Ann Med Res

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Annals of Medical Research

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The relation of anti-Mullerian hormone with final menstrual period and menopausal symptoms in the menopausal transition

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ARTICLE INFO

Keywords:
Anti mullerian hormone
Menopause
Menstrual irregularities
Perimenopause
Pre-menopausal period

Received: Jul 02, 2022
Accepted: Sep 21, 2022
Available Online: 22.10.2022

DOI:
10.5455/annalsmedres.2022.07.200

Abstract

Aim: To determine the role of anti-mullerian hormone (AMH), menstrual hormones and symptoms in predicting final menstrual period (FMP) in menopausal transition (MT).

Materials and Methods: Eighty-two women aged 37-50 years in MT with any degree of menopausal symptoms were included in this prospective study. At the beginning and at the end of two years; serum AMH and menstrual hormone (Follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol) levels were measured, Menopause Rating Scale (MRS) scores were recorded, then compared. The cut-off of initial AMH level to detect FMP was calculated.

Results: Of the 82 patients that were followed for two years, thirty six were in early MT, forty-six were in late MT at the initial. At the end of two years, 15.8 % (13/82) of patients were found to have reached menopause. The rate of AMH decline in two years did not differ significantly between patients who had and did not go through menopause. According to ROC analysis, in patients with menopause the optimal threshold value of baseline AMH to predict FMP over the next 12 months was 0.085ng/ml (area under curve :0.873, 95% CI: 0.726-0.948, $p<.001$). There was a significant positive correlation between AMH change rate and MRS score change in two years ($r=0.462$, $p<0.001$). A significant negative correlation was observed between baseline AMH levels and second year MRS scores ($r=-0.56$, $p<0.001$). Multivariate regression analysis showed no significant independent effect of age, BMI, baseline AMH level, FSH, estradiol, baseline MRS score on AMH change.

Conclusion: In MT, serum AMH level and menopausal symptom scores can help predict FMP and assist in the appropriate management of the MT period to provide women with a long-term healthy life.

Introduction

Anti-Mullerian hormone (AMH) is defined as a marker released by preantral and early antral follicles and reflecting the size of primordial follicle pool. It is known that in adult women, AMH levels gradually decrease as the primordial follicle pool decreases with age [1].

During reproductive period, the number of oocytes gradually decreases with age. The release of inhibin B from the ovary decreases due to the decreased number of oocytes, thus the negative feedback effect on follicle stimulating hormone (FSH) is reduced. Increased FSH causes increased utilization of follicles and accelerates follicular loss. Towards the end of the reproductive age, the number of primordial follicles falls below a critical value, mature oocyte cannot be produced, therefore menstrual bleeding does not occur. Absence of menstrual bleeding for twelve consecutive months is defined as menopause [2].Although the clinical diagnosis of menopause is made one year later, it actually occurs during the last menstrual period (FMP). The time until FMP is defined as menopausal transition (MT).

During MT, menstruation is irregular and fertility is low, various symptoms occur due to estrogen deficiency. Somatic symptoms such as sleep disorders, hot flashes; psychological symptoms such as irritability, lack of concentration and depression; urogenital symptoms such as dysuria, incontinence and dyspareunia could have negative impacts on women's quality of life. In addition, changes in lipid profile and body fat distribution that could be associated with cardiovascular diseases can be observed in women during MT. Decreased bone mineral density, which started several years before FMP, may be associated with the risk of osteoporosis [3]. On the other hand, risks of breast and endometrial cancers increase with age at menopause [4,5].

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Based on studies published in the last decade, serum AMH could be associated with time to menopause and age of menopause [6-10]. It has been reported that the rate of decrease in AMH may be effective in estimating the age of menopause [11]. In another study, it was stated that the rate of decrease in AMH did not contribute to the prediction of menopause, but age-specific AMH levels could predict age of menopause [12]. The literature about relationship between AMH level and age of menopause seems contradictory. Apart from this, the relationship between AMH level and menopausal symptoms is also unclear.
Being able to predict the age of menopause in women can help to define MT, to better evaluate the individual differences in this period, and to prevent or manage the problems that may be associated with this period. For this prediction, evaluating menstrual cycle patterns, serum AMH levels and menopausal symptoms together may be useful. Therefore, this prospective study aims to evaluate the relationship of AMH level with menopausal symptoms and its role in predicting FMP in women in MT.

