



The 6th Scientific Meeting of the Asia Pacific Menopause Federation

Singapore | 20 – 23 Apr 2017

21 Apr 2017

Predicting the menopause

The menopause marks the end of ovarian follicular activity and is said to have occurred after 12 months amenorrhoea.

The average age of the menopause is between 45 and 60 years of age with slight variations between geographic regions and ethnic groups. Menopause between the age of 40 and 45 years is considered early and menopause before the age of 40 premature.

For women who wish to defer (but not avoid) motherhood, in whom there is a family history of premature menopause or who are about to undergo chemo- or radiotherapy for treatment of malignant disease, a means of predicting menopause may be helpful.

The worldwide similarity in age at natural menopause (ANM) suggests it is a tightly regulated biological process under genetic control. Genetic studies show a strong familial concordance for ANM. In mother and daughter pairings, heritability rates are around 50% and even higher for twins. The risk of premature ovarian insufficiency is 6-times higher for women with a family history. Few specific genes have been identified but X chromosome-linked abnormalities and aberrations in chromosomes 8, 9, 11 and 16 have been identified. Most genes identified have a role in steroid pathways or vascular function suggesting reproductive and vascular ageing may be linked.

Predictive factors for age of menopause include personal age, maternal age, fertility status, menstrual irregularity, follicle-stimulating hormone (FSH) levels, antral follicle count (AFC), ovarian volume, inhibin B levels and anti-Müllerian hormone (AMH) levels.

AMH is a glycoprotein member of the transforming growth factor- β family. It is produced in granulosa cells of antral and pre-antral follicles, is independent of gonadotropin stimulation, peaks when women are in their mid-20s and declines thereafter. It has an important role in folliculogenesis and in predicting response to *in vitro* fertilization treatment. It is a promising candidate for predicting menopause, but lacks precision in isolation. AMH levels are affected by



age, body mass index (BMI), smoking, ethnicity, polycystic ovarian syndrome and use of the oral contraceptive. Rates vary slightly throughout the menstrual cycle.

Broer et al. (2011) found age, AMH and AFC were the most accurate predictors of menopause, and following multivariate analysis, that only AMH added extra predictive power.¹ Bentzen et al. (2013) found the rate of decline in AMH and follicle number in AFC increased when maternal ANM was <45 years.² Dölleman et al (2015) found the addition of AMH to models including age, BMI, smoking and menstrual irregularity improved predictability most in younger women with regular cycles.³

Data from The Study of Women Across the Nation (SWAN 2016) found that a very low AMH can help predict a woman's chance of menopause within 12 months whilst an AMH >20 pg/mL meant menopause was unlikely within 2 years.

To summarize, this data suggests that AMH, AFC and maternal ANM are the most promising predictors of ANM. Most models are less accurate at predicting extremes of ANM and provide wide prediction intervals. Thus, these models are not yet suitable for day-to-day clinical practice in predicting ANM, particularly for those who need it most. We may still not have identified the single best predictor.

References

1. Broer SL, et al. *J Clin Endocrinol Metab* 2011;96:2532–2539.
2. Bentzen JG, et al. *Hum Reprod* 2013;28:247–255.
3. Dölleman M, et al. *Hum Reprod* 2015;30:1974–1981.



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Can we predict age at menopause ?

- For most women menopause will be diagnosed retrospectively after >12 months amenorrhoea
- For some women, particularly those with a family history of premature menopause, those who are about to undergo chemo- or radiotherapy and those who wish to defer, but not avoid, motherhood, the ability to predict the onset of sterility and menopause will be important
- Anti-Müllerian hormone (AMH), antral follicle count (AFC) and mother's age at natural menopause (ANM) are currently the most promising predictors of ANM, but most models are less accurate at predicting extremes of ANM and provide wide prediction intervals
- AMH, AFC and maternal ANM are not yet suitable for predicting menopause or fertility in day-to-day clinical practice, particularly for those women who need this information most
- Larger cohorts containing more detail on mother's ANM, serial AMH, AFC, corrected for smoking and other confounders are required to further improve predictive power
- We may still not have identified the single best predictor
- Any young woman with >3 months menstrual irregularity is at risk of premature ovarian insufficiency and requires investigation



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Menopause symptoms: How long and how bad?

Menopausal vasomotor symptoms (VMS) affect women across the world. A recent systematic review indicates that the prevalence of VMS amongst Asian women may have been underestimated in the past, such that the prevalence in women in Asia may be more similar to that of women in developed countries.

The Study of Women Across the Nation (SWAN) reported a mean duration of VMS of women in the USA of approximately 7.5 years, but the oldest women in that cohort were in their mid-60s. A study of women aged 60–79 years found that one-third of older women had VMS, but only 10% of these women reported their symptoms to be moderate-to-severe. Recent studies have also shown that VMS are significantly associated with lower general well-being and poorer self-reported work performance. Furthermore, VMS are associated with lowered mood and greater anxiety. Australian peri- and early postmenopausal women are more likely to use psychotropic medications, smoke and binge drink than premenopausal and older postmenopausal women, with each of these behaviours associated with the severity of VMS. As the use of prescription therapy to alleviate



menopausal symptoms remains low, these data suggest that women are “self-medicating” to manage their symptoms.

Vulvovaginal atrophy (VVA) is substantially undertreated. Australian data indicates that whereas 20% of women aged 40–65 years have severe VVA symptoms, less than 5% of all women are using vaginal oestrogen. Similar findings have been reported in the USA.

