

## Short communication

# Cigarette smoking damages women's reproductive life

Filiberto Di Prospero<sup>1</sup>, Stefania Luzi, Zeno Iacopini

Maternal and Child Department, Gynaecology Endocrinology Unit, Civitanova Marche General Hospital, 62012 Italy.

<sup>1</sup>Correspondence: Tel: +39 328 9768252; e-mail: f.diprospero@inwind.it

### Abstract

Female smokers experienced menopause significantly ( $P \leq 0.000001$ ) earlier than non-smokers ( $47.1 \pm 3.3$  versus  $49.4 \pm 3.6$  years, mean age at menopause  $\pm$  SD) and the prevalence of cigarette smoking is more frequent in females with ovarian failure before 46 years of age. These data are consistent with a possible detrimental effect of cigarette smoking on ovarian function and suggest new investigations are needed in this field. Detailed information about this important negative effect is strongly recommended, particularly for female smokers of reproductive age.

**Keywords:** cigarette smoking, menopause, ovarian failure, ovary, reproduction, smoking

### Introduction

Premature and early menopause are important medical and social problems. Iatrogenic, genetic, immunological and some endocrinological diseases may also influence the onset of menopause. Environmental factors and lifestyle may have a significant role too (Kato *et al.*, 1998; Keck and Breckwoldt, 2002). In recent years, a possible role of cigarette smoking has been highlighted as one of the factors that can damage reproductive life (Bromberger *et al.*, 1997; Windham *et al.*, 1999; Hardy *et al.*, 2000). However, little effort has been made to confirm such a hypothesis and to assess the real impact of smoking on ovarian function. The aim of this study was to evaluate whether the age of menopause in smoking women is significantly different from that of non-smokers.

### Materials and methods

Seven hundred healthy Caucasian women that attended the Menopause Centre in the Reproductive Endocrinology Unit, from 1997 to 2001, with menopausal symptoms were examined. All consecutively observed women with secondary amenorrhoea that had lasted more than 6 months, and menopausal status confirmed by FSH and 17- $\beta$ -oestradiol radioimmunoassay evaluation were included in the study. Patients with a previous hysterectomy, surgical menopause or endocrinological diseases and patients with secondary amenorrhoea of less than 6 months' duration were excluded from the study. Smoking status was assessed by a specific written interview, according to the NCHS definition (1996). None of the patients included in the study took a hormonal replacement therapy (HRT). A total of 350 women were enrolled. All patients gave their informed consensus to use data for scientific research. Student's t-test and the chi-squared test were used for the statistical analysis.

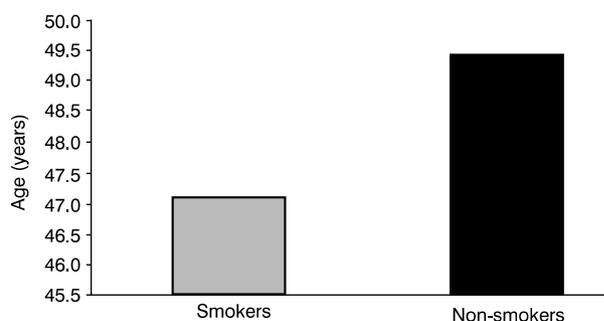
### Results

Eighty-seven women were assessed as smokers, while 263 were non-smokers. The age of menopause was significantly different in the two groups:  $47.1 \pm 3.3$  years in smokers versus  $49.4 \pm 3.6$  years in non-smokers ( $P < 0.000001$ ) (**Figure 1**). No differences were found between the two groups regarding body mass index (BMI) ( $26.9 \pm 4.6$  in smoking women versus  $26.1 \pm 4.6$  in non-smokers,  $P > 0.05$ ). Furthermore, all women were placed into one of three groups according to the age at which their menopause occurred: (i) between 40 and 45 years; (ii) between 46 and 50 years; and (iii) over 50 years. The highest percentage of smoking women was found in the first group (46.3%), significantly greater than that in the second and in the third groups (31.6% and 13.3% respectively,  $P < 0.0001$  in both groups) (**Figure 2**).

