Arh. farm. 2025; 75: 1 – 14 *Review article/Pregledni rad*

Biomarkers of menopause

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Received: 10 December 2024; Revised in revised forme: 3 February 2025; Accepted: 9 February 2025

Abstract

Natural menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. This significant phase in women's reproductive aging has notable effects on fat distribution, dyslipidemia, and neurodegeneration. These changes contribute to an increased risk of dementia and cardiovascular disease as women age. Estimating the age at which natural menopause will occur is crucial for cancer survivors, women with a family history of premature ovarian insufficiency or early menopause, and those delaying their first pregnancy. Additionally, the timing of natural menopause is an important clinical indicator of longevity and a risk factor for morbidity and mortality. Beyond age and menstrual cycle characteristics, biomarkers related to menopause are essential for confirming its onset and predicting its premature occurrence.

Key words: menopause, STRAW criteria, follicle stimulating hormone, FSH, inhibin B, anti-Müllerian hormone, AMH

https://doi.org/10.5937/arhfarm75-55314

Introduction

The term “menopause” is derived from the Greek words “pausis” (pause) and “men” (month). It signifies the end of a woman’s reproductive and childbearing years, marked by twelve consecutive months of amenorrhea (1). The World Health Organization (WHO) defines natural menopause as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity (2). It represents a serious phase in women’s reproductive ageing, and it has significant repercussions on the distribution of fat tissue and its mass, dyslipidemia, and neurodegeneration (3–6). These changes provide the basis for the demonstrated increasing risk for dementia and cardiovascular disease in women with advancing age (7, 8).

Menopause typically occurs between the ages of 45 and 56, with the median age of natural menopause being 51 years. Given the increased life expectancy, women now spend approximately 40% of their lives in the postmenopausal phase, which translates to over 30 years for most women (9). For that reason, new approaches to women’s health are oriented towards understanding the biological mechanisms of menopause and predicting its onset, in order to reduce the disruptive symptoms and avoid long-term complications.

Typically, laboratory tests are not necessary to diagnose menopause, as it is usually determined clinically based on the patient’s age and symptoms (1). Symptoms often appear before any changes in laboratory values. However, in certain clinical situations, such as in women who are amenorrheic due to a previous hysterectomy, endometrial ablation, or anovulation, measuring biomarkers can aid in diagnosing menopause. In this review, we will present the current guidelines for determining the stage of woman’s reproductive ageing, discuss the significance of biomarkers that these guidelines include, and mention new genetic markers that may gain importance in the future.

Phases in menopause development

For many years, the nomenclature used to define menopause development varied significantly in the literature (10). According to the WHO guidelines (2), natural menopause occurs when amenorrhea is present continuously over a twelve-month period, which cannot be explained by any other pathological or physiological cause. Its beginning is marked by the final menstrual period (FMP), which is recognized as such only after one year or more. Menopause can also be induced surgically, after an oophorectomy of both ovaries, or with the extirpation of ovarian function caused by chemotherapy or irradiation, for example. The WHO guidelines defined four critical stages of menopause: 1) premenopause, which might refer to a period of maximum two years before menopause, or to the whole reproductive period ending with the FMP; 2) menopausal transition, a period of increased variability in the menstrual cycle before the FMP; 3) perimenopause, encompassing the period immediately before the FMP in which particular features of menopause (i.e., endocrinological, biological and clinical) appear, and the first year after the FMP; 4) postmenopause, the period after the FMP.

Since the WHO criteria for describing menopause development did not precisely define the start of each phase, which in some parts overlap, this resulted in new, more objective guideline criteria agreed upon in the Stages of Reproductive Ageing Workshop (STRAW) (10). The STRAW guidelines, introduced in 2001, defined seven clearly separated phases of women's reproductive ageing (designated with numbers from -5 to +2), not only based on menstrual cycles, but also including endocrine and biochemical parameters, signs and symptoms manifested in other organ systems, and the anatomy of the uterus and ovaries (11). However, these criteria had several limitations. First, they were based only on menstrual bleeding and the increase of FSH levels, without clear criteria regarding the timing of this change or a specific cut-off value that would indicate menopause. In addition, they were applicable only on healthy women, and excluded a significant population of women that either smoked, had a BMI > 30 kg/m^2 or < 18 kg/m^2, got > 10 h/week of aerobic exercise, had an irregular menstrual cycle, had a hysterectomy, or an abnormal uterine or ovarian anatomy (10). Therefore, in order to address some of these limitations, but also to introduce recent advances in the field, the updated criteria, STRAW + 10, were published in 2011 (9). The STRAW + 10 criteria are presented in Table I.