Overall, menopausal symptoms are common, adversely impact women’s lives, can persist well into the 8th decade of life, yet symptoms remain under-recognized and undertreated.

Menopausal symptoms: How long and how bad?

- Menopausal vasomotor symptoms (VMS) affect women across the world
- The prevalence of symptoms in Asian countries is likely to have been underestimated
- VMS may persist into the 8th decade of life
- VMS are associated with lowered well-being, mood and work ability
- Women are mostly trying to manage their symptoms with ineffective therapies
- Systemic hormonal therapy is under-prescribed
- Despite the high prevalence of symptomatic vulvovaginal atrophy, few women are prescribed vaginal oestrogen therapy



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What are the best menopausal hormone treatment dose, regimen and route of delivery?

The Global Consensus Statement on menopausal hormone treatment (MHT)¹ states that:

- The principal reason for using MHT is to alleviate menopausal symptoms.
- The lowest effective dose of oestrogen should be used and a progestogen must be added for women with a uterus.
- Topical oestrogens are preferred if symptoms are limited to vaginal dryness and dyspareunia.

The 'best' MHT regimen will thus be simple to use, acceptable to the patient, will alleviate her symptoms, will maximize ancillary benefits and will have minimal short-term side effects and potential harms.

The short-term side effects of MHT include irregular, prolonged vaginal bleeding, breast tenderness and fluid retention. Choosing the lowest effective dose when initiating therapy can minimize all of these. Women should be advised that bleeding may occur and that, generally, no further investigation is required during the first 4–6 months of MHT. Thereafter, all postmenopausal bleeding should be investigated.

Serious long-term harms of MHT include an increased risk of venous thromboembolism (VTE), and perhaps breast cancer. VTE risk is greatest in the first year of therapy and is dose-related. Evidence is clear that synthetic oestrogens increase VTE risk more than natural oestrogens. Observational studies also show that synthetic progestogens may further increase that risk and that natural progestogens do not have an additive effect on VTE risk. Observational studies also suggest that transdermal oestrogens do not increase VTE risk. Long-term observational studies have reported no increased risk of breast cancer for oestrogen-only users for up to 20 years, whilst randomized, controlled trials have also found no increased risk of breast cancer with oestrogen-only therapy for up to 7 years and a reduced risk with long-term (12-year) follow-up.



Synthetic progestins will sometimes bind to hormone receptors other than progesterone receptors. This is particularly true of medroxyprogesterone acetate (MPA), which binds to glucocorticoid receptors. In the Women's Health Initiative (WHI) randomized, controlled trials, whilst oestrogen only increased VTE risk (relative risk: 1.3) the risk with combined conjugated oestrogens (CE) + MPA was 2.0. Similarly, breast cancer risk was not increased with oestrogen only, but showed a trend towards increased risk after 7 years in *de novo* users of CE and MPA.

Observational studies from both France and the UK have shown no increase in breast cancer risk for users of natural oestrogens plus natural progesterone or dydrogesterone.

The 'ideal' MHT will therefore be a low-dose, non-oral, natural oestrogen, which should be combined with natural progesterone in women with a uterus.

If non-oral therapy is unacceptable, a low-dose oral oestrogen plus a natural progesterone may be considered.

A combination of low dose CE plus a selective oestrogen receptor modulator (bazedoxifene) represents another option for women intolerant of progestogens or seeking low-dose oral therapy.

In reality, we must choose what we know to be the 'best regimen' and adjust that to meet the needs and expectations of each woman.

References

1. De Villiers TJ, et al. *Maturitas* 2016;91:153–155.



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What is the ideal menopausal hormone treatment dose, regimen and duration

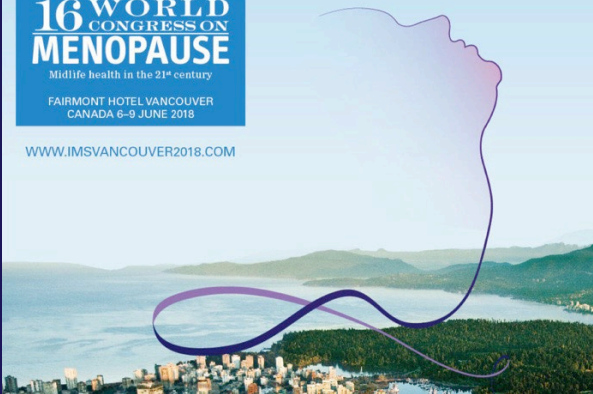
- The most important point is that MHT should always be individualized
- The 'ideal' oestrogen dose is the lowest effective dose consistent with treatment goals that will minimize short-term risks, such as breast tenderness and fluid retention
- Long-term risks of oestrogen therapy, such as venous thromboembolism (VTE), are reduced by using the lowest effective dose and may be eliminated by the use of non-oral oestrogen therapy
- Oestrogen-only therapy in women within 10 years of menopause reduces risk of coronary heart disease and does not increase the risk of breast cancer
- Data from randomized, controlled trials and observational studies suggest that synthetic progestins may increase breast cancer risk and attenuate the reduction in cardiovascular risk seen with oestrogen-only therapy
- The ideal progestogen will bind only to progesterone receptors and have minimal effect on CVS and breast
- Although non-oral administration has benefits with regard to VTE risk the route of administration should be determined in discussion with individual women
- The ideal regimen is that which suits the individual woman
- Therapy should be continued as long as is required, consistent with treatment goals



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