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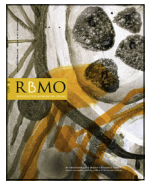

COUNTERCURRENT

Early menopause results from instead of causes premature general ageing

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ABSTRACT

Recent genome-wide association studies have shown that the majority of genes involved in menopause are also instrumental in double-strand break repair and mismatch and base excision repair of DNA. Cumulative DNA damage causes cellular senescence resulting in exhaustion of somatic cell renewal capacity and cellular dysfunction, and eventually to accelerated cell death, generally called ageing. A similar erosion of the genome occurs within the germ cell line and thus in the ovaries. Subsequently, the systemic 'survival' response intentionally suppresses the sex-steroid hormone output, which in turn may contribute to the onset of menopause. The latter occurs in particular when age-dependent DNA damage accumulates. Both effects are expected to synergize to promote ovarian silencing resulting in menopause. Consequently, ageing of the soma seems to be a primary driver for the loss of ovarian function in women. Therefore menopause is the result rather than the cause of ageing.

INTRODUCTION

Menopause is defined as the permanent cessation of ovulation and hence menstruation due to ovarian failure. There is a substantial variation in the timing of the age at menarche and menopause, and both impact on social, health and economic outcomes. The median age of menopause has remained constant at around 51 years. However, menopause might occur early at the age of 40 years while late menopause might happen as late as 62 years of age. Lifestyle factors that might influence the age at which menopause occurs are nutritional status, the degree of exercise and tobacco use. Moreover, socioeconomic factors and a person's educational level also seem to play a role. Finally, the number of pregnancies and childbirths are also associated with menopausal age. In addition, menopause is a highly heritable condition and genetic variants are known to cause 50% of the variation in age at which menopause occurs (*Gruhn et al., 2019*).

GENETICS OF MENOPAUSE

Several genetic studies have tried to unravel this genetic background of menopause making use of different genetic techniques in population studies as well as in animal models. Reproductive senescence, which menopause actually is, is also dependent on multiple intrinsic genetic factors. Reproductive ageing is not isolated from the overall somatic ageing process, and several studies strongly support the link between an early age of menopause and morbidity and mortality (*Laven, 2020*).

A recent genome-wide association study (GWAS) identified some 290 genetic determinants of reproductive ageing, using normal variation in age at natural menopause in a huge cohort of about 200,000 women of European ancestry. The majority of loci seem to be involved in a broad range of DNA damage response (DDR) processes. Moreover some are loss-of-function variants in key DDR-associated genes. Genetic modifications in some of these variants revealed that these DDR processes act across the life-course to shape the ovarian reserve and its rate of depletion (*Ruth et al., 2021*).

The nuclear genome accumulates more damage the older an individual gets. Indeed, numerous studies have revealed that the burden of DNA damage is greater in older mammals compared with younger ones. The DNA damage theory of ageing, which argues that genomic instability plays a causal role in ageing of the soma, is also instrumental in the ageing of the germ cell line. Indeed,

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KEY WORDS

Ageing
DNA damage response
DNA repair and maintenance
Menopause

TABLE 1 SUMMARY OF MOST RELEVANT FINDINGS IN FAVOUR OF THE THEORY THAT AGEING PRECEDES MENOPAUSE

Type of study	Main finding	Reference
Genetic studies		
Genome-wide association studies	Variants in DDR genes are associated with age at menopause	*Ruth et al. (2021)*
Animal studies		
Genetically modified mice	Genetic manipulation of *CHECK1* and *CHECK2* in mice shapes the ovarian reserve and its rate of depletion Genetic manipulation of the DDR system resulted in accelerated depletion of both ovaries very similar to premature ovarian insufficiency	*Ruth et al. (2021)* *Laven (2020)*
Epidemiological data		
Cohort study	Indicated a higher cardiovascular disease susceptibility in women with vasomotor signs before menopause	*Gast et al. (2011)*
Case-control study	Lower ovarian reserve in women with pre-eclampsia	*Woldringh et al. (2006)*
Case-control study	Lower ovarian reserve markers in type 2 diabetes mellitus	*Isik et al. (2012)*
Case-control studies	Showed reduced ovarian reserve markers in girls with newly diagnosed cancer, women with type 1 diabetes mellitus and women with rheumatoid arthritis	*Laven (2020)*
Fecundity, ageing and longevity		
Cohort study	Shorter menstrual cycles are associated with lower anti-Müllerian hormone levels	*Younis et al. (2020)*
Cohort study	Number of births and age at last birth are associated with overall survival and all-cause mortality	Roman et al. (2020) *Laven (2020)*
Cohort study	Genetic risk score for centenarians overlaps with menopause DDR variants	*Sebastiani et al. (2013)*

