Prediction of premature ovarian insufficiency: foolish fallacy or feasible foresight?

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Abstract

Prediction of premature ovarian insufficiency (POI) would be of substantial individual benefit, but as a heterogeneous and fluctuating condition, with an extensive range of complex aetiologies, and arbitrary diagnostic criteria, might make this seem foolhardy. However, contemporary and complementary genetic strategies assessing consanguineous and large POI pedigrees and cohorts with age at natural menopause have shown strong enrichment in genes regulating DNA damage repair, homologous recombination and meiosis, processes that are critical to oogenesis and folliculogenesis. Recognition of the molecular architecture of POI and its contribution to baseline genotypic risk may enable these estimates to be refined further by estimation of the residual ovarian reserve. Increasing data derived from spontaneous and gonadotoxic induced POI cohorts demonstrate the utility of anti-müllerian hormone (AMH) to predict POI. This review presents current understanding of how genetics in combination with AMH may facilitate the prediction of POI.

Premature ovarian insufficiency (POI) is a heterogeneous condition resulting from a wide range of aetiologies and affects an increasing proportion of women of reproductive age, with a recent pooled global prevalence estimate of 3.7% (95% CI 3.1, to 4.3) [1]. The implications of a diagnosis of POI are substantive, with significant somatic, psychological, and economic burdens [2]. POI not only interferes with a woman's autologous reproductive potential but is also associated with an increased risk of osteoporosis, cardiovascular disease, and premature mortality [3].

Despite these weighty implications, the diagnosis is based on a relatively arbitrary age threshold of <40 years, oligo/amenorrhoea of at least 4 months and an elevated FSH of > 25IU/l on two occasions > 4 weeks apart [4,5], albeit different guidelines may recommend alterative FSH thresholds. The implications of a non-robust diagnostic definition for analysis of the potential for prediction of POI are profound, as this limits the inherent accuracy and potential for comparison across studies. That there are also very distinct aetiologies of POI such as genetic and chromosomal abnormalities, following chemotherapy, autoimmune and the large proportion who are apparently idiopathic in origin, combined with a wide range of age at onset from early adolescence to age 40 years, and thus with correspondingly different phenotypes, all adds to the complexity of prediction [2]. Up to ~25% of women experience some evidence of ovarian function after the diagnosis of POI [2]. Although this supports the use of insufficiency rather than failure to more accurately describe the fluctuating function of the residual ovarian tissue, it further adds to the difficulty of prediction as for many women loss of ovarian function is not a dichotomous event, at least in the initial years after diagnosis. Collectively, these inherent limitations in the diagnostic framework for POI would suggest that prediction is far from a frivolous undertaking but rather may be fiendishly difficult and indeed inherently flawed other than in tightly defined subgroups, with thus limited wider value. However complementary strategies assessing baseline risk, quantification of iatrogenic insults where appropriate and estimates of the remaining ovarian reserve may be fruitful. In this regard, both genetics and functional ovarian reserve biomarkers, of which anti-Müllerian hormone (AMH) is the most dynamic and responsive to insults, are likely to facilitate future prediction and identification of at risk individuals across the range of phenotypes and aetiologies.

Recognition of the importance of baseline phenotype and underlying genetic risk

Elucidation of the genetic and molecular basis of POI has continued to identify a growing multitude of genes in some of which mutations can be causative, and many others where genetic variation is implicated though effects on various linked critical processes. These include gonadal development, DNA replication, DNA repair, hormonal signalling, immune functions and metabolism (Figure 1a).

Several recent reviews have detailed the heterogeneous genetic architecture of POI, the genetic complexity of inheritance patterns and the limited prevalence of single pathological mutations[2,6]. While most women with sporadic POI harbour heterozygous mutations, analysis of pedigrees frequently reveal autosomal recessive, or less commonly dominant inheritance patterns. In addition to these classical Mendelian inheritance structures, a more complex genetic architecture for POI has been documented, wherein mutations in two or more POI genes are found in a single case[7]. These coexisting mutations could therefore play the role of 'second hits' or act as 'modifier' genes involved in POI [6]. Comparable findings have advanced understanding of the oligogenic nature of hypogonadotropic hypogonadism [8].

