Spring[d]	−0.850 (0.228)	−1.297 to −0.403	0.0002
Summer[d]	−0.776 (0.225)	−1.218 to −0.334	0.0006

[a]Reference category: never smokers.
[b]Reference category: low education.
[c]Reference category: housewives.
[d]Reference category: autumn.

When stratified by month of birth, age at menopause, but not age at menarche, showed a sinusoidal variation, with peak value in October (50.3 ± 0.25 years) and a nadir in March (48.9 ± 0.25 years) (Figure 2). Stratification by season of birth showed the earliest menopause for women born in the spring (49.04 ± 0.15 years) and the latest menopause for women born in the autumn (49.97 ± 0.14 years). Intermediate values were observed in women born in the winter and in summer (Figure 2).

By stratifying women with earlier (≤40 years) and later (≥55 years) menopause by seasons, we observed that the proportion of women with earlier menopause was similar in winter (3.6%), spring (3.2%), summer (4.4%) and autumn (2.6%). In contrast, the proportion of women with later menopause was higher in autumn (8.1%) than in spring (3.7%; $P = 0.013$) or in the other three seasons combined (4.9%; $P = 0.008$).

Discussion

Fetal development is becoming increasingly recognized as a key determinant of future life events. For example, several

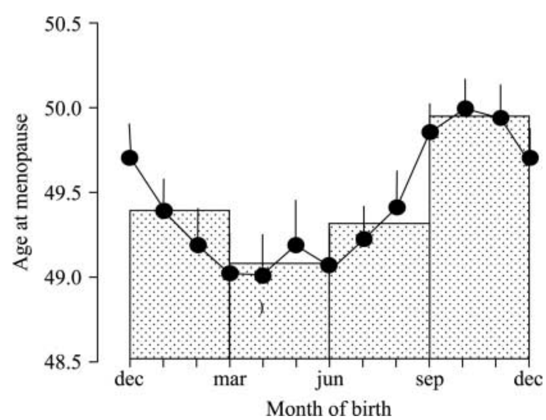

Figure 2. Mean (±SEM) age at menopause of 2822 women, stratified by month (filled circles) or season (grey bars) of birth.

studies have shown that reduced fetal growth is associated with a higher risk of non-insulin-dependent diabetes (Lithell *et al.*, 1996), metabolic syndrome (Valdez *et al.*, 1994; Fall *et al.*, 1995; Yarbrough *et al.*, 1998), neonatal morbidity, neonatal mortality (McIntire *et al.*, 1999) and death from cardiovascular diseases (Barker *et al.*, 1989, 1993). Probably, a reduced prenatal growth is capable of conditioning future fertility in both men and women. In men, it is associated with a less likely possibility of marrying (Phillips *et al.*, 2001) and a reduced fertility (Francois *et al.*, 1997). The latter is probably consequent to a reduced number of Sertoli cells, which are necessary for future spermatogenesis (Orth *et al.*, 1988). In women, a reduced prenatal growth is associated with reduced ovarian fraction of primordial follicles (de Bruin *et al.*, 1998), reduced ovarian and uterine volume at adolescence (Ibanez *et al.*, 2000), ovarian hyperandrogenism and anovulation in late adolescence (Ibanez *et al.*, 1999). Environmental factors linked to seasons, by an action exerted in prenatal life, influence fetal growth (Rantakallio, 1971; Selvin and Janerich, 1971; Bantje, 1987; Matsuda *et al.*, 1993, 1995; Weber *et al.* 1998; Murray *et al.*, 2000), human lifespan (Gavrilov and Gavrilova, 1999; Doblhammer and Vaupel, 2001) and fertility of both men (Francois *et al.*, 1997; Huber *et al.*, 2004a) and women (Smits *et al.*, 1997; Lummaa and Tremblay, 2003; Huber *et al.*, 2004b), including the timing of menarche (Albright *et al.*, 1990; Jongbloet *et al.*, 1994; Tavares *et al.*, 2004). Our data show that the timing of ovarian exhaustion can also be influenced by prenatal factors linked to seasons, as previously suggested (Jongbloet *et al.*, 1994). Women born between September and December experience the latest menopause, and those born between March and June the earliest. Interestingly, this is similar to the reported seasonal variation of birth weight observed in Northern Ireland (Murray *et al.*, 2000) and to the effect of season of birth on human lifespan observed in Denmark and Austria (Northern hemisphere) which is exactly mirrored by the pattern observed in Australia (Southern hemisphere) (Doblhammer and Vaupel, 2001). Depending on the geographic area, the effect of seasons may differ. Accordingly, our present data cannot be generalized. For example, reproductive performance was reported at its minimum in women born in June and July in Austria (Huber *et al.*, 2004b) and in women born between July and September in The Netherlands (Smits *et al.*, 1997).

In our analysis, timing of menarche was not dependent on the month/season of birth, but, in contrast to a previous study (van Noord *et al.*, 1997), it was positively related to the timing of menopause. Perimenopausal and ageing women may have difficulties in precisely recalling the date of their menarche. In addition, we collected only the referred chronological age at menarche, and not the date of menarche. This may have generated random errors and impaired the capability to detect an effect of season of birth on the timing of menarche. The same bias has probably influenced other studies incapable of showing a relationship between menarche and menopause (van Noord *et al.*, 1997).

It is not known which one of the seasonal environmental factors is capable of influencing the future timing of the menopause by an action exerted during prenatal life. Modifications of environmental temperature and photoperiod may influence fetal growth (Weber *et al.*, 1998; Murray *et al.*, 2000), and therefore also future reproductive capabilities. Seasonally linked diet modifications (Godfrey *et al.*, 1996; Mathews *et al.*, 1999) or exposure to infections (Finch and Crimmins, 2004) may also be involved. Seasonal environmental factors may be operative even before conception when, by influencing oocyte maturation, they may contribute to the development of defective embryos and weak adult individuals (Jongbloet *et al.*, 1994). It has been suggested that such a mechanism can explain the influence of season of birth on the timing of menarche, on the occurrence of menstrual irregularities and on the incidence of earlier and later menopause (Jongbloet *et al.*, 1994). Beside the effect of season of birth on mean age at menopause, we also confirmed an influence of season of birth on the occurrence of later menopause. We were not able to document a similar effect on the occurrence of earlier menopause, which was instead previously reported in more numerous data sets (Jongbloet *et al.*, 1994).

Our present data seem to indicate that women born in autumn develop better during their prenatal life and are born with a higher number of oocytes than women born in spring. An alternative explanation might be that early mortality is highest among children born in autumn, thus selecting the fittest for survival. However, the findings of Doblhammer and Vaupel (2001) do not support this explanation. The present study has limitations. The study is retrospective, and mainly based on data collected during a medical interview. Accordingly, a recall bias is possible. Furthermore, the study was not performed in the general population but in women referred to menopause centres of one Italian region. Accordingly, generalization of the present results may be incorrect. Many events may play a role in timing of menopause. We controlled for several of them but we cannot exclude that our analysis was partial and/or insufficient. Several items were categorized in a way which may have led to inaccurate considerations. However, taking into consideration these limitations, the data seem to suggest notable effects of the month/season of birth on the length of a woman's fertile life, further supporting a role for environmental factors in regulating adult reproductive life and the timing of its termination.

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