

PREDICTORS AND PROTECTORS OF PATHOLOGICAL MENOPAUSE

ABSTRACT

A prospective study of 1484 women aged 35-70 years was conducted, which were divided into 3 groups - late reproductive, perimenopausal and postmenopausal. Menopausal syndrome (MS) was detected in 1369 (93.3%) women. Every third woman in peri- and postmenopause had a moderately severe MS. The metabolic imbalance worsened more as the severity of the MS increased, rather than with increasing age. Predictors of pathological menopause are identified - these are the main components of the metabolic syndrome (diabetes mellitus, hypertension, obesity); uterine fibroids, as well as urbanization and higher education. The protective factors for the development of the MS was the absence of the fact of marriage (single), medical education and waist circumference of 80 cm or less.

Key words: late reproductive stage, perimenopause, postmenopause, menopause, menopausal syndrome, metabolic syndrome.

INTRODUCTION

The demographic situation in the world is characterized by an increase in the number of women who have reached menopause from 30% in developed countries, to 50% in developing countries [1-3]. The state of health of women, starting from late reproductive to postmenopausal age, is subject to the generally recognized mechanisms of aging, due, among other things, to increasing estrogen deficiency. The hormonal imbalance that occurs during the menopausal transition leads to the emergence of vasomotor and psycho-emotional, metabolic-endocrine symptoms with the formation in 30-85% women of the menopausal syndrome (MS) [4-7], and in 13-53% of metabolic syndrome (MetS) [8-10]. Domestic researchers note that MS occurs in 20–40% of women [11, 12]. In 51% of women in the period of

31 menopause, there is a severe course of MS, which requires urgent medical
32 treatment. [12]. Burdened somatic and obstetric-gynecological history, as well as a
33 cascade of pathological conditions caused by the extinction of ovarian function,
34 provides a high comorbidity [13]. The sociocultural, ethnic characteristics of
35 women in the region of Central Asia, and in particular, Uzbekistan, require a
36 comparative assessment of therapeutic and preventive measures in this period of
37 life.

38

39 The purpose of the study was to conduct a comparative assessment of the
40 health status of women in the late reproductive, perimenopausal and
41 postmenopausal periods, as well as to determine factors contributing to the
42 pathological course of menopause.

43

44 **MATERIALS AND METHODS**

45 1484 women (mainly Asian nationality 1381 - 93.1%) aged 35-70 years
46 were examined. Depending on the age, women were divided into 3 groups: Group
47 I, (n = 618) were women aged 35-44 who are conditionally in the late reproductive
48 period; Group II, (n = 627) women 45-54 years old - in perimenopause and Group
49 III, (n = 239) women 55-70 years old - in postmenopause. All women underwent
50 general clinical examination (general examination, anthropometry, changing causal
51 blood pressure (BP)) and special gynecological examinations. In order to detect
52 signs of MS, and determine its severity, the Modified Menopausal Kupperman
53 Index (MMKI) was used. 256 women were determined by the colorimetric method
54 on the analyzer firm "Hoffman-La-Roche" determined lipid fractions of blood
55 serum: cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL),
56 low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol
57 (VLDL) and fasting glucose level. The atherogenic coefficient (AC) was calculated
58 by the formula A.N. Klimov: $AC = (Cholesterol - HDL) / HDL$.

59 Statistical processing of the results was performed using the software
60 package Statistica 6.0. The significance of differences in groups was assessed

Formatted: Font: Not Bold

Comment [M1]: Please check

61 | using Student's t-test, the differences were considered significant at $P \leq 0.05$. To
62 | identify predictors and protectors of the pathological course of menopause (MS), a
63 | comparative assessment of the results of the study in women with CS and without
64 | it was carried out, the odds ratio (OR) was calculated.

65

66 | RESULTS

67 | The somatic status of women was most severely affected by goiter - in 588
68 | (39.6%), gastritis - in 334 (22.5%), chronic kidney diseases - 313 (21.1%), anemia
69 | - 246 (16.6%), and this pathology was significantly more common in women in
70 | the late reproductive period ($P \leq 0.05$). While hypertension 272 (18.3%), depression
71 | 238 (16.0%), diseases of the respiratory system 220 (14.8%) and colitis 217
72 | (14.6%) were more common in peri- and especially postmenopausal (P ≤ 0.05).