Insights from whole exome sequencing (WES) on POI pedigrees and genome wide association studies (GWAS) on age of menopause have revealed a preponderance of genes enriched in DNA damage repair and homologous recombination (HR). As early menopause (<45 years) and POI represent the tail of the menopause age distribution, a concomitant presence of POI and early menopause in the same pedigree might indicate a similar genetic pathogenesis but with a variable expressivity. Compared with age at natural menopause or early menopause, POI may have genetic generality and specificity. The hypothesis that overlapping polygenic aetiology, with individuals carrying more variants associated with a lower age at natural menopause having an increased risk of early menopause and POI would be plausible. The additive effect of now well recognised environmental factors that deplete the ovarian reserve [9], may also contribute to tipping these individuals into presenting with the classic POI phenotype.

Whether distinct phenotypes, such as ovarian dysgenesis, primary amenorrhea, secondary amenorrhea, or early or late onset of POI share the same or overlapping genetics with different cumulative effects remains unclear. With the adoption of next generation sequencing (NGS), a large and unexpected number of variants of unknown significance has emerged, with analysis of their causative relevance required. However, as many of the established POI genes seem to act synergistically, while individually displaying features of incomplete penetrance or variable expressivity, it is becoming ever more difficult to label a single genetic change in any individual POI patient as 'causative', with clarification of the genotype–phenotype correlation still required. The future for genetic prediction of POI could be potentially through targeted panels of hotspot mutations and/or validated causative genes, or wider analysis such as whole-exome and whole genome sequencing in individuals at risk based on family history or in those deemed at greater risk due to concurrent medical treatment. A polygenic risk score may enable initial stratification of

baseline risk but for those who are assessed early in life, wide estimates of time frames are likely. That the ovarian reserve may be further modifiable through environmental exposures accumulated across the lifecourse will further limit accuracy of time to event predictions. Consequently, irrespective of the potential for genetics to contribute to prediction, additional readouts to refine estimates of the remaining true and functional ovarian reserve will be required.

AMH production and temporal changes across the lifecourse

AMH is produced by granulosa cells of growing follicles from the earliest growing primary stages [10], through the early antral stages with a fairly sharp drop in production at approximately 10mm follicular diameter [11] which is the stage at which a follicle is selected for dominance. The maximal contribution to AMH serum concentrations is from follicles in the 5mm to 8mm range, with the contribution from these follicles constituting approximately 60% of circulating AMH [11]. While there are many fewer follicles at that stage than at earlier stages, the cuboidal increase in number of granulosa cells all producing AMH with the increase in follicle diameter drives this relatively sharp peak in AMH output per follicle over this narrow size range. AMH concentrations determined from peripheral blood samples are therefore quite removed from directly reflecting the number of primordial follicles, although from detailed histological studies it is clear that the number of growing follicles in the healthy ovary i~~n~~s indeed related to the number of primordial follicles [12], at least in health. It has also been shown that AMH levels do correlate with the histologically determined number of primordial follicles within the ovary ($r = 0.72$) [13], as in the rodent [14], although these clinical data are based on a very limited number of samples, and across a narrow age range. More recent data from girls and young women undergoing ovarian biopsy for fertility preservation [15] generally support this, with increasing strength of correlations in women over the age of 25 for follicular density and primordial follicle number respectively. The strength of the correlation is ~~-~~weaker ~~-~~in children, adolescents and early adulthood up to age 25, reflecting both the developmental gap between primordial follicles and the antral follicles that produce most AMH, and the complex and changing relationship between AMH and primordial follicle numbers during childhood and up to early adulthood. During those periods of life, AMH levels show a progressive increase despite the fact that the number of primordial follicles is falling [16]. There is therefore a complete change in the relationship between the size of the primordial follicle pool and AMH levels between the first quarter century of life and the second [17]. Nevertheless, these findings support the potential value of AMH as a marker of the number of growing follicles in the ovary particularly in adults, and certainly to a much greater extent than do serum estradiol levels which are largely from pre-ovulatory

follicles, or from FSH concentrations which are subject to feedback from fluctuating oestradiol concentrations.

AMH and POI prediction.

Several prospective longitudinal studies with repeat measures have confirmed that AMH becomes undetectable approximately five years before the final menstrual period [18-23] (Figure 1b), and that AMH concentrations measured in adult life are associated with the age at natural menopause [24] (Figure 1c). However, recognition of the lack of precision of these estimates, and that the imprecision is even greater in younger women with a longer time to menopause [25], limits its clinical utility. Furthermore, prediction of age at natural menopause, for example, whether it is 47 or 53, may not be important to a 27-year-old as it has limited repercussions for decision making. In contrast, in the pathological setting of POI where a more extreme phenotype is evident, and decision regarding immediate reproductive choices may be required, a biomarker may have greater chance of accurate prediction and also be of substantially wider interest, even if it is to exclude POI as a possibility. By definition a diagnosis of POI is also associated with a shorter time to event horizon than natural menopause, thereby enabling potentially greater accuracy.

