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REVIEW

The evolution of the human menopause

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ABSTRACT

The females of most species die soon after ceasing to reproduce, their purpose in life being to ensure survival of their kin. Human females may live more than one-third of their lives after they cease to reproduce, a property shared by few species, one of which is Orca whales. Orcas have been extensively studied because families live together in stable units or pods and individual whales have distinctive markings, enabling them to be identified. The females survive long after the menopause, one possible reason for this being that the older females provide a survival advantage since they are seen to lead the pods more often than younger females or males, thus providing a survival advantage in times of food shortage.

The female lifespan is increasing in most countries worldwide, principally due to decreased infection and maternal mortality. Women are now more active through middle and into older age. Whatever sort of life they wish to lead, women need to be as fit as possible to facilitate healthy aging. Chronic diseases that affect millions of women are cardiovascular disease, osteoporosis, cancer, and dementia. The incidence of all these is increased by obesity, the prevention of which is a major challenge in our society. Hormone therapy may have a place for some women but for many others taking control of their health by lifestyle intervention is a major contributor to disease prevention. It is our duty as doctors to encourage this at every opportunity to help all women live a fruitful and healthy old age.

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Introduction

Why females of some species cease reproduction before the end of the natural lifespan is a puzzle, particularly as this only occurs in a very small number of species in their natural environment[1]. In humans as well as some species of whales and insects, reproductive senescence occurs much faster than somatic aging and females exhibit a long post-reproductive lifespan (PRLS). There are many hypotheses as to why this might occur which bare closer scrutiny as women now face the possibility of spending 30–40% of their lifespan in the post-reproductive period. Menopause may be welcomed by some women but is often feared, particularly in the West where youth is worshiped, and many women spend a great deal of money on cosmetics, creams, and surgery. A recent publication suggested that women with fewer children were rated as more attractive in middle age than those of high parity[2].

If the main purpose of women is to propagate the species (survival of the fittest), as postulated by Darwin for all species, then going through menopause many years before dying should be selected against unless there are distinct advantages to it[3]. In most species that demonstrate a prolonged PRLS, the interval between ceasing reproduction and death is very short and only seen in captivity, as has been recorded in some species of elephant and non-human primates[4]. Also, this occurs only in a very small proportion of the female population. Maintaining reproductive function beyond a certain point of somatic aging is of no benefit to a population. A PRLS in captivity is likely to be a result of accelerated reproduction of breeding programs and removal of natural predators of all types.

Among the small number of exceptions are some insects and two types of whale. Why are the two types of aging uncoupled? It is only recently that data have emerged after very prolonged, longitudinal studies, particularly in Orca whales, that begin to provide some answers[5]. Humans living with high rates of mortality and without access to modern medicine still exhibit a PRLS even if it is not as long as those in more protected environments. In addition, there is evidence that, in these whales and other species such as social aphids, post-reproductive females increase the survival and/or reproductive success of their kin.

What is menopause in humans?

Menopause occurs because of depletion of follicles within the ovary. The maximum number of follicles is present in the fetus at about 5 months' gestation (between 3×10^5 and 7×10^6 follicles) and declines consistently until the age of around 38 years, when this decline accelerates[6]. Natural menopause is reached when there are insufficient follicles to enable enough estrogen to be produced from the granulosa

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cells. Ovulation contributes only a little to follicle depletion and thus follicle depletion through atresia is what leads to menopause.

Fertility declines before there is total depletion, and age at last birth tends to occur around 10 years prior to menopause in most women; age of menopause is influenced by many factors, including genetic. Menopause also manifests itself at various different levels, individual, cell and molecular. The age of menopause varies little between different ethnic groups and does not appear to have altered significantly over the recent past, unlike the age of menarche which is affected by demographic factors. It is possible that diverse groups of women share a similar age of menopause due to a common descent.

What might contribute to menopause?

There are three principal theories as to why menopause occurs[7].

Mate choice

If the male wishes to have the highest chance of procreating successfully, he is likely to select a young female, as there is a greater chance of reproductive success. There is increased mortality of late pregnancy in many species and older females do better to use energy in a different way[8]. Reproductive conflict also means that, in killer whales for example, mothers suffer disproportionate costs when breeding at the same time as their daughters, which may be one of the reasons why reproductive and somatic aging have been uncoupled[9]. In humans, older birth is accompanied by an increase in birth complications, and maternal death compromises the survival of the children. However, this is not true for chimpanzees, which prefer older to younger females for mating[7]. Also, chimps prefer parous mates. However, female chimps do exert some choice in that they select a mate to give the best result and may mask their fertility in order to control their own reproduction.

