Menopause, A Stage in the Life of Women

1

Gita D. Mishra

Natural menopause is defined as the permanent cessation of menstruation due to the natural loss of ovarian follicular function [1]. It marks the end of the reproductive life span. It is accompanied by changes in the neuroendocrine and immunology systems [2, 3]. Natural menopause is distinct from cessation of the menstruation due to medical treatments or surgical interventions, such as radiation and bilateral oophorectomy.

Humans, gorillas, killer whales, and short-finned pilot whales are the only species known to experience menopause [4, 5]. While discussion on the reasons for the existence of menopause is still under debate, from an evolutionary perspective there are three main explanatory hypotheses. The *grandmother hypothesis*, which speculates that older (nonreproductive) mothers help their child-bearing daughters and thus increase her reproductive fitness. The *mother hypothesis* assumes that older women stop reproducing because it is too risky for them to give birth, and to increase the chance of survival of their offspring [5]. A more recent proposition, *the reproductive conflict hypothesis* (also known as *the mother-in-law conflict hypothesis*), suggests that the cost of intergenerational reproductive conflict between older females and younger females of the same social unit impacts the reproductive fitness calculations [6]. A Finnish study, using birth, death, and marriage records kept by the Lutheran church from 1702 to 1908, found that when both mothers-in-law and daughters-in-law gave birth around the same time, their offspring had a 66% lower chance of survival, with offspring of the older mothers having even lower chance of survival (50%) [7].

For most women, age at natural menopause (ANM) usually occurs between the ages of 40 and 60 years. Findings from our meta-analysis of 46 studies across 24 countries showed that the mean ANM was 48.8 years (95% confidence interval 48.3–49.2). There was substantial heterogeneity across nations: African 48.4 (48.1–48.7); Asian 48.8 (48.1–49.4); Latin American 47.2 (45.9–48.6); Middle

G.D. Mishra
School of Public Health, The University of Queensland, Herston, QLD 4006, Australia
e-mail: g.mishra@sph.uq.edu.au

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Eastern 47.4 (46.9–47.8); USA 49.1 (48.8–49.4); Europe 50.5 (50.0, 51.1); and Australia 51.3 (49.8, 52.8) [8].

A woman's age at natural menopause is not only a marker of reproductive ageing, but also an indicator of underlying health and can even act as a sentinel for her future health status [9]. For instance, earlier age at menopause has been shown to be associated with increased risk of cardiovascular disease, stroke, atherosclerosis, and osteoporosis, and by contrast with a reduced risk of breast cancer and ovarian cancer [8]. This does not necessarily imply any causal relationships, but could result from common risk factors, including genetic factors and exposures in early life. For example this may be the case for cardiovascular disease, where recent findings suggest that pre-existing risk factors, such as raised total serum cholesterol and blood pressure, are associated with both earlier menopause and CVD [10]. Our meta-analysis revealed that overall, each year of delay for ANM is linked with a 2% reduction in all-cause mortality [8].

Factors across the life course have been shown to be associated with the timing of menopause, which appears to reflect a complex interplay of factors, from genetic to cumulative socioeconomic and lifestyle factors. Family and twin studies have revealed a significant genetic influence on ANM with estimates of heritability ranging from 30 to 85% [11, 12]. Supporting evidence from observational studies also demonstrates that a direct relationship between a woman's ANM and her mother's reported ANM [11, 13–18].

Epidemiological evidence indicates an important role for factors in early life, including postnatal nutrition. For instance, women in the Medical Research Council 1946 British birth cohort who had been breastfed experienced later ANM than those who had not [18, 19], and women who had a low weight at age 2 years had earlier ANM [19]. Similarly Dutch women who experienced severe caloric restriction as a result of the famine of 1944–45, especially those who were aged 2–6 years at that time, had earlier ANM than those who were not exposed [20]. Lower family socioeconomic position (SEP) in childhood has also been associated with earlier ANM. More specifically, emotional stress at a young age may impact reproductive aging, with evidence that women who experienced parental divorce early in life tended to have earlier ANM [19, 21].

The timing of menarche is another key reproductive marker that has been shown to be associated with ANM. The International collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE) is a large-scale multinational study that provides pooled data, including for over 50,000 women from nine observational studies in the UK, Scandinavia, Australia, and Japan. From this InterLACE data, we showed that almost one in ten women had premature menopause (ANM <40 years) or early menopause (ANM <45 years). Having early menarche (11 years or younger) increased the risk of premature and early menopause by 80%, while the risk doubled for nulliparous women. Furthermore, the combination of early menarche and nulliparity resulted in a fivefold increased risk of premature menopause and twice the risk of early menopause compared with women having later menarche and two or more children [22]. The sparse evidence from low- and middle-income countries also

suggests that earlier age at menarche is associated with earlier age at natural menopause [23, 24].

Of the various lifestyle and environmental factors in adulthood known to affect the timing of menopause, only cigarette smoking [8, 25] and nulliparity [22, 25] are consistently related to an earlier ANM. Some studies have found that women with lower adult SEP, which may indicate greater exposure to stress, tend to experience ANM earlier than women of higher SEP even after adjustment for smoking and parity [26–29]. A recent systematic review found a modest association of moderate to high physical activity with earlier ANM in unadjusted, but not adjusted, meta-analysis, whereas for BMI it was found that being overweight had a modest association with later ANM. As with many other aspects of the menopausal transition, further research is needed on the combined effects of BMI, weight change, and physical activity.

While a significant body of research has been conducted on identifying the factors associated with the timing of menopause, limited evidence exists on the timing and duration of perimenopause. The length of perimenopause has been shown to have an adverse effect on the quality of life. Using data from the 1946 British birth cohort, it was found that women who experienced prolonged perimenopause had a higher decline in two aspects of quality of life: perceived physical health (including energy level) and psychosomatic status (such as nervous emotional state, ability to concentrate) [30]. This is consistent with an earlier study from the USA that found that longer perimenopause was associated with a higher rate of medical consultations [31].

While vasomotor symptoms are among the most frequently reported physiological symptoms during and after menopause [32, 33], their prevalence among women in high-income countries ranges widely from 30 to 75% [34, 35]. Recently, epidemiologic studies have attempted to provide a more detailed picture of the various distinct trajectories of symptoms experienced through the menopausal transition and into postmenopause. For instance, findings from two studies have both shown that groups of women whose vasomotor symptoms peaked strongly either before or after ANM tended to decline relatively quickly in postmenopause [36, 37]. Such trajectories for the severity of these symptoms were not evident when based on chronological age, but only when their timing was examined with respect to the ANM. In the future this information may help guide women in the management of their symptoms in selection of appropriate treatment options.

Overall, risk factors from prenatal stage through to adult life influence the age at menopause, with consequent implications for health risks in later life. Our understanding from epidemiological studies of the effects of menopausal transition on women and the factors that influence its duration and timing remains unclear and incomplete, especially on those from low- and middle-income countries. Expanding life course research in these countries will demonstrate whether social trends, such as growing income inequality during childhood and adulthood and upward mobility, similarly relate to women's age at menopause as is the case in rich nations. Basic questions, such as the variation in the length of perimenopause globally or the impact of the menopausal transition on weight gain, remain essentially unanswered.

One way forward lies in expanding studies such as InterLACE that combine individual-level data from numerous international studies of women's health [38, 39]. This would provide a more comprehensive and detailed picture of the menopausal transition, its timing, and long-term health implications, for women not just in high-income countries but from across regions and from diverse populations.

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