At present, given the low prevalence of POI within the general population and availability of appropriate cohorts, there are limited data assessing the value of AMH for the prediction of a specific diagnosis of POI. This is particularly the case when considering cohorts which have used the newer more sensitive assays with lower Limits of Quantitation (Manufacturer reported values Ansh pico amh = 3.2 pg/mL, Roche AMH Plus = 30pg/ml, Beckman Access AMH = 70 pg/mL). Supporting data is however emerging, with the first utilizing a subset of participants within the Nurses' Health Study II who experienced early menopause (<45 years old), and matched and unmatched controls [26]. A strong inverse association of AMH levels and the risk of early natural menopause was found, and this was independent of established risk factors for early reproductive decline. In adjusted analyses each 0.10 ng/ml decrease in AMH was associated with a 14% higher risk of early menopause (95% confidence interval (CI) 1.10 to 1.18; $P < 0.001$). Similar associations of low AMH and an increased risk of early menopause were found a subsample of a Dutch cohort [27]. In women with Turner Syndrome, a known pathological cause of POI, an AMH level that was lower than 2 standard deviations from the age-related mean was also predictive of imminent POI [28]. Furthermore, in that study, both the sensitivity (probability of having POI when AMH ≤ 3 pmol/L [approximately 0.42ng/ml]) and the specificity (probability of having ovarian function when AMH > 3 pmol/L) were

95%. Further large prospective cohorts of young women with prolonged follow-up are however be required to be able to accurately determine the performance of AMH as a predictor of POI.

One important question that has yet to be addressed is whether POI (or specific POI aetiology) is associated with a more rapid decline in AMH, and therefore repeat testing on more than one occasion to assess the rate of decline may improve accuracy. For age at natural menopause the data are conflicting, with an initial study suggesting that repeat AMH measures did not improve the predictive ability with more than one test for both early or natural menopause [27]. In contrast, both the Penn Ovarian Aging Study [29] and the extended follow-up of the Tehran and Lipid Glucose cohort [30] have suggested that determination of the rate of decline improves the prediction of age of menopause, albeit marginally. Whether these opposing findings between studies reflect different populations studied, differences in the frequency of follow-up, or differences in the methodology for ascertainment of AMH concentration remains unclear [31]. Future prospective population studies, specifically targeting young women of reproductive age with repeat measurements and accurate ascertainment of whether they experience POI, perhaps subdivided by aetiology, will be essential to ascertain the overall utility of repeat measurements. These studies would also be able to determine the added value and utility of biochemical measurements beyond baseline genetic risk.

Prediction of POI secondary to gonadotoxic therapy

As precision medicine continues to refine cancer therapy, guidance as to the extent to which novel or established gonadotoxic treatments are associated with POI will be required, and whether gonadotoxic-related POI can be predicted. For both indications, clarification whether AMH measurements either prior to, during or after treatment will be useful or not are required. While AMH levels may be reduced compared to age matched controls in women with lymphoma at the time of diagnosis and the relative reduction may reflect the severity of illness, this does not appear to be the case for women with breast cancer [32,33]. In the context of a new diagnosis of breast cancer, measurement of AMH prior to treatment has reasonable performance in predicting whether or not they will have ongoing ovarian activity after completion of initial chemotherapy [34,35], with age further refining this risk. In a combined analysis of two small cohorts of women with early breast cancer (total n = 75), incorporating eight different chemotherapy regimens, pretreatment AMH combined with age gave a sensitivity of 98.2% and specificity of 80.0% for the prediction of amenorrhea as a proxy for POI at two to five years after treatment [36]. In a separate cohort of women with hormone receptor-positive early breast cancer (n = 120) receiving eight different chemotherapy

