Premature ovarian failure: frequency and risk factors among women attending a network of menopause clinics in Italy

Progetto Menopausa Italia Study Group *

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Objective: To determine the frequency and causes of preterm ovarian failure (menopause before 40 years of age) and early menopause (menopause between 40 and 45 years).

Design: Cross sectional study.

Setting: Menopause clinics in Italy.

Population: Women attending menopause clinics in Italy.

Methods: Between 1997 and 1999 we conducted a large cross sectional study on the characteristics of women around menopause attending a network of first-level outpatient menopause clinics in Italy for general counselling about menopause or treatment of menopausal symptoms. Eligible for the study were all women aged 45–75 years consecutively observed for the first time at the participating centres on randomly selected days during the study period.

Main outcome measure: Factors associated with preterm ovarian failure.

Results: Out of 15,253 women aged 55 years or more with spontaneous menopause who entered the study, 269 (1.8%) reported preterm ovarian failure, and 1085 (7.1%) reported spontaneous menopause at age 40–45 years. The risk of preterm ovarian failure and of early menopause was higher in women reporting lifelong irregular menstrual cycles: in comparison with women reporting menopause at age z45 years, the OR (irregular vs regular mestrual cycles) of preterm ovarian failure was 1.3 (95% CI 1.0–1.7) and of early menopause of 1.2 (95% CI 1.0–1.5). Parous women reported less frequently preterm ovarian failure (m2 trend P < 0.05) and early menopause (OR 0.8, 95% CI 0.7–1.0). No significant association emerged between risk of preterm ovarian failure or menopause at age 40 to <45 and education, age at menarche, oral contraceptive use and smoking habits.

Conclusion: Nulliparity and lifelong irregular menstrual cycles are associated with an increased risk of preterm ovarian failure.

INTRODUCTION

Little is known about the frequency and causes of preterm ovarian failure (spontaneous menopause at age <40 years) [1–4]. A family history increases the risk of early menopause (menopause at age 40-45) [3]. Several chromosomal abnormalities have been linked with preterm ovarian failure [2,5– 7], indicating genetic factors in preterm ovarian failure. It is also of interest to understand the role of environmental factors and their interactionwith genetic ones [4].
Early age at menarche, never oral contraceptive use, nulliparity and smoking are all factors associated with age at spontaneous menopause [8,9]. However, how these factors affect the risk of preterm ovarian failure or early menopause is not known.

Risk factors for preterm ovarian failure and spontaneous menopause at age 40-45 years using data from a large epidemiologic study on menopause conducted in Italy were analysed. This study confirmed the role of smoking, parity, oral contraceptive use and lifelong regular cycles as determinants of age at menopause among Italian women [10].

METHODS

Between 1997 and 1999, we conducted a large cross sectional study on the characteristics of women around menopause attending a network of first-level outpatientmenopause clinics in Italy for general counselling about menopause or treatment of menopausal symptoms [10–12]. Eligible for the study were all women aged 45-75 years consecutively observed for the first time at the participating centres on randomly selected days during the study period. The study protocol did not set any exclusion criteria.
All women who agreed to participate underwent a gynaecologic examination. They were also interviewed, all using the same questionnaire, about their general characteristics and habits (age, education, occupation, height, weight), reproductive and menstrual history and selected medical history (cardiovascular, neoplastic, metabolic diseases and osteopoenia). Data were collected on lifetime history of the use of oral contraceptive hormones and non-contraceptive oestrogens for replacement therapy. This interview was done during the visit to the centre.
The women were asked to participate in an epidemiologic study on menopause. Specifically, the project was presented as an epidemiologic study with the objective of collecting data on a sample of women attending Menopause Centers in order to obtain information on menopause and related conditions. The women were told that participation in the study did not involve any instrumental examination or laboratory tests.
We did not collect information centrally on the participation rate. However, a questionnaire was sent to the centres to estimate the proportion of non-responders among eligible women: the mean proportion reported was 3%.
The study started in 1997 in 25 centres: the number had increased to 268 by March 1999. Of these, 63 were in the north, 81 in the center and 124 in the south of Italy. As of March 1999, a total of 42,464 women (mean age 54 years) had entered the study. The mean number per centre was 158.
For the purpose of this analysis, we considered only women aged 55 years or more, in spontaneous menopause (i.e. natural cessation of menses for 12 or more months). A total of 15,253 women (median age 57, range 55-71) were included.
We defined three groups of women: the first included women with preterm ovarian failure (i.e. spontaneous menopause at <40 years); the second women with early spontaneous menopause (i.e. between 40 and 45 years); and the third, women with spontaneous menopause at age over 45 years.
The characteristics of women with pretermovarian failure and early menopause were compared with those with spontaneous menopause at age over 45 years. Odds ratios (OR) of preterm ovarian failure and early menopause, and the corresponding 95% confidence intervals (CI), were derived using unconditional multiple logistic regression (MLR), fitted by the method of maximum likelihood [13].
Two models were considered: the first included only terms for age; the second all the variables considered as presented in the Table 1. Because the estimates from the two models were largely consistent, only the latter are reported. Variables included in the models are indicated in a footnote to the table.