Materials and Methods

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki in a tertiary hospital gynecology clinic. Local ethics committee approval (Bursa Yuksek Ihtisas Clinical Research Ethics Committee, 2011-KAEK-25 2021/04-07) and informed consents from each patient were obtained. Patients aged between 35-50 years of who presented to our gynecology clinic with any menopausal symptoms more than six months were invited to this prospective cohort study. Non-probability sampling method was used. Menstrual irregularity, hot flushes, sleep disorders, urinary symptoms due to atrophy, vaginal dryness and irritability were accepted as menopausal symptoms.
Patients with uterus, no previous ovarian surgery, no systemic disease, no hormone replacement therapy, no oral contraceptive or any other medication were included in the study. Smokers, patients with endometrioma and patients with previous COVID- 19 infection were excluded from the study.
A total of 89 patients who met the inclusion criteria followed up for two years. Demographic data, medical histories, physical and gynecological examination findings, menstrual cycle pattern of patients in the last year were recorded at initial admission. In follow-up, seven patients were excluded because three patients could not be reached, one patient had hysterectomy, one patient had COVID-19 infection, and two patients received HRT (Figure 1). The remaining 82 patients were divided into two groups as early menopausal transition (EMT) group and late menopausal transition (LMT) group according to the 2011 Stages of Reproductive Aging Workshop (STRAW) criteria [13]. According to the menstrual cycle pattern; those with regular cycle (n=36) were defined as EMT, and those with oligomenorrhoea (n=46) were defined as LMT. Menopause defined as amenorrhea for 12 months with no other underlying cause.
The nationally valid Menopause Rating Scale (MRS) was administered to the patients for the assessment of menopausal symptoms at baseline and at follow-up two years later, in a way that they could answer alone in a quiet room [14]. MRS is a 5-point Likert-type scale consisting of 11 questions that evaluates the woman in three subscales: somatic, psychological and urogenital (Table1). The total score is calculated by summing the subgroup scores. MRS change was calculated by subtracting the initial total score from the second year total score.
Venous blood samples were obtained from the antecubital vein after fasting - in early follicular phase for premenopausal patients and on any day for postmenopausals- at the beginning of the study and at the follow-up 2 years later. FSH, luteinizing hormone (LH), estradiol (E2), total testosterone levels were measured using an immunoassay analyzer (Cobase602, Roche Diagnostics GmbH, Mannheim, Germany). After serum was taken into lithium heparin tubes, AMH levels were measured by electrochemiluminescence Immunoassay (ECLIA) method with the Elecsys reagent kit (Elecsys Corporation, Lenexa, KS, USA) using the Cobas device (Roche Diagnostics, Risch-Rotkreuz, Switzerland). The range of detection of AMH was 0.01–23 ng/mL, and the limit of detection (LOD) was 0.01ngml.
AMH decline rate was calculated by subtracting initial AMH from 2nd year AMH and dividing this difference by initial AMH and expressed as a percentage. The rate of estradiol decline was also calculated as defined.

Statistical analysis

The sample size was calculated using G-power software (version 3.1) as a total of 72 patients with alpha=0.05 and power 80% based on the study of Tehrani et al [7]. Data were analyzed using the IBM SPSS Statistics 22.0 ©Copyright SPSS Inc. software (Chicago,IL.USA).Kolmogorov-Smirnov test was used to evaluate the normality of the variables. Data with normally distribution were presented as mean± standard deviation (SD), data with non-normally distribution as median (min-max).Categorical variables were presented with frequency (n) and percentage (%). Parametric variables were compared using independent samples t-test, and the Mann-Whitney U test was used where parametric test assumptions were not provided in two-group mean comparisons. In the analysis of categorical variables, Fisher's exact test was used if the expected frequencies of more than 20% of the cells were less than five; otherwise Pearson's Chi-square test was used. Because of the non-normally distribution, Wilcoxon test was used for dependent variables. Since the parameters did not show normal distribution, Spearman correlation analysis was used in the relations of the variables with each other. A multivariate linear regression analysis was performed by enter method to clarify the independent effects of age, BMI, initial AMH level, FSH, estradiol, initial total MRS score on the AMH decline rate. The p value and the coefficient of determination (R^2) were used for the validity of model. Receiver operating characteristic (ROC) curve analysis was performed and area under curve (AUC) was calculated to find the initial AMH level to predict FMP and to determine the sensitivity and specificity of this value, p value $<.05$ was considered statistically significant.