or adjuvant regimens, an AMH <0.965ng/ml (equivalent to <6.89 pmol/l) predicted amenorrhea at 2 years (AUC 0.84, sensitivity 74% and specificity 81.8%), with marginal improvement in overall performance (C-index of 0.88, 95% CI 0.84-0.91), when age and FSH were included as covariates in the model [37]. In a cohort of 144 women with breast cancer receiving cyclophosphamide-based chemotherapy, an age effect (>35 years as threshold) was also identified, with both pre- and post-treatment AMH levels inversely associated with the risk of chemotherapy-induced amenorrhoea [38]. The rate of fall of post-chemotherapy AMH levels (thus already reduced compared to pretreatment) has also been investigated, finding that AMH levels fell at the same rate as in same-age controls, thus slower than in older controls with more comparable AMH levels [39]. Similarly, a large study of cancer survivors with a combination of cross-sectional and longitudinal analysis showed a long-duration plateau of post-treatment AMH levels in women exposed to low and medium risk treatment [40]. As in women in the general population therefore [27] , the finding of a low post-treatment AMH level in a relatively young woman may be at risk of overinterpretation of the likelihood of POI. Evaluation of the utility of AMH in prediction of POI for different types of malignancy and their associated treatments are ongoing, with expert opinion calling for it to be routinely assessed in oncological trial follow-up. This concept of evaluation of gonadotoxic insults and their long-term implications has also been extrapolated to other clinical situations, including endometriosis. Ovarian cystectomy for endometriomas is known to be associated with concomitant removal of normal ovarian tissue, and sustained reductions in AMH even when assessed up to 18 months post surgery[41]. In this context, pre-surgical measurement of AMH may inform POI risk, and post-operative samples may inform decision making regarding duration of the reproductive lifespan.

Conclusions

The heterogeneous etiology and phenotypes of POI inevitably limit the potential generalizability of any individual test to accurately ascertain or predict POI. For women with a familial history of POI or early menopause, whole exome sequencing, with non-ambiguous curation of well-validated pathogenic variants is likely to be influential on baseline risk, with further calibration of where that women is on her timeline potentially feasible through measurement of AMH. Similar contemporary genetic approaches would be useful for proposita, to ensure thorough evaluation and maximize the chance of diagnosis and inform sibling or offspring risk. For women with clear gonadotoxic insults, knowledge of their AMH levels prior to and after treatment samples have already been shown to be of benefit for prediction of POI, with cascading of this to other scenarios for evaluation of predictive performance underway. For populations, where upward shifts in childbearing may have profound impact on de-novo index cases, an understanding of the residual ovarian reserve is potentially a

desirable commodity. While assessment of AMH, potentially sequentially, may appear to be likely to be of value in the prediction of POI in a general population, current data indicate that is likely to substantially over-estimate the risk and the way forward may require interpretation in the context of other information, perhaps including a detailed genetic analysis. Prospective studies will be required to confirm or refute this.

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Conflict of Interest

SM. Nelson reports personal fees from Access Fertility, Merck, Modern Fertility and The Fertility Partnership and grants and personal fees from Ferring and Roche Diagnostics, outside the submitted work. RAA has participated in Advisory Boards and received speakers or consultancy fees from Roche Diagnostics, Ferring Pharmaceuticals, IBSA, Merck Serono, KaNDy Therapeutics and Sojournix Inc, outside the submitted work.

Figure 1: POI: Schematic representation of molecular architectures of POI and changes in AMH relative to the menoapuse.

Panel A shows a schematic representation of premature ovarian insufficiency (POI) causative genes involved in oogenesis and folliculogenesis, with a clustering of genes involved in DNA damage repair, homologous recombination and meiosis. Meiosis prophase I (from oogonia to primary oocyte) includes four substages: leptotene, zygotene, pachytene, and diplotene. POI causative genes are involved in cohesion of sister chromatid, pairing, synapsis, and recombination between homologous chromosomes.
Panel B shows the hormonal changes for AMH, FSH and LH observed over the menopause transition. The left Y axis shows mean FSH and LH concentrations in IU/L, and the right axis shows mean AMH concentration in ng/ml. Figure modified from Reference 23.
Panel C shows the relationship of AMH and age at natural menopause

Highlights:

Recent advances in elucidation of molecular architecture of POI have revealed new causative genes, with a preponderance for DNA damage repair, homologous recombination, follicle development and maturation.

Insights from cohorts on age of natural menopause support an association between lower AMH concentrations at younger age at menopause, however, predicted menopausal age estimates based on AMH are wide, particularly in young women.

For women at risk of POI, small cohorts have suggested that undetectable AMH may be predictive of POI, but larger studies are required to evaluate performance before this can be recommended for routine practice.

For women receiving gonadotoxic therapy both low / undetectable pre and post- treatment AMH concentrations are associated with onset of POI, but age modifies this association with greatest sensitivity and specificity in women over the age of 40.