RESULTS

Of the 15,253 women with spontaneous menopause who entered the study, 269 (1.8%) reported preterm ovarian failure, and 1085 (7.1%) spontaneous menopause at age 40-45 years. Table 1 shows their distribution and those with menopause at age >45 years according to selected factors.
The risk of preterm ovarian failure and of menopause at age 40-45 was higher in women reporting lifelong irregular menstrual cycles compared with women reporting menopause at age >45 years, the OR (irregular vs regular menstrual cycles) of preterm ovarian failure was 1.3 (95% CI 1.0–1.7) and of menopause at age 40-45, 1.2 (95% CI 1.0–1.5). Parous women less frequently reported preterm ovarian failure and spontaneous menopause at age 40-45, and the OR estimates of preterm ovarian failure and early menopause tended to decrease with number of births and the X^2_1 for trend was statistically significant (Table 1).

No significant association emerged between risk of preterm ovarian failure or menopause at age 40 to <45 and education, age at menarche, oral contraceptive use or smoking habits.

DISCUSSION

This study found that nulliparity and lifelong irregular menstrual cycles were associated with an increased risk of preterm ovarian failure. No relation emerged with age at menarche, oral contraceptive use, smoking and risk of preterm ovarian failure. Similar findings emerged when we compared women with menopause at age 40 to <45 and women with menopause at ≥45 years.

Before discussing the results of the study, potential limitations must be considered. The women analysed were part of a large study whose main goal was to describe the characteristics of women attending first-level outpatient menopause clinics in Italy. Thus, they cannot be considered formally representative of the Italian population, and are presumably particularly interested in health problems and, particularly, menopause-related health issues. Thus, the main problem of this study is the selection of the sample. In fact, there is a high chance of selection bias, which may lead to some risk factors for early menopause not being significant. For example, women who smoke are more likely to have severe menopausal symptoms than women who do not. Such women may be more likely to go to a menopause clinic than non-smokers. This selection bias may reduce the apparent effect of smoking on menopausal status. However, the general characteristics of this population are not markedly different from those of Italian women aged 45-65 years [14].

The objective of this analysis was to evaluate the determinants of preterm ovarian failure and early menopause so any inference has been drawn in strictly comparative terms from women with preterm ovarian failure and these with menopause at age ≥45 years. However, these results are applicable only to the population studied. Data collection should not be affected by recall bias. In fact, we only considered information that was easy to collect, and a great effort was made to train the physicians to pay similar attention to data collection for all study subjects. In particular, age at spontaneous menopause was selfreported. However, mean age of women included in the analysis was 57 years, thus important recall bias should not be likely. Finally, inclusion of terms for participating centres in the multivariate analysis did not change the estimates (data not shown).

In this analysis, nulliparous women were at greater risk of preterm ovarian failure. A recent case–control study of 100 women with preterm ovarian failure found that women with preterm ovarian failure had fewer pregnancies than the control group [4]. However, the association between parity and preterm ovarian failure was limited to sporadic cases of preterm ovarian failure (i.e. women without a family history of preterm ovarian failure), and disappeared when patients with familial preterm ovarian failure were considered separately, these women having a similar number of pregnancies to controls. A possible explanation is that patients with a history of familial preterm ovarian failure may pay more attention to their reproductive patterns: they are aware of the earlier age of their relatives at menopause and, as a consequence, tend to conceive earlier. Unfortunately, the present study did not collect information on maternal age at menopause. Lower parity can also be explained as an effect rather than a cause of early menopause.

Another interesting finding is the association between lifelong history of irregular menstrual pattern and preterm ovarian failure. This confirms previous suggestions[4], although an irregular menstrual pattern may be associated with late menopause, too[9]. To explain these conflicting findings, it can be suggested that irregular menstrual cycles are an effect of impaired ovarian function, present in women who subsequently develop preterm ovarian failure.

Finally, smoking, never oral contraceptive use and late age at menarche were associated with later age at menopause [10]. These factors did not affect the risk of preterm ovarian failure in this study, or in the few other reports on the issue [4].

REFERENCES

1. Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. Obstet Gynecol 1986; 67: 604-606.

2. Vegetti W, Marozzi A, Manfredini E, et al. Premature ovarian failure. Mol Cell Endocrinol 2000; 161: 53-57.

3. Torgerson DJ, Thomas RE, Reid DM. Mothers and daughters menopausal ages: is there a link? Eur J Obstet Gynecol Reprod Biol 1997; 74: 63-66.

4. Testa G, Chiaffarino F, Vegetti W, et al. Case–control study on risk factors for premature ovarian failure.Gynecol Obstet Invest 2001; 51: 40-43.