In STRAW + 10 guidelines, menopause is the central point, marked as point zero. Five stages (labelled as -5 to -1) precede, and two (marked as +1 and +2) follow the FMP. The reproductive period covers stages -5 to -3, menopausal transition encompasses stages -2 and -1, and postmenopause covers stages +1 and +2. The subtle changes in the menstrual cycle and variations in follicle stimulating hormone (FSH) levels start towards the end of the late reproductive period, which is for that reason subdivided into stages -3a and -3b. In menopausal transition, the length of the menstrual cycle varies and the level of FSH increases. In its early phase, the menstrual cycle increasingly varies in length by 7 or more days between consecutive cycles, and there are diverse increases in FSH levels. The late menopausal transition is characterized by amenorrhea that lasts 60 days or longer, together with constantly increased levels of FSH > 25 IU/L. This stage ends with the FMP. Early postmenopause, or stage 1, is subdivided into stages +1a, +1b, and +1c, when FSH continually increases and estradiol decreases over a period of two years after the FMP. In the +1a stage, which covers the first 12 months after the FMP, perimenopause ends; +1b refers represents the period of one year before the high FSH and low estradiol levels finally stabilize in stage +1c (12).

In STRAW + 10 staging guidelines, hormone levels are regarded as supportive criteria due to the lack of international standardization of immunoassays and generalized cut-off values, but also due to their cost, invasiveness of sample collection for some of them, and unequal availability in countries with a low socioeconomic status (12). Additionally, FSH levels have been incorporated into various prediction models, but their inclusion alongside age has not significantly enhanced the accuracy of predicting the timing of natural menopause (13). Therefore, reproductive hormone levels should be measured only in particular cases when the clinical presentation does not clearly indicate advancing reproductive ageing.

Table I STRAW + 10 staging system of reproductive ageing (8, 10)

Tabela I STRAW +10 sistematizacija stadijuma reproduktivnog starenja (8, 10)

Menarche ↓ **Menopause** (final menstrual period) ↓

Stages	**-5**	**-4**	**-3b**	**-3a**	**-2**	**-1**	**+1a**	**+1b**	**+1c**	**+2**
Terminology	**Reproductive**				**Menopausal transition**		**Postmenopause**			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Principal criteria Menstrual cycles	variable to regular	regular	regular	subtle changes in flow or lenght	variable length persistent, 7 or more days difference in length of consecutive cycles	60 or more days of amenorrhea				
Supportive criteria										
FSH			low	variable*	variable*↑	>25 IU/L↑	variable ↑		stabilizes	
AMH			low	low	low	low	low		very low	
Inhibin B				low	low	low	low		very low	
Antral Follicle			low	low	low	low	very low		very low	
Descriptive characteristics										
Vasomotor symptoms						likely	most likely			
Urogenital atrophy										symptoms increasing
Stage duration	variable				variable	1–3 years	2 years		3–6 years	until decease

* blood drawn on cycle days 2–5; ↑increased; FSH – follicle stimulating hormone; AMH – anti-Müllerian hormone

Over the last decade, anti-Müllerian hormone (AMH) has emerged as a potential biomarker because of its insensitivity to acute endogenous rise in FSH and estrogen, as well as its presence in the blood in measurable quantities (14–17). Moreover, there have been studies investigating the value of combining AMH with age to predict the time of menopause onset, but there has been no statistically significant improvement in prediction compared to the models that used age alone (18). Therefore, age is suggested to be introduced as a supplementary criterion for the staging of reproductive ageing (19).