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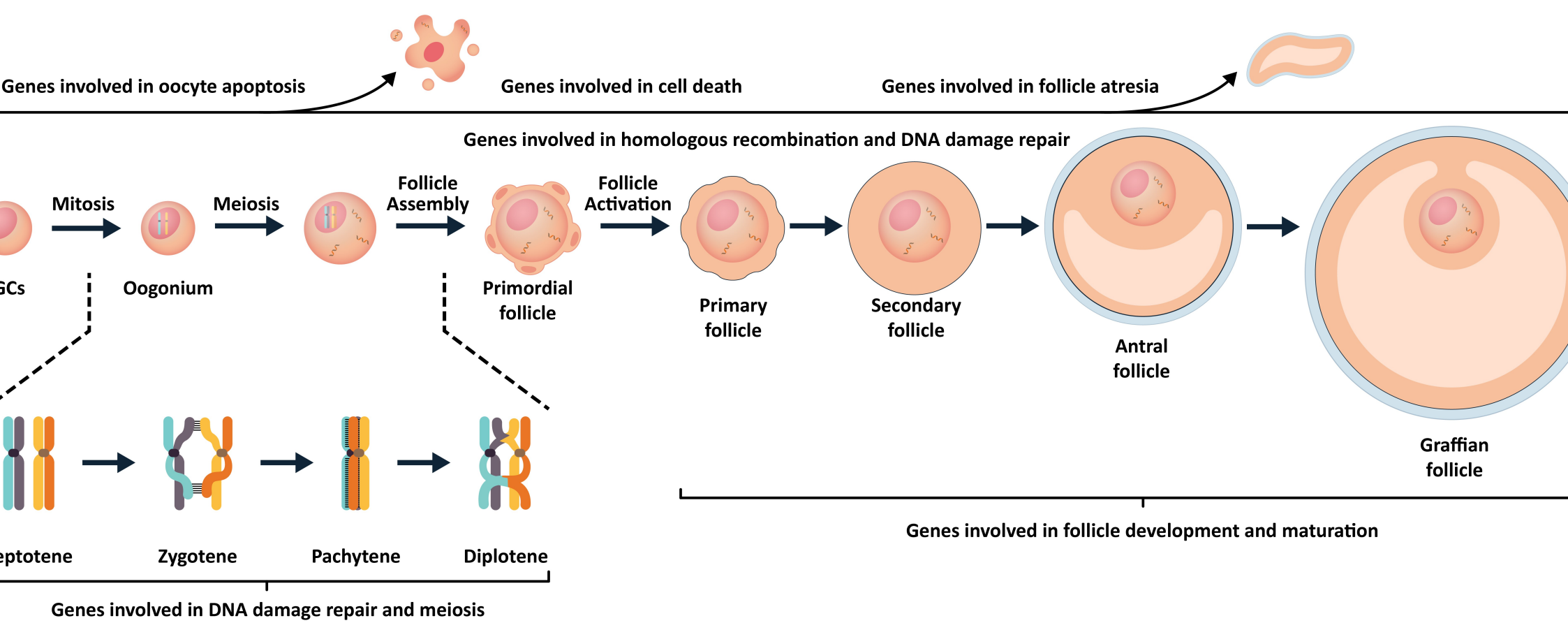
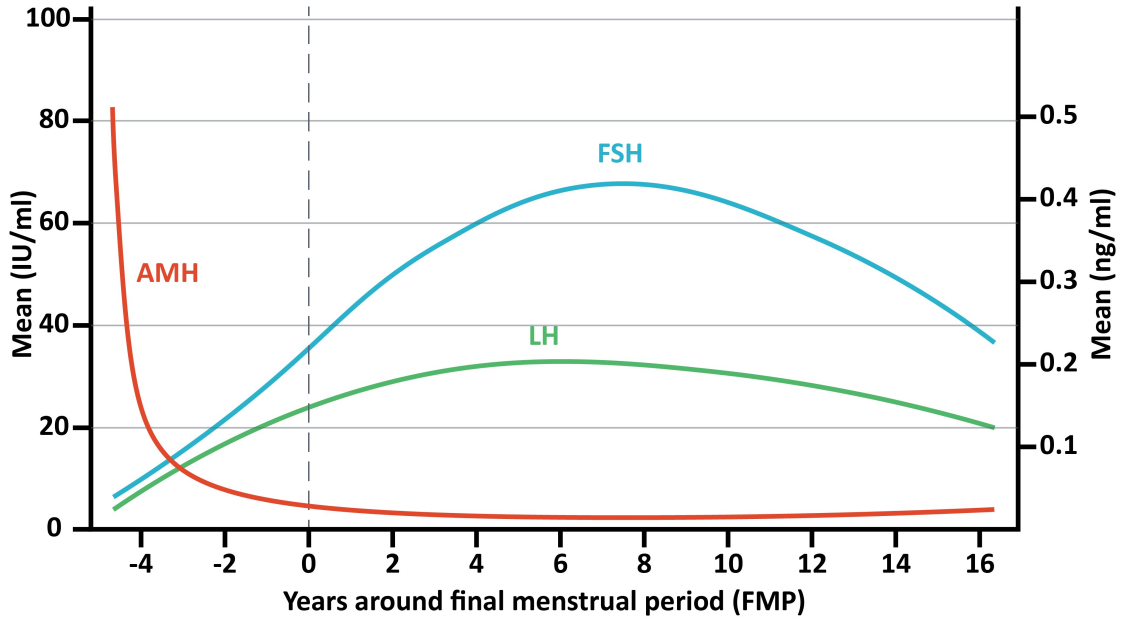