Results

At the end of 2-year follow-up, in 82 patients, changes in variables were as follows (Table 2). Mean age of patients was 40.62±3.28 years. Baseline characteristics and hormone levels of groups were given in Table 2. Thirty-six of 82 patients were in the EMT group, 46 were in the LMT group. While there was no difference between the groups in terms of BMI and gravida, patients in EMT group were younger than those in LMT group (39.11±2.42 vs. 41.80±3.40 p<0.001) (Table 3). 2nd year AMH levels were lower and MRS scores were higher in LMT group, but there was no significant difference in AMH decline rate between groups (47% vs. 51% p=0.205) (Table 3).

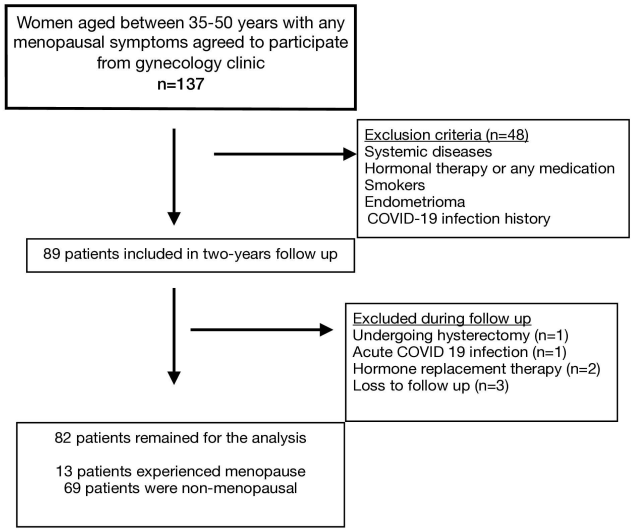

Figure 1. Flowchart of the study population.

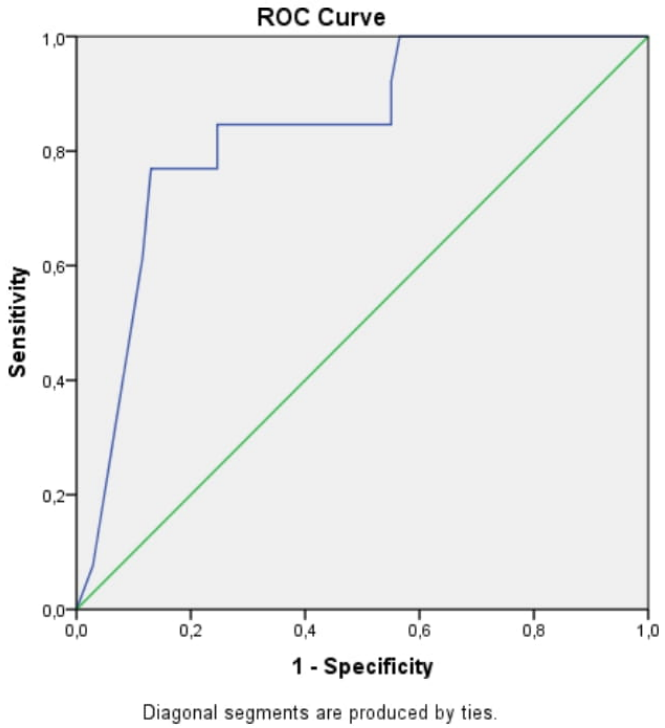

Figure 2. Receiver operating characteristic (ROC) curve for initial AMH level to detect final menstrual period.