Endocrine changes in women's reproductive ageing

The main benchmark of women's reproductive ageing is the shortening of the menstrual cycle due to a decrease in time between the beginnings of menstruation. The first studies performed fifty years ago showed that this was accompanied by a constant increase in FSH secretion, and periods of hypo-estrogenemia which were not followed by significant changes in luteinizing hormone (LH), together with folliculogenesis with sporadic absence of ovulation (20). Furthermore, together with the high menopausal concentrations of LH and FSH and low levels of estradiol (E2) and progesterone, normal maturation of follicles and normal function of the corpus luteum were present (21). There was no evidence that the decline in ovarian function occurred gradually, but it was unpredictable and highly variable. That was explained by the lower pregnanediol and increasing gonadotropin excretion that followed different patterns, causing sporadically anovulatory cycles (22).

During the menopausal transition, FSH concentrations constantly increase and E2 concentrations decrease, while the concentrations of LH and progesterone do not change (Figure 1). This is the reason why menstrual cycles remain ovulatory at this point. The constant decrease in E2 concentrations will cause vasomotor instability and so-called "hot flashes".

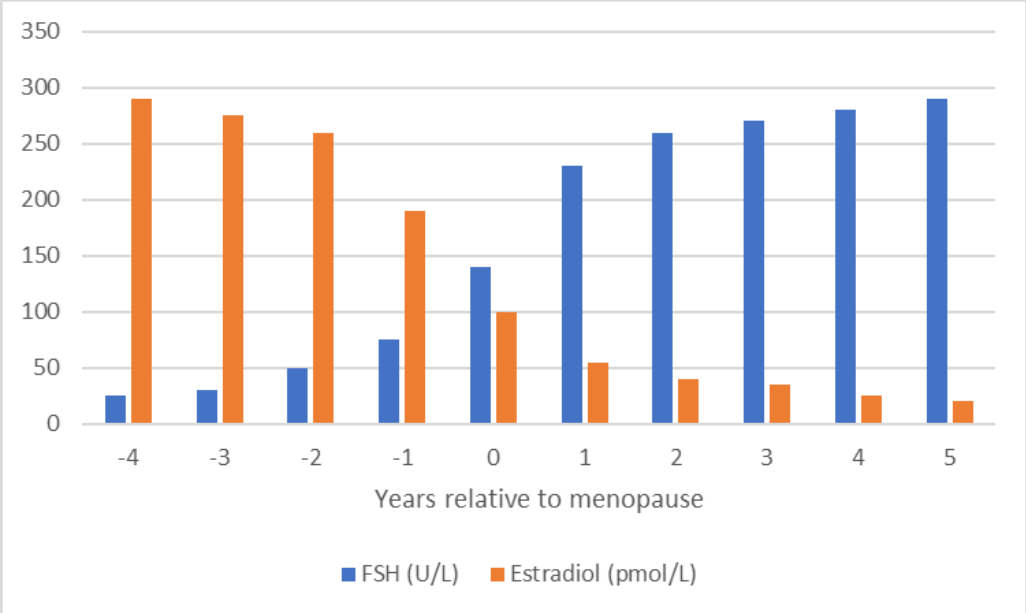

Figure 1. **Changes of geometric means for FSH and estradiol with women's reproductive ageing (23)**

Slika 1. **Promene geometrijskih sredina za FSH i estradiol sa reproduktivnim starenjem žena (23)**

Expected hormone levels in menopause compared to the phases of a normal menstrual cycle are presented in Table II. These values are just illustrative, since neither immunochemistry nor chromatography-mass spectrometry assays for measuring reproductive hormones are standardized, which is the reason why differences in assay accuracy, specificity, imprecision, and calibration exist. Therefore, values obtained from different clinical studies cannot be transferred to clinical practice if a different assay method is used, and generalized cut-off values or reference intervals cannot be established.

