Early Menopause and Brain Health: From Clinical Risk to Neuroscience

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AT THIS year's International Society of Gynecological Endocrinology (ISGE) Congress 2026, held in Rome, Italy, the symposium 'The Troubled Journey of the Menopausal Transition' brought together leading experts to explore the complex clinical and biological changes occurring across this critical life stage. Chaired by Antonio Cano, University of Valencia, Spain; and Mark Brincat, University of Malta, Msida, the session examined the menopausal transition through multiple lenses, from cardiometabolic risk and musculoskeletal health to brain ageing and hormone therapy optimisation.

Panagiotis Anagnostis, Aristotle University of Thessaloniki, Greece, examined whether early menopause represents a distinct clinical entity from premature ovarian insufficiency (POI), while Roberta Brinton, University of Arizona, Tucson, USA, provided insights into the neurobiological impact of the menopausal transition and its implications for hormone therapy initiation timing.

EM VERSUS POI: CLINICAL OVERLAP AND DISTINCTION

The average age of menopause is 50–51 years. While menopause occurring more than two standard deviations below the average age (i.e., before 40 years) has been widely, though somewhat arbitrarily, classified as 'premature',[1,2] loss of ovarian function before the age of 40 is more specifically termed POI, a condition affecting approximately 1% of women.[3] Diagnostic criteria for POI include disordered menstrual cycles for ≥4 months, alongside elevated follicle-stimulating hormone >25 IU/L (on at least one occasion).[3]

If menopause occurs between 40–45 years of age, it is considered early menopause (EM).[3] This condition is relatively common, affecting up to 10% of postmenopausal women.[3]

Some of the well-recognised long-term health consequences of POI are an increased risk of cardiovascular disease, osteoporosis and associated fracture risk, cognitive dysfunction, and a significant reduction in both quality of life and life expectancy.[4-6]

Regarding the type of menopause, there are currently no clear conclusions on whether surgical versus natural menopause differentially affects long-term outcomes.[7]

Long-Term Health Risks in POI Compared to EM

However, we must address the question: do women with EM demonstrate the same long-term health risks as women with POI, particularly regarding cardiovascular disease?

Women with POI are at increased risk of both fatal and non-fatal cardiovascular disease, mainly driven by coronary heart disease and stroke.[7] In women with EM, hazard ratios appear to converge; though to a lesser extent, they remain significant across these outcomes. Recent evidence from Anagnostis's group confirms that these women are indeed at increased risk.[8]

Understanding Cardiovascular Risk

Why does this happen? One explanation is the higher prevalence of cardiovascular risk factors in this population. A meta-analysis conducted in 2019 showed that women with EM have a 12% increased risk of Type 2 diabetes, while those with POI have a 50% increased risk.[7]

These findings have been replicated in later studies.[9,10] Arterial hypertension is also increased by around 10% in women with EM.[9] This association was not significant in POI, possibly due to oestrogen therapy.[10]

Importantly, non-coronary outcomes such as heart failure and atrial fibrillation have been highlighted in meta-analyses, showing that both EM and POI are associated with increased risks.[10] These are under-recognised issues that should be considered.

In summary, there is substantial evidence that women with EM are at increased risk of fatal and non-fatal cardiovascular disease, primarily due to coronary heart disease. This is largely driven by increased cardiovascular risk factors, particularly diabetes and hypertension, alongside non-coronary outcomes, such as heart failure and atrial fibrillation.[5]

> **Women with EM are at increased risk of fatal and non-fatal cardiovascular disease**

Osteoporosis and Fracture Risk

What about the musculoskeletal system? Data from the Australian Longitudinal Study on Women's Health (ALSWH) show that women with POI have a 2.5-fold increased risk of osteoporosis.[11] Women with EM also have a significantly increased risk, though to a lesser extent, while those with late menopause show reduced risk.[11]

However, findings are not entirely consistent. The Canadian study did not show increased osteoporosis risk in early menopause, though it remained elevated in POI.[12] Regarding fractures, Panagiotis and colleagues' analysis of approximately 500,000 menopausal women demonstrated that EM is associated with a 36% increased fracture risk compared to both women with menopause before 45 years of age and those with menopause at around 50 years of age.[13] These findings have been replicated in subsequent studies.[14]

Additional analyses show that women with EM or POI have an increased risk

of osteoporosis and fractures, with an estimated risk of around 1.4. Risk factors include increasing age, lower BMI, and comorbidities.[14] EM and POI are also recognised as independent risk factors in tools such as FRAX® (University of Sheffield, UK) highlighting the importance of assessing secondary osteoporosis.[1,13]