DDR, DNA damage response.

reproductive capacity in women starts to decline beyond their mid-thirties, and pregnancies in older women result in higher rates of miscarriage with aneuploidy. This age-related decline in fertility is strongly attributed to ovarian ageing, diminished ovarian reserve and decreased developmental competence of oocytes. Moreover, ageing oocytes seem to lose protective mechanisms against reactive oxygen species (ROS), giving rise to increased DNA damage (TABLE 1). Hence, accumulated ROS activity and increased vulnerability of oocytes to ROS lead to spindle instability, chromosomal abnormalities, telomere shortening and reduced developmental competence of aged oocytes (*Laven, 2020*). Last but not least there was an extensive overlap between the genetic variants associated with menopausal age and neurodegenerative and cardiovascular disease (CVD) as well as with diabetes mellitus (*Ruth et al., 2021*).

ANIMAL STUDIES

On the one hand manipulation of DDR pathways in genetically modified mice can increase fertility and extend the reproductive lifespan (*Ruth et al., 2021*). On the other hand, making the DDR pathways defective in genetically manipulated mice showed, apart from accelerated ageing, also an infertile phenotype in female mice characterized by an accelerated depletion of both ovaries within 4 weeks after birth. A phenotype very similar to the anti-Müllerian hormone (AMH) knockout mouse greatly resembles premature ovarian insufficiency (*Laven, 2020*). Hence, multiple lines of evidence support a causative role for DDR damage response defects in natural ageing and associated morbidities such as neurodegenerative diseases, diabetes mellitus and CVD. A persistent decrease in transcription output redesigns glucose metabolism and endocrine function, and augments the reductive capacity of the cell – the so-called systemic 'survival' response. Hence, defective DNA repair, metabolism and ageing are linked (TABLE 1). These new insights also challenge the old paradigm that menopause precedes ageing.

OVARIAN FUNCTION AND DISEASE

There is also epidemiological evidence that challenges the classical view. In a large population-based Dutch study the presence of vasomotor signs, for example night sweats, was associated with a modest but significantly increased risk of coronary heart disease in premenopausal women. Hence women with vasomotor symptoms had a significant increased CVD risk compared with women of a similar age without these conditions (*Gast et al., 2011*). Similarly, in another Dutch study, of women who became pregnant after IVF, women with pre-eclampsia were compared with matched healthy control participants without pre-eclampsia. The group who developed pre-eclampsia had needed more exogenous FSH and had had a lower oocyte yield during their previous IVF treatment. The administered dose of FSH per follicle and per obtained oocyte was higher in the women with pre-eclampsia, indicating an a priori diminished ovarian reserve prior to the occurrence of any CVD (e.g. pre-eclampsia), and therefore supporting more pronounced ageing in women who developed pre-eclampsia (*Woldringh et al., 2006*).

It is not only CVD that seems to be linked with ovarian ageing: other diseases also show associations with decreased ovarian reserve markers. A study comparing women with type 2 diabetes mellitus (T2DM) with age- and weight-matched healthy controls showed that both ovarian volume and antral follicle count were significantly reduced in women with T2DM (*Isik et al., 2012*). It was also shown that relatively young women with type 1 diabetes mellitus (T1DM) had lower AMH concentrations compared with healthy controls without diabetes. There are also some scarce data indicating that women with T1DM enter menopause earlier in life (*Laven, 2020*).

It is also known that the incidence and prevalence of Parkinson's disease is higher in postmenopausal than premenopausal women of a similar age. This is consistent with numerous studies showing that sex hormones exert trophic actions on neurons and glial cells, promote neuron survival and have a neuroprotective role in several models of neurological disease (*Labandeira-Garcia et al., 2016*). Indeed, a fairly large proportion of the genetic variants determining menopause were also involved in the pathophysiology of Alzheimer's disease (*Ruth et al., 2021*).

A large study in girls with newly diagnosed cancer showed reduced AMH concentrations even before cancer treatment was initiated. Moreover, AMH concentrations were very well correlated with impairment of their general health status. These phenomena were seen in all girls independent of the type of cancer that they had. Similarly, ovarian reserve seems to be lower in women suffering from rheumatoid arthritis, as was shown in another recent study from our own group (*Laven, 2020*).