In follow-up, 13 patients were diagnosed as menopause. All 13 patients were in LMT group. Initial and second year AMH levels of menopausal patients were significantly lower than non-menopausal. The AMH decline rate showed no significant difference between menopausal and non-menopausal (p=0.814) (Table 4).

ROC curve analysis showed that the area under curve was 0.873 (95% CI:0.726- 0.948, p <.001) for initial AMH level. The optimal cut-off value of initial AMH level to predict FMP occurring over the next 12 months was calculated as 0.085 ng/ml with a specificity of 78.3% and a sensitivity of 76.9% (shown in Fig. 2). The accuracy rate of this cut-off was 78%, the positive predictivity was 60%, the negative predictivity was 94.7%.

A significant negative correlation was observed between initial AMH levels and second-year total MRS scores (r= - 0.566, p <0.001). The AMH decline rate and the change in total MRS score showed a significant positive correlation (r = 0.462, p<0.001). There was no correlation between initial estradiol levels and second year total MRS scores (r =-.084, p= 0.45) (Table 5).

Multivariate linear regression analysis revealed no significant independent effect of age, BMI, initial AMH, FSH, estradiol, initial total MRS score on the change in AMH level (p=0.913, R2 = 0.027). The β-values (95% confidence intervals) and p-values were as follows: Age -0.006, p = 0.96; BMI -0.11 p=0.32; initial AMH-0.02 p=0.86; FSH-0.02, p=0.87; E2 <0.001, p=0.99; initial total MRS score -0.13, p=0.35 (Table 6).

Discussion

In the current study, women with complaints about menopause, who are in MT period were followed up for two years in terms of AMH levels and menopausal symptoms. At the end of two years, 15% of the subjects were diagnosed as menopause. Considering the baseline and second year AMH levels, we reported significant differences between EMT and LMT groups. In addition, AMH levels were significantly lower in menopausal patients at first admission and at 2nd year compared to non-menopausal patients. However, AMH decline rate was different neither for the EMT-LMT groups, nor for the menopausal-non menopausal patients.

Similarly to our results, in a study including fifty women with a mean age of 42 years, it was concluded that the AMH decline rate was not associated with the timing of menopause [15].Gohari et al. reported that low AMH level and advanced age are the most important prognostic factors for the timing of menopause [16]. In our study, the mean initial AMH level was low and the mean age was high for the patients defined as menopause in follow-up.

The AMH value may have a role in predicting ovarian aging in women with menopausal complaints. We determined that a baseline AMH level below 0.085 ng/ml predicted the onset of FMP within 12 months with a sensitivity of 76.9% and a specificity of 78.3%. Despite having comparable baseline AMH levels to ours (0.49ng/dL vs 0.44ng/dL), according to Tehrani et al, only 1 in 10 women in the late reproductive stage with an initial AMH > 0.39ng/dl would enter menopause within 6 years [7]. In

Table 1. Menopause Rating Scale (MRS) (14).

Symptoms	Scores				
	0	1	2	3	4
1. Hot flashes, sweating (episodes of sweating)					
2. Heart discomfort (unusual awareness of heart beat, heartskipping, heartracing, tightness)					
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through the night, waking up early)					
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)					
5. Irritability (feeling nervous, inner tension, feeling aggressive)					
6. Anxiety (inner restlessness, feeling panicky)					
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)					
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)					
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)					
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)					
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)					

Table 2. Comparison of the hormone levels and Menopause Rating Scale Scores of patients in2 years follow-up.

	At initial application (n=82)	At the end of 2nd year (n=82)	P*
AMH (ng/mL)	0.44 (0.01-5.29)	0.06 (0.01-2.98)	<0.001
FSH (mIU/mL)	11.50 (2.33-112.80)	15.58 (1.45-138.50)	<0.001
LH (IU/L)	6.40(1.59-64.21)	11.53 (1.62-77.60)	<0.001
E2 (pg/mL)	52.11 (10.33-154.46)	35.06 (5.00-128.10)	<0.001
Total testosteron (ng/dL)	17.96 (2.50-84.79)	21.42 (0.82-61.39)	0.02
PRL (mcg/L)	8.92 (3.30-32.30)	9.94 (3.96-23.54)	NS
TSH (mU/L)	2.0 9 (0.01-6.30)	1.85 (0.07-6.83)	NS
Total MRS score	12 (4-24)	16.50 (6-29)	<0.001