Table II Reference intervals for FSH, LH, E2 and progesteron in distinguished phases of menstural cycle and postmenopause (23, 24)

Tabela II Referentni intervali za FSH, LH, E2 i progesteron u različitim fazama menstrualnog ciklusa i postmenopauze (23, 24)

	FSH* (IU/L)	LH* (IU/L)	E2** (pmol/L)	Progesteron** (nmol/L)
Folicular phase	1.4 – 9.9	1.7–15.0	143–1377	≤8.6
Midcycle	0.2 – 17.2	21.9–56.6	345–2797	≤8.6
Luteal phase	1.1 – 9.2	0.6–16.3	176–1615	≤100
Postmenopausal	19.3 – 100.6	14.2–52.3	≤37	≤0.6

*Abbott Architect immunoassay method; **liquid chromatography-tandem mass spectrometry method; FSH - follicle stimulating hormone; LH – luteinizing hormone; E2 – estradiol.

The results from the longitudinal FREEDOM study demonstrated five consecutive endocrine phases of reproductive ageing according to cycle duration and changes in urinary hormone levels (25, 26). In the first stage, the menstrual cycle was regular and the mean urine excretion of FSH in early follicular phase was < 5 IU/L. In the second phase, cycles were still regular, but urinary FSH levels were > 5 IU/L. This was associated with an elevation of FSH in the beginning of the cycle and the shortening of the follicular phase, which was recognized as the first sign of reproductive ageing (27). The third stage was characterized by irregular cycles in terms of length, which were prolonged due to a so-called “delayed response” of ovaries, demonstrating their decreasing ability to react to the change in FSH levels (the time between day 1 of the cycle and the consequent rise of estrogen in the follicular phase is delayed) (27). A possible explanation of the underlying mechanism was the decrease in pregnanediol-glucuronide excretion and elevation of estrogen in the luteal phase (26). In the fourth phase, acyclical ovarian activity was noted, with no evidence of ovulation or luteinization (25–27). The fifth and final stage was associated with ovarian irresponsiveness, together with low estrogen and high gonadotropins levels (25–27).

The role of inhibins

The advancing reproductive age studies of women with irregular menstrual cycles in menopausal transition, that is, with a considerable increase in FSH, increase in LH, irregular changes in E2 (which was either higher or lower than expected), decrease in progesterone, and unpredictable menstrual cycles, led to the discovery of so-called inhibins, i.e., inhibin A, inhibin B and anti-Mullerian hormone (AMH), which helped to explain the basic mechanisms of these hormone disturbances (28).

Inhibins are part of a closed negative feedback loop of the hypothalamic-pituitary-ovarian axis. Their role is the regulation of secretion of pituitary gonadotropins, together with ovarian steroids. Inhibin B is produced by antral follicle granulosa cells, and its levels decrease with the regression in the number of follicles with advanced reproductive ageing. It is the decrease of inhibin B in late reproductive age that provokes the increase of FSH in the follicular phase, which then regulates the production of E2 (28). Inhibins are undetectable in the serum of postmenopausal women, both in physiologically occurring menopause and after bilateral oophorectomy (29, 30).

In a study that compared two groups of older women with a regular menstrual cycle, but with normal and elevated FSH levels, with a group of young women, the levels of inhibin B in the early follicular phase were lower, as well as the levels of inhibin A before the increase of LH in the middle of the cycle, and in the middle of the luteal phase, in the group of older women with elevated FSH levels. The conclusion was that the increase of FSH in the early follicular phase in older women was influenced by lower concentrations of inhibin B in the early follicular phase. Decreased circulating concentration of inhibin A in the luteal phase might also play a role in this process. This remained to be clarified since, as a product of the corpus luteum, it should not inhibit the secretion of gonadotrophins (31–33).

The study that investigated mean levels of FSH, LH and E2 and progesterone in the luteal phase in women with an ovulatory cycle showed an increase in FSH, LH and E2, and a decrease in progesterone, with the progression of the STRAW stages. In the group with an anovulatory cycle, an increase in FSH and LH was emphasized, but not in E2, which became undetectable. Inhibin B levels in both ovulatory and anovulatory cycles decreased gradually with the advancement of the STRAW stages, reaching the lowest levels in late menopausal transition. Inhibin A levels, on the other hand, were correlated with concentrations of E2. These results demonstrated that the decrease in inhibin B, and not in inhibin A, is the principal cause of elevated FSH, and consequently LH levels, with the advancement of reproductive age. Furthermore, low levels of inhibin B indicate a decreasing ovarian follicle pool (34).

