

Predictive **Factors** to **Determine** Age of Onset of **Menopause**

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Menopause is defined as the last ovarially regulated uterine bleeding in a woman's life. It marks the transition from the fertile phase of life with regular ovulatory cycles to the phase of perimenopause with increasing climacteric symptoms through to postmenopause with amenorrhea and often the sign of hypoestrogenism. It can be assumed on the basis of population development, in industrialized as well as developing nations, that the number of postmenopausal women will rise from 467 million women in 1990 to over 1.2 billion women by 2030 (Hill, 1996). Forty seven million women reach menopausal age worldwide each year. On the basis of increased life expectancy, it can be assumed that a woman will experience on average 30 postmenopausal years of life (Khaw, 1992).



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The ability of predicting the probable time point of menopause would have enormous consequences for individual life planning:

- ◆ It would influence family planning and the decision, for example, to undergo active sterilization therapy.
- ◆ The ideal time point for beginning hormone replacement therapy could be determined to prevent the secondary effects of hypoestrogenism.

It has been demonstrated, that menopause is associated with a dramatically increased risk of cardiovascular disease, osteoporosis, urogenital disease, Alzheimer's disease, and depression (Sowers *et al.*, 1995). The early – and therefore unexpected – onset of menopause poses additional risk, in that the symptoms associated with the aforementioned diseases are often not promptly considered in light of an existing estrogen deficit. The following chapter discusses epidemiolog-

ical, endocrinological, and anatomical factors which can be used as parameters for predicting the probable time point of menopause.

The response to hormonal ovarian stimulation therapy decreases with increasing age (Roest *et al.*, 1996) and the number of egg cells obtained during in vitro fertilization (IVF) therapy (Piette *et al.*, 1990) or fertilization and pregnancy rates (DIR, 1998) fall dramatically. These effects can also be observed in women reporting regular menstruation at the time point of IVF therapy. For this reason, serum FSH concentration on the third day of the cycle has been increasingly used as a predictive factor for evaluating ovarian reserve rather than just the patient's age alone (Scott *et al.*, 1995). What remains unclear, however, is how to imagine the transition from the phase of impaired ovarian reserve to the actual onset of menopause.

These considerations, taken strictly, apply only to natural menopause, and not for "surgical menopause," which is defined by the WHO as the absence of uterine bleeding because of removal of the ovaries with or without the removal of the uterus (WHO, 1981), or for medically induced menopause (e.g., through GnRH analog administration or GnRH antagonists), since the time point of menopause remains undetermined in these cases.

Epidemiological Factors

Epidemiological studies have shown many associations between socioeconomic factors and age at menopause. Among these are:

- ◆ Smoking
- ◆ Reproductive Behavior
- ◆ Genetic Disposition
- ◆ Nutrition Habits
- ◆ Exposure to Exogenous Noxious Agents
- ◆ General Socioeconomic Factors

The predictive value of epidemiological studies is limited by their often retrospective nature. Beyond that, most of these studies are subject to selection bias. Despite these limitations, valuable conclusions can be drawn from the results of these studies, which are summarized below:

Smoking

The relationship between cigarette smoking and early onset of menopause can be considered firmly established (Parazzini *et al.*, 1992; Torgerson *et al.*, 1994; Bromberger *et al.*, 1997; van Noord *et al.*, 1997). It can be assumed that smokers will experience menopause one to two years earlier than nonsmokers. Beyond that, it has been shown that smokers are more likely to be infertile than nonsmokers independently from age and socioeconomic status (Hughes *et al.*, 1996). This can possibly be explained in that smokers show a distinctly reduced ovarian reserve compared to nonsmokers of the same age. This was confirmed by assaying serum FSH concentration on the third day of

the cycle, as well as through the results of the clomifen tests (Cramer *et al.*, 1994; Sharara *et al.*, 1994).

It remains largely unclear which factors lead to this dramatic reduction of ovarian reserve. The generally reduced serum estradiol level in female smokers could play a role in this phenomenon, as could the reduced effect of estrogen at its receptor (Longcope *et al.*, 1988; Van Voorhis *et al.*, 1992; Sterzik *et al.*, 1996). Beside the already discussed endocrine effects, several substances in cigarette smoke also exert directly toxic effects on the egg cell, so that the early onset of menopause in smokers can best be explained by a combination of factors.