AMH: Anti-Mullerian hormone, FSH: follicle-stimulating hormone, LH: luteinizing hormone, E2: estradiol, PRL:prolactin, TSH: thyroid-stimulating hormone MRS: menopause ratingscale *Wilcoxon test was used. Values are given as median (range). p<0.05 was considered significant.

that study, the mean age, follow-up period and therefore the rate of being diagnosed with menopause of the patients were higher than our study (40.8 % vs 15.8%).

In a recently published study, it was emphasized that an AMH value>100 pg/mL in women younger than 48 years, with a positive predictive value of 97%, ensures that FMP will not occur within the next 12 months [17].This cut-off is higher than the threshold in the current study. However, data on women younger than 42 years of age were not included in that study, while individuals between the ages of 35-50 were included in our study. Besides that, the average age of menopause in populations varies around the world and it is known that the average age of menopause in our country is lower than in the world [18].These may be the reasons why this study's threshold for predicting menopause was higher than ours.

To the best of our knowledge, this is the first article in the literature in which laboratory and clinical findings are evaluated together to determine the menopausal age of women in the MT period. In this context, in addition to measuring AMH and other hormone levels, the severity of the menopausal complaints of the patients was determined using MRS. When AMH and estradiol levels were evaluated separately in terms of their relationship with MRS scores, we showed a significant negative correlation between initial AMH levels and second year total MRS scores and a significant positive correlation between the rate of AMH decline and the change in total MRS score. Nevertheless, we could detect no correlation between initial estradiol levels and second year total MRS scores. Based on this, it could be concluded that menopausal symptoms are more associated with changes in AMH levels than changes in estrogen levels. Although the possible mechanism of some menopausal symptoms is known as estrogen deficiency, these findings can be interpreted as that AMH level may be more effective than estradiol in predicting the severity of symptoms in the follow-up of women in the MT period.

In addition, 2-year prospective follow-up of the patients, the use of a validated scoring system, the exclusion of women using drugs or smoking, the evaluation of serum AMH and other reproductive hormone values, the collection of serum samples in the early follicular phase and measurement on the same day without storage, the calculation of a threshold AMH value, which could predict the age of menopause within 12 months, are the other strengths of the study. The limitations of our study are the limited number of patients with menopause and the relatively short follow-up period. Although AFC measurement in advanced age is not recommended due to the inability of ultrasonography to distinguish atretic or small follicles,

Table 3. Comparison of the demographic characteristics, hormone levels and Menopause Rating Scale scores of patients.

	Late Menopause Transition- oligomenorrheic cycle (n=46)	Early Menopause Transition- regular cycle (n=36)	p
Age	41.80 ± 3.40	39.11±2.42	<0.001
BMI (kg/m^2)	26.14±4.05	26.20±3.08	NS
Gravida[a]	2(0-6)	2(0-5)	NS**
Paritya	2(0-4)	1(0-3)	0.04**
Initial MRS subscale scores[a]			
Somatic	6.5 (3-12)	3 (1-10)	<0.001**
Psychological	6 (2-9)	4 (2-7)	<0.001**
Urogenital	4.5 (0-9)	2 (0-6)	<0.001**
Initial total MRS score	15.26 ±4.33	8.86±3.22	<0.001
Second-year MRS subscale scores[a]			
Somatic	9 (4-13)	4 (2-11)	<0.001**
Psychological	7 (4-10)	4.5 (2-9)	<0.001**
Urogenital	3 (0-7)	1.5 (0-4)	<0.001**
Second-year total MRS score	20.45 ±4.81	12.41±4.61	<0.001
Hormone levels[a]			
FSH(mIU/mL)	17.48 (3.22-112.80)	6.41 (2.33-21.88)	<0.001**
E2 (pg/mL)	52.37 (10.33-134.10)	52.11 (28.38-154.46)	NS**
LH(IU/L)	7.17 (1.89-64.21)	4.86 (1.59-13.80)	<0.001**
Total testosteron (ng/dL)	17.96 (9.62-84.79)	17.98 (2.50-56.02)	NS**
PRL(mcg/L)	9.03 (3.30-32.30)	8.52 (4.42-26.11)	NS**
TSH(mU/L)	2.14 (0.01-6.30)	2.05 (0.05-5.60)	NS**
InitialAMH (ng/mL)	0.32±0.46	1.26±1.09	<0.001
Second-year AMH(ng/mL)	0.10±0.20	0.62±0.64	<0.001
AMH decline rate[a]	51 (-50.98)	47 (0-98)	NS**