Anti-Müllerian hormone

AMH is a dimeric glycoprotein from the family of growth and differentiation factors with a principal role in gender differentiation, directing the development of testes from gonads. After sexual differentiation, Sertoli cells in men and granulosa cells in pre-

antral and small antral follicles in women continuously produce AMH (35, 36). The role of AMH is to inhibit follicle growth stimulated by FSH, and it might be involved in follicle recruitment and selection. AMH does not change through the menstrual cycle or pregnancy, it is not correlated with FSH or E2 concentrations in reproductive age, and its synthesis is not affected by FSH (37, 38).

Over the past three decades, AMH emerged as a potential marker of the ovarian reserve, i.e., of the number of resting primordial follicles in ovaries, and, as such, as a predictive biomarker for post-menopause, when the ovarian storage is finally exhausted (39). The true ovarian reserve can only be determined with histological analysis of ovarian tissue. All other tests – antral follicle count (AFC), which represents the number of developing antral follicles counted by ultrasound, or FSH, which starts to rise with the decline of follicles that produce estrogen, represent surrogate markers (40). Elevated FSH levels relate to the late stage of the advancement of reproductive age. On the other hand, AMH is independent of FSH, and in comparative studies it was proved to be the most promising ovarian reserve surrogate marker for predicting the age when menopause will occur (41, 42).

Even though studies have demonstrated the statistical significance of AMH's individual predictive value, the performance of predictive models based on it should also be considered. Most of the studies showed that the addition of AMH to a predictive model with age improved the model's predictive capability (C-statistics increased from 84% to 92% at most, and at least from 84% to 86%) (39). Another aspect that needs to be considered is the non-proportional predictive effect of AMH with age, i.e., the fact that the predictive potential of AMH added to age alone decreases (43). This may be a consequence of the fact that an older woman has an *a priori* lower chance of early menopause than a younger one. However, we also need to keep in mind that the predictive accuracy of AMH is lower for younger women. Therefore, when using a model based on age and AMH for a younger woman, the predicted age range of entering menopause will be wider. However, this is a limitation related to a single AMH measurement. More reliable information may be provided if the speed of the decrease of AMH over the years is used (44). The results of a recent cohort study show that the predictive value of AMH improved when its decline rate over 18 years was included (45). This cannot be extrapolated to a shorter period because of the high variation of the AMH decrease rate, thus limiting its application in medical practice. Finally, as previously mentioned for reproductive hormones, immunoassays available for the determination of AMH also have different analytical performances due to the lack of standardization and harmonisation, which restricts direct comparison of results obtained on different analytical platforms and the use of unique cut-off values (14). Therefore, if the levels of these biomarkers are measured to monitor reproductive age, it is crucial that these tests should be consistently performed in the same medical laboratory and using the same analytical platform. The implementation of Laboratory Information Systems, which are integrated with each patient's Electronic Health Record, has made follow-up much easier and more reliable in that regard.

Genetic biomarkers

Recent studies employing whole genome sequencing revealed that a considerable number of genes involved in menopause are also included in the processes of DNA repair. This comes as no surprise, considering that the concentration of DNA damage leads to cellular senescence, inability of somatic cells to renew, and eventually to cellular dysfunction, thus leading to cell death, and the whole process is referred to as ageing (46). A similar process of genome degradation happens in the ovaries with the germ cell line, which provokes a systemic response that inhibits the production of sex-steroid hormones, promoting menopause. This is further promoted by the accumulation of DNA damage caused by ageing. All these processes combined lead to ovarian suppression and, finally, menopause (47).