Later-life helping is more advantageous to the whole population than reproductive conflict, which is likely to increase the relatedness (in breeding) in communities, although women will only forgo late-life reproduction when it boosts the fitness of their kin. In humans, there is little reproductive overlap between generations. In a pre-industrial Finnish population, reproductive conflict decreases survival by 66%, although this is less apparent with unrelated females across the generations[10].

Lifespan artifact

Increasing lifespan has enabled menopause to occur. The difference in somatic and reproductive lifespans was initially thought to be an artificial phenomenon because lifespan and reproduction were thought to be of similar length in primitive communities. However, this is not always the case and some primitive populations (e.g. the Kung Hunter Gatherers) have always had a long lifespan even when far from modern life and medicines[11]. Lifespan is determined at a molecular level and includes factors affecting telomere length which could be an interesting area of study.

Grandmother hypothesis

This hypothesis postulates the increased success of the species because older females play a role in supporting the development of the grand offspring[12,13], such as by providing food after weaning. For example, whales contribute to offspring survival well into adulthood and death rates are much greater for males. There is evidence that post-reproductive females act as repositories for ecological knowledge and frequently lead the pods of whales to food, which is crucial to the survival of the entire pod[14].

In humans, the grandmothers benefit their grandchildren. Post-reproductive females can help by capitalizing on their two distinct characteristics in that they are typically older members of the population and are no longer burdened with fertility. They can help find food, detect predators, and solve problems as well as navigate and avoid social conflicts. In the whales, the older females lead the groups to food sources in times of scarcity[14]. Post-reproductive Hazda women forage for tubers, and weight gain in the grandchildren is dependent on this post weaning. In modern society, the older women can often advise the younger, having benefited from experiences throughout their lives

The fitness benefits of post-reproductive helping could, in principle, select for menopause but the magnitude of these benefits is insufficient to be the single explanation for the timing of menopause and it is probable that reproductive conflict within the same social unit is also critical.

Killer whales

Reproductive lifespan is from around 15–30 to 40 years (sometimes younger) whereas whales may live until over 60–70 years. This has been observed by researchers since individual whales can be identified visually and their age and genealogy are well known. Reproductive relatedness means the young whales fight harder to reproduce than older whales. Forty-three years of observation have shown that calves from the older generation have a greater chance of dying than those of the younger generation[9]. In killer whales, neither sex disperses from the matrilineal group. Both female and male offspring do not leave the mothers' pod. Reproductive senescence occurs when relatedness is at its peak. Males survive less long than females so relatedness decreases. Since reproducing females will compete for the same food sources and forage in social groups, food sharing is essential within communities. This is particularly important as the young female whales need much more food to support lactation. Post-reproductive females will then pass knowledge of food sources to their offspring. Older females are a 'repository of ecological information', with older females helping the younger animals navigate a complex range of social and environmental situations[10].

Table 1. Symptoms of metabolic syndrome.

- Metabolic syndrome may be diagnosed as having three or more of the following symptoms
- A waist circumference ≥94 cm (37 inches) in European men or ≥90 cm (35.5 inches) in South Asian men
- A waist circumference ≥80 cm (31.5 inches) in European and South Asian women
- High triglyceride levels and low levels of high-density lipoprotein in the blood
- High blood pressure that is consistently 140/90 mmHg or higher
- Insulin resistance
- An increased risk of developing venous thromboembolism
- Increased inflammation

Primitive humans

In humans, several studies have shown the benefits of being a grandmother – for example, in premodern Finnish and Canadian women, women with grandchildren live longer lives[10]. Early human studies suggest that initially survival did not extend beyond the reproductive years, but this, of course, has changed over the last 50–100 years in Europe and the developed world.

Behavior, life history, and social changes are important as well as genetic changes. Importantly, mutations increase with age, as does the risk of pregnancy. Pregnancy is very demanding for large-brained primates, causing women to slow down during pregnancy and lactation.

What does menopause mean to today's woman in midlife?

Many of the theories discussed are also relevant to modern populations. In many parts of Asia, a family covering several generations will also live under the same roof and this particularly facilitates child care. This has not been so popular in western society where young adults are often encouraged to become independent and 'leave the nest'. This has inherent problems as the rise in cost of living and necessary income may outstrip the potential to care for children adequately. Many grandparents play a significant role now in the lives of their grandchildren, as well as finding that the young fledglings return to the nest when money for the rent runs out! The other advantage is care of the elderly, the numbers of whom are increasing exponentially. Those of the 'sandwich generation' with dependent young and sick parents often find this extremely hard.