Role of Sarcopenia in Fracture Risk

Is fracture risk solely due to reduced bone mineral density (BMD)? The answer is no. Sarcopenia also plays a role.[15] While categorical data are limited, Panagiotis's group found reduced muscle mass in women with EM, with marginal effects on muscle strength, and more significant findings in POI, including reduced physical performance.[15]

Frailty, a broader concept encompassing both sarcopenia and overall health, is also increased, with approximately a two-fold higher risk in both EM and POI.[16]

Rationale for Using High Oestrogen Doses

Turning to hormone replacement therapy (HRT), in women with POI, recommended oestrogen doses, 100 µg/day transdermal or 2–4 mg/day oral oestradiol, are approximately twice the conventional dose, combined with appropriate progestogen in women with an intact uterus.[4,17] While specific recommendations for EM are lacking, a pragmatic approach is to follow the same principles.

Why should we use higher oestrogen doses? The rationale for this is to restore physiological oestrogen levels (50–100 pg/mL), achievable with transdermal 17β-estradiol 100 µg/day or oral 17β-estradiol 2–4 mg/day.[17-19] Evidence suggests that conventional HRT may be insufficient to prevent bone loss in POI, whereas higher doses can restore BMD to normal levels.[18,19] Limited cardiovascular data indicate that higher oestrogen doses may reduce carotid intima-media thickness.[18,19] This approach supports physiological levels and bone health, with potential cardiovascular benefit.[18]

Safety and Efficacy of HRT: Evidence from Clinical Studies

HRT is recommended until at least the average age of natural menopause, unless contraindicated.[2,4] While it is generally considered safe, there is a lack of evidence from RCTs assessing the cardiovascular and bone effects of HRT in women with POI or EM.[8]

However, evidence from both retrospective and prospective cohort studies provides insight into the protective effects of HRT on the cardiovascular and musculoskeletal systems in women with POI or EM. For example, in a USA-based study, mortality was increased in women undergoing bilateral oophorectomy; however, this was not observed in those receiving HRT.[20]

Another study demonstrated a 35% reduction in cardiovascular mortality in women with surgical EM who received HRT.[21] Similarly, a large Korea-based study showed that the risk of ischaemic stroke and all-cause mortality was increased in women with POI or EM who did not receive HRT, but not in those treated for more than 5 years.[22]

Although data on the effects of HRT on bone health in women with POI and EM are currently limited, there is substantial evidence that HRT significantly reduces fracture risk in postmenopausal women. Meta-analysis of 28 RCTs, involving over 33,000 participants, concluded that HRT significantly reduces the risk of total, hip, and vertebral fractures, with the most pronounced benefit (a 45% reduction) observed in women under the age of 60 years.[23]

Furthermore, another Korea-based study reported a 20% reduction in the risk of sarcopenia among postmenopausal women receiving HRT for more than 13 months.[24]

Panagiotis concluded that it is reasonable to recommend oestrogen therapy for women with EM, emphasising that this is not simply menopausal hormone therapy (MHT), but true HRT that helps reduce multiple long-term health risks.[8]

Suboptimal Long-Term Use of HRT

However, overall HRT use remains suboptimal.[14] Although around 70% of women initiate HRT, only one in four use it for more than 5 years, and just 6% for over 10 years.[14] This likely contributes to the persistent burden of cardiovascular and fracture risk.

Future Perspectives

Future research should focus on longitudinal and randomised studies to determine optimal oestrogen dosing for women after the age of 45 years, as well as the role of serum oestradiol monitoring, and management strategies following HRT discontinuation. Limited data suggest that agents such as alendronate or raloxifene may help maintain BMD after HRT cessation.

Panagiotis proposed a unified approach, advocating for the management of women with POI or EM using similar principles. This strategy may facilitate earlier and more appropriate use of HRT; however, optimal regimens and long-term outcomes remain to be established.

MENOPAUSAL TRANSITION AND BRAIN HEALTH: METABOLIC AND IMMUNE REPROGRAMMING

Brinton opened the talk by stating that "women are at a two-fold greater risk of developing Alzheimer's disease. Worldwide, there are currently one billion menopausal women who share a common critical period in brain ageing: the perimenopause to menopause transition." They went on to add that menopause represents a critical period, just like adolescence and early development.