73 | The overwhelming majority of women had pregnancy and childbirth in history -
74 | 1432 (96.5%), 1046 (70.5%) had artificial abortions and 326 (22%) had
75 | miscarriages. The average number of pregnancies was 5.1 ± 0.06 , childbirth -
76 | 3.0 ± 0.03 , abortions - 2.6 ± 0.05 , miscarriages - 1.4 ± 0.05 . The ratio of birth:
77 | abortion: miscarriage averaged 2.5:2:1. Every tenth (10.8%) woman with a history
78 | of chronic salpingo-oophoritis suffered, uterine myoma was diagnosed in 175
79 | (11.8%) (significantly more often in perimenopause - in 105 (16.7%)), abnormal
80 | uterine bleeding was observed in 97 (6.5%), in perimenopause - in 54 (8.6%). The
81 | average age of menopause (last menstrual period) was 46.7 ± 0.2 years, the duration
82 | of postmenopause was 6.8 ± 0.3 years (1-38 years). Surgical menopause was in 92
83 | (6.2%) women, premature - in 49 (3.3%), early - in 150 (10.1%).

84 | The clinic of the MS was observed in almost all women - 1369 (93.3%),
85 | while the 1 st grade MS was more common: in women of the 1st age group - in
86 | 426 (68.9%) (%) (Tabl. 1). The average severity of MS in peri- and
87 | postmenopausal women was were observed 1.5 times more often - in 212 (33.8%)
88 | and 83 (34.7%), respectively, compared with women aged 35-44. Severe MS was
89 | noted much less frequently in all studied groups and amounted to 1.2% - in just 18
90 | patients. The MMKI score showed a predominance of the clinic of neurovegetative

Comment [M2]: Please check the spelling

Comment [M3]:

Comment [M4]: Please check the spelling

91 (18.9 ± 0.3 points) and psycho-emotional (8.2 ± 0.2 points) disorders in
 92 perimenopausal women, while metabolic and endocrine disorders were most
 93 pronounced in postmenopausal (5.3 ± 0.2 points). The total MMKI score was most
 94 pronounced in women in the peri- (31.6 ± 0.5) and postmenopausal (31.7 ± 0.79),
 95 compared with women of the late reproductive period (P≤0.05).

96 We carried out a comparative analysis of the frequency of the components of
 97 the MetS depending on age (Table 2) and on the presence/absence of signs of MS
 98 (Table 3). The average waist circumference for women aged 35-44 years was
 99 87.3±0.8 cm, whereas for women the menopausal transition and postmenopause
 100 was were significantly (P<0.05) higher and amounted to 90.6±0.9 and 94.6±1.4
 101 cm, respectively.

102 Table 1.

103 The frequency of menopausal syndrome in severity, (abs,%) and the total
 104 score MMKI, (M±δ)

	group I, n=618		group II, n=627		group III, n=239		General, n=1484	
	abs	%	abs	%	abs	%	abs	%
without MS	52	8,4±1,1	52	8,3±1,1	11	4,6±1,4	115	7,7±0,7
MS	566	91,6±1,1	575	91,7±1,1	228	95,4±1,4	1369	92,3±0,7
MS I	426	68,9±1,9	355	56,6±2,0	142	59,4±3,2	923	62,2±1,3
MS II	133	21,5±1,7	212	33,8±1,9	83	34,7±3,1	428	28,8±1,1
MS III	7	1,1±0,4	8	1,3±0,4	3	1,3±0,7	18	1,2±0,3
The total score MMKI	28,1±0,44 ** *** ***)		31,6±0,46* ****)		31,7±0,79* ****)		30,1±0,30 * ** ***)	
	(12-73)		(12-70)		(12-65)		(12-73)	
MODA	27		30		32		29	
MEDIA	33		30		20		33	
NA								

Comment [M5]:

Comment [M6]: ?

Comment [M7]: Include P values in legend

*P≤0.05 compared with 1 group
 ** P≤0.05 compared with group 2
 *** P≤0.05 compared with group 3
 ****P≤0.05 compared with the general group

105 The frequency of women with waist circumference >80 cm (criterion for
 106 women in the Asian region) was 69.7; 75.9% and significantly more frequently in
 107 postmenopausal women - 87%, respectively, in groups.

108 The presence of MS significantly influenced the waist circumference
 109 indicator - there was a progression of severity of abdominal obesity with increasing
 110 severity of MS. Thus, waist circumference in women with MS I and III degrees
 111 was significantly more - 91.8±1.0 and 103.8±4.5 cm compared to women without a
 112 pathological course of menopause - 86.4±2.2 cm. The frequency of abdominal
 113 obesity in women with MS was recorded significantly more often - from 75.2%
 114 with grade 1 MS to 87.5% - with severe, whereas without MS, an frequency the
 115 waist circumference of more than 80 cm was observed in 68.4%.