What can we learn from each other regarding living into a healthy old age? Lifestyle and 'wellness' are becoming a vogue in western society, and this possibly might avoid the polypharmacy of most of the current elderly. How can we help women live a long older age regardless of how they wish to live it? There is tremendous importance in being fulfilled and able to achieve as appropriate for any individual. Women should always be advised to consider their lifestyle and take control of their own health. There are wide differences in the burden of disease within and between countries. Specific diseases and risk factors such as high body mass index (BMI), poor diet, high fasting plasma glucose level, smoking, and alcohol use are increasing in many countries and warrant increased attention. Data from the large national databases can be used to inform national health priorities for research, clinical care, and policy.

Chronic disease in middle and older age in women

The lifespan of women has increased over the last 50 years in most countries around the world. World Bank figures suggest that, in the UK, the lifespan increased from 74 years in 1960 to 83 years in 2016, whereas in low-income countries it increased from 41 to 65 years over the same time period; this is probably partly due to decreased maternal mortality in most countries (e.g. the significant increase in Afghanistan from 33 to 65 years[15]).

A substantial proportion of women throughout the world are postmenopausal and this number is increasing. In many communities, at least one-third of the lifespan is lived after the menopause, exceeding even pampered animals in zoos. However, this means that the importance of good health in old age has increased significantly in order that independent living can continue as long as possible and, also, the approach to aging is affected by culture and ethnicity[16].

The causes of death and chronic disease have changed over the past 50 years in many parts of the world. The proportion of adults dying from non-communicable disease has risen exponentially and now cardiovascular disease tops the league tables[17,18]. One of the main contributing factors to this is obesity.

Obesity and weight gain

In some countries, obesity is a sign of prosperity and wealth, but in most it is a sign simply of excess. In the West, weight gain occurs in the majority of middle-aged men and women at a rate of about 0.5–0.7 kg/year. It is uncertain as to the exact cause of this but most likely it is a decrease in activity whilst maintaining a similar diet. There is an increase in both subcutaneous and visceral fat in mid-life women but the latter increases to a greater extent in women going through the menopause related to decreased estrogen levels and/or increased relative levels of androgens. This means fat distribution changes with menopausal stage and this is associated with altered insulin resistance and metabolic risk[19]. This has become known as metabolic syndrome, which includes many of the well-known cardiovascular risk factors (Table 1)[20,21].

In Caucasian women, metabolic syndrome is common, affecting 20–40% of women after the menopause, and the incidence increases through the premenopause and menopause. However, ethnic differences are present, with a greater incidence being found in South Asian women. Weight gain across the menopause impacts differently on insulin resistance in the two groups, with significant implications for metabolic health. The impact of altering lifestyle

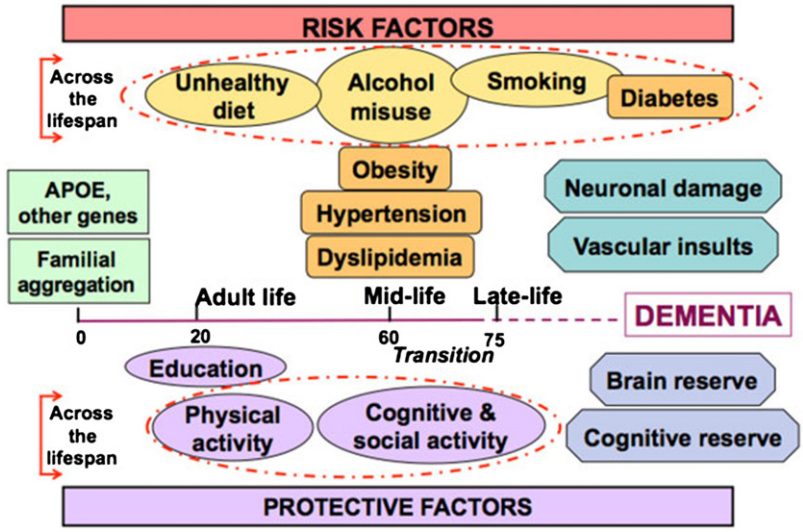

Figure 1. Risk factors for and prevention of dementia[43,44]. APOE, apolipoprotein E.

factors such as diet and exercise also impacts differently between ethnic groups[22]. It is beholden on every clinician to discuss metabolic and cardiovascular risk with their patients and ensure the risk factors are kept under control[23].

Body mass index and obesity

Women should maintain or lose weight through an appropriate balance of physical activity, caloric intake, and formal behavioral program to maintain/achieve a BMI of between 18.5 and 24.9 kg/m^2 and a waist circumference $\leq$35 inches. Recommendations may vary between different ethnic groups; for example, South Asians in whom increased risk occurs at lower BMI than in Europeans[24].