The perimenopause to menopause transition, while often considered a transition in reproductive capacity, is in fact a transition that occurs in the brain.[25] When you look at the symptoms of perimenopause and menopause, many have nothing to do with reproduction and everything to do with the brain. For example, sleep disturbance, depression, and cognitive complaints are all related to changes occurring in the brain.[25]

Role of Oestrogen in Brain Energy Metabolism

Oestrogen is a key regulator of glucose metabolism in the brain. It promotes glucose uptake, its metabolism, and ultimately the generation of ATP in the mitochondria.[25-30] Brinton often refers to oestrogen as the 'Queen of Darwin', as it leaves nothing to chance, from glucose uptake to energy production. The brain is the most energetically demanding organ in the body.

Metabolic Reprogramming in the Brain

The decline in oestrogen availability activates a starvation response in the brain. Oestrogen supports approximately 20–25% of glucose uptake and metabolism, and its loss triggers the brain to utilise auxiliary fuels, as if it were starving. These auxiliary fuels are ketone bodies, which can provide energy for ATP generation.

While this is beneficial, the brain, being the most lipid-rich organ, begins to catabolise its own lipids, specifically white matter, to generate these ketone bodies. This leads to a loss of myelin density and impaired synaptic conduction. Additionally, the integrity of axonal structure is compromised. Lipidomic analyses confirmed that white matter lipids are converted into ketone bodies to sustain energy requirements.[25]

Brinton sought to characterise the complex process of metabolic reprogramming of the brain following the decline in oestrogen levels. They found out that initially, there is a decline in glucose metabolism, followed by a transient increase in the use of amino acids as alternative fuel sources. This diverts amino acids away from their role in synaptic protein formation.[25-32]

Subsequently, mitochondrial efficiency declines, shifting towards a phenotype that produces less energy and more heat. There is also an increase in fatty acid β-oxidation, necessary for ketone body production, and a rise in ketone levels.[25-32]

This process generates myelin fragments, which are taken up by microglia, the brain's immune cells. This triggers a strong immune

response. Microglia present these fragments on their surface, and T cells from the peripheral immune system recognise them as foreign, suggesting an autoimmune-like response. Interestingly, 95% of individuals after the age of 50 years diagnosed with multiple sclerosis are women.[25-33]

Hot Flashes and Mitochondrial Heat Production

Brinton's group has also investigated whether this metabolic reprogramming is linked to menopausal hot flashes: "Our findings suggest that the catabolism of white matter and the uptake of myelin fragments by microglia induce a mitochondrial burst. The loss of oestrogen leads to inefficient mitochondria that generate both ATP and heat, and this heat production may contribute to the experience of hot flashes." Brinton also shared for the first time that "the generation of menopausal hot flashes, characterised by the release of heat, is likely associated with a microglial respiratory burst, during which lipids are taken up and converted into myelin fragments."

Sequence of Biological Changes During Menopause

The first sign of this transition appears to be activation of the innate immune system, followed by reduced glucose metabolism and increased amino acid utilisation. This is followed by a mitochondrial deactivation and heat generation, increased fatty acid oxidation, and rising ketone levels. Both innate and adaptive immune systems become activated, which may explain the increased prevalence of autoimmune diseases during menopause.[25-28,30-32,34-36]

MHT: Timing of Intervention and Impact on Neurodegenerative Risk

When MHT is introduced early in this process, oestrogen can help sustain brain health; however, it does not reverse established disease.[25,28,31] In clinical practice, women typically seek MHT when symptoms such as hot flashes arise, by which point significant neuroendocrine changes have already occurred.

> **"The generation of menopausal hot flashes, characterised by the release of heat, is likely associated with a microglial respiratory burst"**

The brain at this stage differs markedly from that seen earlier in the transition, and differs again once the endocrinological ageing process is complete. As a result, the response to MHT varies depending on the timing of initiation. This likely contributes to the ongoing controversy and challenges surrounding MHT.[25,28,31]

Brinton and colleagues examined the impact of MHT on the risk of neurodegenerative diseases in a retrospective analysis of 379,352 women.[37] MHT was associated with a reduced risk of Alzheimer's disease, Parkinson's disease, dementia, multiple sclerosis, and amyotrophic lateral sclerosis. Longer duration of therapy was associated with greater risk reduction, with an overall 50–60% decrease in the risk of Alzheimer's disease.[38]

However, the timing of MHT initiation is crucial. When started during the menopausal transition, it reduces Alzheimer's disease risk. However, initiation after the transition may increase risk. Brinton and colleagues hypothesise that this may relate to oestrogen's effects on microglial activity.

CONCLUSION

The menopausal transition is a complex and critical stage with significant implications for long-term health. A clear message emerged across the presentations: early recognition and timely intervention are essential, particularly for reducing cardiovascular, musculoskeletal, and neurological risks. The speakers emphasised that menopause should be viewed as a dynamic process rather than a single event, requiring a personalised and evidence-based approach to care.

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