Irradiation

The prevalence of premature ovarian failure (POF) as a consequence of irradiation therapy is correlated to the radiation dose received. An average radiation dose of 4500 rad is used in the treatment of Hodgkin's lymphoma of the pelvis. It is known that premature ovarian failure must be expected in 66% of cases exposed to a radiation dose of 250-500 rad, and nearly all patients are subject to premature ovarian failure at a dose of 800 rad (Cohen & Speroff, 1991). These numbers show how important proper shielding of the ovaries is during pelvic irradiation for the maintenance of the patient's ovarian function. Beside external shielding, the ovaries can also be fixated "behind" the uterus, thereby minimizing the radiation dose reaching this organ. Such a procedure is generally done laparoscopically today (Williams & Mendenhall, 1992).

Through combination of external shielding with laparoscopic oophoropexy, the radiation dose reaching the ovaries can be significantly reduced and therefore also the rate of premature ovarian failure. It can be hoped that further reduction of the radiation dose can be achieved, especially through further development of modern concepts of therapy, above all by combination of chemotherapy and radiation therapy.

Generative Factors

In contrast to the studies showing associations between smoking and early termination of ovarian function, the indications in the literature of an association between generative factors and menopausal age are less definitive. Nonetheless, several factors are considered firmly established:

Most studies indicate an earlier onset of menopause in childless women than those with multiple births. There even appears to be a correlation between the number of children born and a later onset of menopause (Parazzini *et al.*, 1992; Torgerson *et al.*, 1994; van Noord *et al.*, 1997). The reason for the increased age of onset of menopause with the number of children born is unclear.

While earlier studies were able to establish an association between early age of menarche and later menopause (Frisch 1978; 1987), more modern studies have not been able to confirm this effect (Whelan *et al.*, 1990; van Noord *et al.*, 1997).

An effect of genetic disposition on the onset of menopause can also be considered firmly established. Women whose mothers experienced early menopause have a five to six fold elevated risk of also experiencing early menopause. Beyond that, twin studies show evidence of a genetic basis of early menopause. Characteristic deletions on the long arm of the X chromosome have been discovered in families with increased incidence of early menopause (Veneman *et al.*, 1991; Cramer *et al.*, 1995). Further details on this topic are discussed elsewhere in the book.

It has been attempted to establish an association between menstrual cycle pattern and onset of menopause. Associations have been found between a shortened cycle between the ages of 20 and 35, as well as cycle irregularities before the 25th year of age and the age of menopause. (Whelan *et al.*, 1990). On the other hand, factors such as smoking, nutritional habits, and parity were ignored in these studies. In newer studies on this topic, no association could be established between

cycle pattern and age of menopause (Parazzini *et al.*, 1992). It is well known that the pattern of the menstrual cycle changes immediately before menopause, resulting from an increase in anovulatory cycles and cycles with luteal phase deficit.

The question of whether consumption of oral contraceptives affects the age of menopause is controversially debated today. There are studies showing that oral contraceptives lead to a later onset of menopause (van Noord *et al.*, 1997), while other studies fail to show this association (Stanford *et al.*, 1987). Recent prospective studies on this topic have shown that the consumption of oral contraceptives has no effect on the onset of menopause (Bromberger *et al.*, 1997).

Nutrition

It is well known that female reproductive factors are closely dependent on the

woman's nutritional status. Women with anorexia nervosa often show anovulatory cycles, amenorrhea, and — in the event that the disorder arises during puberty — pubertas tarda. Relative obesity is associated by some authors with an earlier onset of menopause (Beser *et al.*, 1994), while others associate it with a later onset of menopause (Sherman *et al.*, 1981). Elevated alcohol and meat consumption appears to be associated with a relatively late onset of menopause (Torgerson *et al.*, 1994) whereas women who follow a regular dietary weight reduction plan experience menopause on average one year earlier than a control cohort (Bromberger *et al.*, 1997).

The partially contradictory results regarding the relationship between nutrition and age of menopause can be traced back to many studies that ignored important confounding factors such as smoking.

Socioeconomic Factors

Numerous socioeconomic factors have been studied for associations with the age of menopause. It has been postulated that married women of high social class experience menopause later than others (Torgerson *et al.*, 1994; van Noord *et al.*, 1997). It is highly probable that this is an epiphenomenon resulting from the effects of diverse other factors (Bromberger *et al.*, 1997; Parazzini *et al.*, 1992). Epidemiological studies of menopausal age are mostly performed on Caucasian women. Studies of the African-American population are most substantially impaired by the fact that the proportion of this population that undergoes premenopausal hysterectomy is disproportionately high. The age of menopause in African-American women appears to be earlier on average than in Caucasian women.

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