5. Vegetti W, Tibiletti MG, Testa G, et al. Inheritance in idiopathic premature ovarian failure: analysis of 71 cases. Hum Reprod 1998; 13: 1796-1800.

6. Marozzi A, Manfredini E, Tibiletti MG, et al. Molecular definition of Xq common-deleted region in patients affected by premature ovarian failure. Hum Genet 2000; 107: 304-311.

7. Marozzi A, Vegetti W, Manfredini E, et al. Association between indiopathic premature ovarian failure and fragile X premutation. Hum Reprod 2000; 15: 197-202.

8. Bromberger JT, Matthews KA, Kuller LH, et al. Prospective study of the determinants of age at menopause. Am J Epidemiol 1997; 145: 124-133.

9. Parazzini F, Negri E, La Vecchia C. Reproductive and general lifestyle determinants of age at menopause. Maturitas 1992; 15: 1 41-149.

10. Progetto Menopausa Italia Study Group. Factors associated with age at menopause in women attending menopause clinics in Italy. Takeshi A, et al, editor. Atti The 9th International Menopause Society World Congress on the Menopause. Bologna: Monduzzi Editore, 1999: 47-50.

11. Progetto Menopausa Italia Study Group. Determinants of hysterectomy and oophorectomy in women attending menopause clinics in Italy. Maturitas 2000; 36: 19-25.

12. Progetto Menopausa Italia Study Group. Risk factors for genital prolapse in women around menopause: results from a large cross sectional study in menopasual clinics in Italy. Eur J Obstet Gynecol Reprod Biol 2000; 93: 135-140.

13. Breslow NE, Day NE. The analysis of case control studies. Statistical Methods in Cancer Research, 1. Lyon, France: IARC (IARC sc. Publ.), 1980: 32.

14. Urbano A, Vivio R. Indagine multiscopo sulle famiglie. Condizioni di salute e ricorso ai servizi sanitari (Anno 1994). Indagine multiscopo sulle famiglie (ISTAT), Informazioni, Istat, Rome, 1997: 54.

Table 1.
Distribution* of cases with spontaneous menopause at age <40 and 40-45 years, and controls with age at menopause >45 years according to selected factors (Italy 1997-1999).

	No. of cases		Controls	OR (95% CI)**	
	Age at menopause <40 years	Age at menopause 40-45 years	Age at menopause >45 years	Age at menopause <40 years	Age at menopause 40-45 years
Education (years)					
<7	137 (57.3)	552 (57.5)	6205 (50.5)	1+	1+
7-11	55 (23.0)	250 (26.0)	3239 (26.3)	0.8 (0.6-1.1)	0.9 (0.8-1.1)
≥12	47 (19.7)	158 (16.5)	2849 (23.2)	0.8 (0.6-1.1)	0.8 (0.6-1.0)
Age at menarche (years)					
≤11	89 (33.1)	330 (30.4)	3692 (26.6)	1+	1+
12	75 (27.9)	257 (23.7)	3442 (24.7)	0.9 (0.7-1.0)	0.8 (0.7-1.0)
13	45 (16.7)	222 (20.5)	2832 (20.4)	0.7 (0.5-0.9)	0.9 (0.7-1.0)
≥14	60 (22.3)	276 (25.4)	3933 (28.3)	0.6 (0.4-1.0)	0.8 (0.6-1.0)
Cycle length (days)					
Regular	205 (87.2)	842 (89.8)	11.146 (90.7)	1+	1+
Irregular	30 (12.8)	96 (10.2)	1141 (9.3)	1.3 (1.0-1.7)	1.2 (1.0-1.5)
Parity					
0	35 (13.1)	169 (15.6)	1728 (12.5)	1+	1+
1	39 (14.6)	175 (16.2)	2048 (14.8)	1.0 (0.6-1.5)	0.9 (0.8-1.2)
2	102 (38.2)	377 (34.8)	5422 (39.1)	0.9 (0.7-1.4)	0.8 (0.7-1.0)
≥3	91 (34.1)	361 (33.4)	4679 (33.7)	0.8 (0.6-1.4)	0.8 (0.6-0.9)
X^2_1 trend				P < 0.05	P < 0.05
Oral contraceptive use					
Never	53 (22.8)	750 (84.4)	9362 (81.1)	1+	1+
Ever	179 (77.2)	139 (15.6)	2177 (18.9)	1.0 (0.7-1.4)	0.9 (0.8-1.1)
Smoking habits					
Never	213 (91.0)	845 (90.2)	10315 (88.4)	1+	1+
Ever	21 (9.0)	92 (9.8)	1348 (11.6)	0.9 (0.5-1.2)	0.9 (0.7-1.1)

* In some cases, the sum does not add up to the total because of missing values.
** Multivariate estimates including terms for age and all the variables listed.