Impact of menopausal hormone therapy on cardiovascular disease

Menopausal hormone therapy (MHT) alone is not recommended for disease prevention, although it has many features that suggest it has a place in supporting lifestyle[25] and other pharmacological interventions aimed at decreasing the disease burden of mid-life[26].

Until the late 1990s, estrogen was thought to protect against coronary heart disease (CHD)[27]. Many cohort studies showed that MHT was associated with a 40–50% reduction in the incidence of CHD. However, a randomized, controlled trial (RCT), the Women's Health Initiative (WHI), found an early, transient increase in coronary events in the combined MHT (estrogen plus progestogen) arm but not the estrogen-alone arm[28]. In the WHI the average age of participants was 63 years, 12 years older than the average age of menopause in the UK and Western Europe; therefore, it is possible that the women in these studies had established subclinical atherosclerosis and the impact of MHT might be different in younger women. This 'window of opportunity' concept has subsequently been supported by several publications[29–32].

In a meta-analysis of clinical outcomes, the 2015 Cochrane review of RCT data found that MHT initiated fewer than 10 years after menopause onset lowered CHD in postmenopausal women (relative risk 0.52; 95% confidence interval [CI] 0.29–0.96)[33]. The review also found a reduction in all-cause mortality (relative risk 0.70; 95% CI 0.52–0.95) and no increased risk of stroke but an increased risk of venous thromboembolism (relative risk 1.74; 95% CI 1.11–2.73), similar to the findings of a prior meta-analysis of studies in women who initiated MHT within 10 years of menopause onset and/or in women aged younger than 60 years[34]. These findings include the subgroup analysis of data from the WHI trials, which examined MHT use stratified by age and time since menopause, and demonstrated more favorable results for all-cause mortality and myocardial infarction in women aged 50–59 years and in those within 10 years of their last menstrual period[34,35].

The Danish Osteoporosis Prevention Study (DOPS)[36], an open-label RCT, showed that MHT was associated with a reduction in cardiovascular disease in women of the same age group. For conjugated equine estrogen (CEE) alone, in the WHI study CHD, total myocardial infarction, and coronary artery bypass grafting or percutaneous coronary intervention showed a lowered hazard ratio in women aged younger than 60 years and fewer than 10 years since menopause onset, even in intention-to-treat analyses[35]. Age group analysis in the WHI CEE/medroxyprogesterone acetate trial found that in the age group 50–59 years, the hazard ratio for CHD 1.34 (95% CI 0.82−2.19) for CEE/medroxyprogesterone acetate ie not statistically elevated.

Estrogen has many beneficial effects that could contribute to this finding. The effects of estrogen administration may be modified by the route of administration[37]. It may lead to maintenance of a 'female' fat distribution which is associated with less cardiovascular risk; some of the cardiovascular disease risk factors may also be improved by estrogens. These include the impact on lipid profiles, insulin resistance, and vascular reactivity. Potentially, estrogen may help prevent plaque formation but, once plaque has formed, the impact of starting MHT is less clear and may have a detrimental effect in older women. The situation is made more complex

in that data suggest that stopping MHT may increase cardiovascular events[38]. However, MHT alone will never be the answer, but must be combined with a good lifestyle and exercise[39,40].

Bone health

One of the factors that limits mobility in old age is hip fracture, the incidence of which increases exponentially in the postmenopause. Twenty percent of elderly people die within 1 year of a hip fracture and 80% have decreased mobility that impacts significantly on quality of life[41].

Impact of MHT on the incidence of fracture

Studies consistently demonstrate the beneficial effect of MHT on decreasing hip fracture by preventing bone loss and possibly by helping maintain muscle strength. These benefits must be weighed against the potential disadvantages of prolonged use of MHT, as breast cancer incidence is known to be duration dependent. It also appears that any benefits disappear after treatment is stopped, although the data for this assertion are inconclusive[26].

Dementia

One of the greatest scourges of old age is dementia that removes independence and requires institutionalization for many, and the incidence of which is increasing with the lifespan. There are many factors that impact on risk[42], including genetic but also many of the risk factors for cardiovascular disease described earlier (Figure 1). Risk can be predicted to a degree and prevention strategies put into place[45]. Pharmacological intervention is largely confined to those at high risk, but lifestyle factors can be modified. The impact of MHT is unclear, although it is possible that there is a preventative effect of starting MHT at the age of the menopause[26].

However, is estrogen the elixir of youth and does it prevent aging? There is no evidence it does this, although many women feel better when taking estrogen and thus tend to look younger. It may have a beneficial impact on skin quality and certainly benefits bones, but beyond this the effect on aging is questionable and MHT should not be taken for that reason. The license granted by all regulatory authorities is for symptom relief and not for disease prevention, although it is probably that, in the current climate, many women will continue to take MHT for both reasons well into older age.

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