Genes involved in oocyte apoptosis
Genes involved in cell death
Genes involved in follicle atresia
Genes involved in homologous recombination and DNA damage repair
Mitosis
Meiosis
Follicle Assembly
Follicle Activation
GCs
Oogonium
Primordial follicle
Primary follicle
Secondary follicle
Antral follicle
Graffian follicle
eptotene
Zygotene
Pachytene
Diplotene
Genes involved in DNA damage repair and meiosis
Genes involved in follicle development and maturation


100
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Mean (IU/ml)
AMH
FSH
LH
0.5
0.4
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0.1
Mean (ng/ml)
-4
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0
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4
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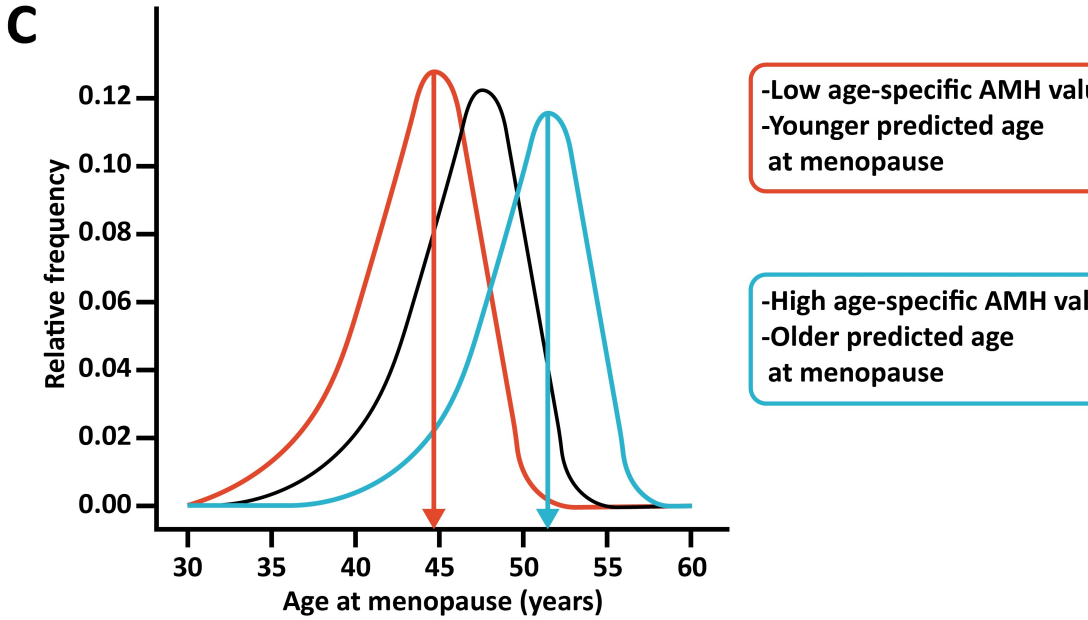
Years around final menstrual period (FMP)


C
0.12
0.10
0.08
0.06
0.04
0.02
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Relative frequency
30
35
40
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50
55
60
Age at menopause (years)
-Low age-specific AMH val
-Younger predicted age
at menopause
-High age-specific AMH val
-Older predicted age
at menopause