BMI: body mass index, MRS: menopause rating scale, FSH: follicle stimulating hormone, E2: estradiol, LH:luteinizing hormone, PRL: prolactin, TSH: thyroid stimulating hormone AMH: anti mullerian hormone. Student t test was used and values are given mean ±SD unless otherwise noted. ** Mann whitney U test was used avalues are given median (range).

Table 4. Hormone levels and change rates in women with and withoutmenopause.

	Non-menopausal status (n=69)	Menopausal status (n=13)	p*
Initial FSH (mIU/mL)	9.92 (2.33-91.9)	28.58 (4.82-112.80)	<0.001
Initial E2 (pg/mL)	54.00 (10.33-154.46)	32.60 (11.80-134.10)	0.008
Second year E2 (pg/mL)	39.26 (5.00-128.10)	12.02 (5.00-60.75)	<0.001
Initial AMH (ng/mL)	0.59 (0.01-5.29)	0.02(0.01-0.86)	<0.001
Second year AMH (ng/mL)	0.15 (0.01-2.98)	0.01 (0.01-0.03)	<0.001
AMH decline rate	50 (0-98)	50 (-50 - 98)	NS

Wo: without, w: with, FSH: follicle-stimulating hormone, AMH: Anti mullerian hormone, E2:estradiol. *Mann-Whitney U test was used. Values were given as median (range).

Table 5. Correlations among variables.

	r	p
2nd year total MRS scores- initial AMH level	-0.566	<0.001
2nd year total MRS scores- initial estradiol level	-0.084	<0.001
AMH decline rate- change in total MRS score	0.462	0.45

MRS: Menopause rating scale, AMH: anti mullerian hormone. r: correlation coefficient. p <0.05 was considered significant.

the fact that AFC was not recorded in this study can be considered a limitation of the study [19].

Conclusion

In conclusion, a single AMH measurement could predict FMP in women in the LMT period. Menopausal symptoms appear to be related to AMH level and AMH decline rate rather than estradiol. These results might play a role in improving screening and prevention strategies for menopausal health problems. The use of AMH in the treatment of menopausal symptoms may be considered in future studies. However, long-term prospective studies on the subject are needed.

Conflict of interest

The authors declare no conflict of interest

Table 6. Multivariate linear regression analysis to identify the factors that could affect anti-mullerian hormone decline rate.

	β	Odds ratio (95% CI)	p
Age, years	-0.006	0.95 (0.81-1.12)	0.96
BMI, kg/m^2	-0.11	1.04 (0.92- 1.18)	0.32
Initial AMH level (ng/mL)	-0.02	1.68 (0.82-3.44)	0.86
Initial FSH (mIU/mL)	-0.02	1.04 (0.99- 1.09)	0.87
Initial estradiol (pg/mL)	<0.001	1.00 (0.99- 1.02)	0.99
Initial total MRS score	-0.13	1.04 (0.92- 1.18)	0.35

BMI: body mass index, AMH: anti mullerian hormone, MRS: menopause rating scale, FSH: follicle stimulating hormone. CI: confidence interval (Model statistics: p=0.913, R^2 =0.027).

Authors contributions

Conception, Design: FNA; Supervision: NKE; Data collection/Processing: FNA, NKE; Analysis/Interpretation: FNA, NKE; Literature review: FNA, NKE; Writing: FNA, NKE; Critical review: FNA, NKE.

Ethics approval

Local ethics committee approval (Bursa Yuksek Ihtisas Clinical Research Ethics Committee, 2011-KAEK-25 2021/04-07).

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