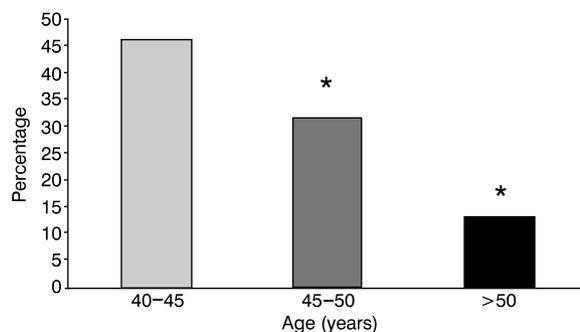
### Discussion

It is well known that smoking damages human health, as its carcinogenic effect has been widely demonstrated; however its action on reproductive function has not been as well studied. In recent years some authors have hypothesized smoke-related damage to menstrual function and during pregnancy (Bromberger *et al.*, 1997; Spangler, 1999; Windham *et al.*, 1999; Jauniaux and Gulbis, 2001).

The data presented here show that in smoking women, the age of menopause is significantly lower than in non-smoking patients. These results partially confirm other published data (Kato *et al.* 1998; Harlow and Signorello, 2000): indeed there was a difference of two years in the menopausal onset between the two groups, with a strong statistical significance. This suggests a detrimental effect of cigarette smoking on ovarian function with consequently biological reproductive damage. It is not clear yet how cigarette smoking can influence the onset of the menopause (Spangler, 1999); however a recent molecular study (Matikainen *et al.*, 2001) suggests that smoke



**Figure 1.** Age at menopause in smokers ( $n = 87$ ) and non-smokers ( $n = 263$ ). The two groups were significantly different ( $P < 0.000001$ ).



**Figure 2.** Smokers (%) in different age groups at menopause. \* indicates significantly different from youngest age group ( $P < 0.0001$ ).

exposes humans to polycyclic aromatic hydrocarbons (PAHs), that induce expression of the *Bax* gene in oocytes, followed by apoptosis. Cotinine plasma levels (Jauniaux and Gulbis, 2001) could represent a useful method of evaluating a possible smoking dose-response effect in further studies.

These data can be used to strongly recommend distribution of detailed information about this important negative effect, particularly to female smokers of reproductive age.

## References

- Bromberger JT, Matthews KA, Kuller LH *et al.* 1997 Prospective study of the determinants of age at menopause. *American Journal of Epidemiology* **155**, 124–133.
- Hardy R, Kuh D, Wadsworth M 2000 Smoking, body mass index, socioeconomic status and the menopausal transition in a British national cohort. *International Journal of Epidemiology* **29**, 845–851.
- Harlow BL, Signorello LB 2000 Factors associated with early menopause. *Maturitas* **35**, 3–9.
- Jauniaux E, Gulbis B 2001 Placental transfer of cotinine at 12–17 weeks of gestation and at term in heavy smokers. *Reproductive BioMedicine Online* **3**, 30–33.
- Kato I, Toniolo P, Akhmedkhanov A *et al.* 1998 Prospective study of factors influencing the onset of natural menopause. *Journal of Clinical Epidemiology* **51**, 1271–1276.
- Keck C, Breckwoldt M 2002 Predictive factors for determination of menopausal age. *Therapeutische Umschau* **59**, 189–192.
- Matikainen T, Tilly JL, Perez GI *et al.* 2001 Aromatic hydrocarbon receptor driver *Bax* gene expression is required for premature ovarian failure caused by biohazardous environmental chemicals. *Nature Genetics* **28**, 355–360.
- Spangler JG 1999 Smoking and hormone related disorders. *Primary Care* **26**, 499–511.
- Windham GC, Elkin EP, Swan SH *et al.* 1999 Cigarette smoking and effects on menstrual function. *Obstetrics and Gynecology* **93**, 59–65.

Received 7 October 2003; refereed 20 October 2003; accepted 29 October 2003.