Bilateral oophorectomy is also associated with an alteration of several fundamental ageing processes at the cellular, tissue and organ levels, leading to multimorbidity, frailty and reduced survival (*Rocca et al., 2018*). In contrast to what is generally believed, these data indicate that the susceptibility to the observed multimorbidity was already present before the ovaries were removed (TABLE 1). Hence, it is a result of accelerated ageing rather than merely a loss of oestrogen action (*Laven, 2020*).

FECUNDITY AND AGEING

Shortening of the menstrual cycle interval, a physiological phenomenon preceding menopause, is usually not perceived as an indicator of decreased ovarian reserve in the general population. However, a recent meta-analysis in regularly cycling women indicated that shorter menstrual cycles were an indicator of ovarian ageing. Indeed, shorter menstrual cycle intervals were associated with lower AMH serum concentrations and lower antral follicle counts compared with women with a longer menstrual cycle interval (*Younis et al., 2020*). Similar findings from another meta-analysis suggest that a previous use of oral contraceptives, age at menarche beyond 13 years of age and having at least one live birth are associated with later menopause (*Roman Lay et al., 2020*).

Another recent study investigated the association between maternal age at birth of the last child and likelihood of survival to advanced age. Women who had their last child beyond age 33 years had twice the odds for surviving to the top 5th percentile of survival for their birth cohorts compared with women who had their last child at an age of 29 years (TABLE 1). A large study from Israel using models adjusted for age at first birth and parity revealed that mortality risks were lowest among parous women with the latest birth at an age exceeding 45 years compared with parous women with their last birth before 35 years of age (*Laven, 2020*).

LONGEVITY AND MENOPAUSE

As premature and early menopause have been associated with an increase in all-cause mortality, later menopause generally leads to a higher life expectancy and hence menopause is also intertwined with longevity.

Recently, a set of 281 genetic markers associated with about 130 genes was identified that was capable of differentiating centenarians from non-centenarians, especially for centenarians who were 106 years or older. This particular set was also used in similar studies in centenarians from the USA, Europe and Japan. The results from this meta-analysis showed that many of these variants were associated with survival to extreme ages. Interestingly, among that set of genetic variants were some of the genes found in the latest GWAS for menopause. Moreover, a considerable number of variants reaching statistical significance in the meta-analysis were associated with neurodegenerative diseases, diabetes mellitus and CVD (*Sebastiani et al., 2013*). A genetic analysis of humans with exceptional longevity identified a set of 20 single-nucleotide polymorphisms associated with higher life expectancy. Four of these single-nucleotide polymorphisms were located in or nearby genes that are also associated with DNA repair and maintenance (*Laven, 2020*).

A large population-based Dutch study among 4000 post-menopausal women revealed that late last reproductive events were protective for all-cause mortality (*Laven, 2020*). Indeed, there seems to be a reciprocal relationship between fertility and mortality (TABLE 1). This is explained by the fact that a genotype moulds the age patterns of mortality and fertility of its phenotype within an environment, thereby determining the genotype's fitness in that environment. In humans this implies that as soon as fertility declines, mortality rates increase (*Jones et al., 2014*). Indeed data from the latest GWAS also indicate that the causal inference associated with some of the identified genetic variants might extend beyond reproductive life in women and also might improve bone health and simultaneously reduce the risk of T2DM and neurodegenerative diseases. However, this also coincides with an increase in the risk of hormone-sensitive cancers (*Ruth et al., 2021*).

CONCLUSIONS

The accumulation of DNA damage in normal and accelerated ageing may affect ovarian function in two different ways. First, a gradual (or in the case of compromised genome maintenance, rapid) accumulation of unrepaired DNA damage causes cellular senescence and consequently (premature) cell death. The latter leads to an exhaustion of cell renewal capacity, hypo-cellularity, cellular dysfunction in affected organs and eventually ageing of the entire soma. It is likely that the ovaries do not escape from erosion of the genome, as apparent from the increased risk of trisomy 21 in pregnancies in older women. Second, the systemic 'survival' response intentionally suppresses the sex-steroid hormone output, which may in turn contribute to the onset of menopause, particularly when the accumulation of age-dependent DNA damage does not stop. Both effects are expected to synergize to promote ovarian silencing and install menopause. Consequently, ageing of the soma seems to be a primary driver for the loss of ovarian function in women, in contrast to the current dogma which implies that a loss of ovarian function initiates ageing of the soma.

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