International guidelines have included genetic testing for identification of FMR1 (Fragile X Messenger Ribonucleoprotein 1) carriers and cytogenetic karyotyping for women with premature ovarian insufficiency (48). It was demonstrated that using genetic data together with the recommended diagnostic investigations significantly improved diagnosis of premature ovarian insufficiency, and that it therefore may be used to predict the risk for premature menopause (49).

Hormone replacement therapy in menopause treatment and management

Given the disruptive symptoms and long-term complications associated with hormonal changes during menopause, hormone replacement therapy (HRT) has been recommended to alleviate these issues (50). According to the latest recommendations, for women under 60 years old or within 10 years of menopause onset without contraindications, the benefit-risk ratio of hormone therapy is favourable for treating bothersome vasomotor symptoms (VMS) and preventing osteoporosis. However, for women who start hormone therapy more than 10 years after menopause onset, or those who are over 60 years old, the benefit-risk ratio is less favourable due to increased risks of coronary heart disease, stroke, venous thromboembolism, and dementia. Longer durations of therapy should be considered for documented indications, such as persistent VMS, with shared decision-making and periodic re-evaluation (51). Recent studies, however, suggest that starting hormone therapy early in menopause can be safe and beneficial for long-term use. Additionally, the benefits of initiating hormone therapy later in menopause may still outweigh the risks (52). Although more evidence is needed, applying the principles of personalized medicine mitigates the adverse effects of hormone replacement therapy used to delay and treat menopause symptoms and long-term effects. The biomarkers of menopause will probably have an important role in monitoring the onset of perimenopause and indicating the possible onset of this treatment.

Conclusion

The average age when natural menopause occurs is estimated to be 51 years, when almost the entire primordial follicle pool is exhausted. This ends menstrual cycles, and the FMP represents the beginning of natural menopause. However, the beginning of

menopausal transition happens before this, and it tends to vary among different races and ethnicities and under the influence of sociodemographic and lifestyle factors. The estimation of age when natural menopause will occur is important for cancer survivors, women with suspected premature ovarian insufficiency or early menopause based on their family history, and when delaying the conception of the first child. Moreover, the timing of natural menopause is a clinically important indicator of longevity and a risk factor for morbidity and mortality. Apart from age and menstrual cycle length and regularity, biomarkers related to menopause play a significant role in the confirmation of its onset, but also in the recognition and prediction of its premature beginning.

Acknowledgments

This research was supported by the Science Fund of the Republic of Serbia, Grant No. 7741659, HIgh-density lipoprotein MetabolOMe research to improve pregnancy outcome–HI-MOM. The authors appreciate the support from the Ministry of Science, Technological Development and Innovation, the Republic of Serbia (Grant Agreement with the University of Belgrade Faculty of Pharmacy, No. 451-03-65/2024-03/200161 and No. 451-03-66/2024-03/200161).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

SJ and MP equaly contributed to the study's conception and design. SJ was responsible for literature review, writing and original draft preparation. Both authors have read and agreed to the published version of the manuscript.

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Biomarkeri menopauze

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Kratak sadržaj

Prirodna menopauza se definiše kao trajni prestanak menstruacije usled gubitka folikularne aktivnosti jajnika. Ova značajna faza u reproduktivnom starenju žena ima značajne efekte na distribuciju masti, dislipidemiju i neurodegeneraciju. Ove promene doprinose povećanom riziku od demencije i kardiovaskularnih bolesti kako žene stare. Procena starosti u kojoj će nastupiti prirodna menopauza je ključna za preživele od kancera, žene sa porodičnom istorijom preuranjene insuficijencije jajnika ili rane menopauze i one koje odlažu prvu trudnoću. Pored toga, vreme prirodne menopauze je važan klinički pokazatelj dugovečnosti i faktor rizika za morbiditet i mortalitet. Osim starosti i karakteristika menstrualnog ciklusa, biomarkeri koji se odnose na menopauzu su od suštinskog značaja za potvrđivanje njenog početka i predviđanje njenog preranog nastupanja.

Ključne reči: menopauza, STRAW kriterijumi, folikulostimulirajući hormone FSH, inhibin B, anti-Milerov hormon, AMH