116 Table 2.

117 The average values of metabolic syndrome - circumference waist, blood
 118 pressure (BP) and lipid fractions in women in groups, M±δ

Indicators	group I, n=618	group II, n=627	group III, n=239
Waist circumference, sm	87,33±0,80	90,55±0,85*	94,64±1,38* **
Sistolic BP, mm Hg.	121,3±3,2	130,6±4,1	138,1±3,0*
Diastolic BP, mm Hg.	73,5±3,3	83,3±3,9*	88,6±0,9 *
n=256	n=51	n=118	n=96
Cholesterol, mmol /l	4,96±0,11	5,45±0,08*	5,48±0,08*
TG, mmol/l	1,47±0,07	1,69±0,06*	1,62±0,07
HDL, mmol /l	1,21±0,06	1,14±0,04	1,17±0,04
LDL, mmol /l	3,11±0,10	3,48±0,08*	3,51±0,09*
AC, conv. unit	3,69±0,19	4,12±0,14	4,01±0,17

Glucosa, mmol /l	4,71±0,33	5,55±0,19*	5,68±0,21*
------------------	-----------	------------	------------

*P≤0.05

** P≤0.05

difference significantly compared with group 1
compared with group 2

119

120 Indicators of blood pressure increased with increasing age and on average
121 were: systolic BP - from 121.3±3.2 to 138.1±3.0 mm Hg. and diastolic BP - from
122 73.5±3.3 to 88.6±0.9 mm Hg. The frequency of women with BP higher than
123 135/85 mm Hg. also increased with increasing age - from 20.6% to a significant
124 increase in the frequency in the postmenopausal women to 47.3%.

125 Comparison of BP in women with MS also showed a distinct increase
126 depending on the severity of MS. The frequency of high BP (above 135/85 mm
127 Hg) as the degree of severity increased, the MS increased exponentially and
128 amounted to 21.7% with mild severity of MS, 46.5 and 77.8% with moderate and
129 severe the severity of menopausal disorders.

130 In 265 women, serum lipid fractions were examined. The results showed an
131 increase in the average levels of cholesterol (from 4.96 to 5.68 mmol / l), T (from
132 1.47 to 1.62 mmol / l), LDL (from 3.11 to 3.51 mmol / l), P <0.05), CA (from 3.69
133 to 4.1) and an unreliable decrease in the level of HDL (1.21 to 1.17 mmol / l) in the
134 blood serum of women depending on age. Starting from the perimenopausal age,
135 there is a clear tendency for the development of dyslipidemia and its aggravation in
136 postmenopausal women. Analysis of the incidence of dyslipidemia showed a
137 significant (P <0.05) increase (almost twice) in the number of women with
138 elevated levels of LDL (41.2% in late reproductive and 71.9% in postmenopausal
139 women) and AC (31.4 and 57.3%, respectively). The glyceic profile was
140 represented by hyperglycemia in a small number of women (from 2 to 6.3% in
141 groups) and impaired glucose tolerance (from 3.9 to 10.4%), while the average
142 glycemia did not reach significant indicators - 6.1 mmol/l Another picture was
143 noted in women with MS. Every 10th women (9.1%) with grade 2 MS had
144 hyperglycemia, a violation of glucose tolerance was observed in every 6th (15.2%)
145 and every 4th (23.1%) women with MS 2 and 3 degrees.

146 The MS was diagnosed based on the criteria of the International Diabetes
 147 Federation (ADF), The National Cholesterol Education Program (NCEP), Adult
 148 Treatment Panel III (ATP III) in a modification of 2009, taking into account
 149 ethnicity [14, 15].

150
 151

Table 3.

Average values of MetS in women with MS and without MS, M±s

Comment [M8]: ?

Indicators	MS I , n=923	MS II , n=428	MS III , n=18	General MS, n=1369	Without MS, n=115
Waist circumferen ce, sm	88,71±0,67	91,75±1,02*	103,75±4,53* **	90,0±0,56***	86,44±2,2** ***
Systolic BP, mm Hg.	128,7±1,8	136,2±3,3*	144,0±8,2	132,4±2,2	118,3±3,0 * ** *** *****
Diastolic BP, mm Hg.	78,5±3,0	92,5±1,3*	94,3±7,8*	85,2±1,9**	75,4±1,7** *** *****
	n=256	n=112	n=8	n=208	n=57
Cholesterol, mmol /l	5,36±0,07	5,56±0,09	6,31±0,28* **	5,51±0,06** *	4,68±0,08* ** *** *****
TG, mmol/l	1,65±0,05	1,74±0,08	1,71±0,16	1,68±0,04	1,36±0,07 ** *** *****
HDL , mmol /l	1,14±0,03	1,11±0,05	1,15±0,08	1,13±0,03	1,21±0,04
LDL , mmol /l	3,43±0,07	3,58±0,08	4,38±0,24* **	3,54±0,05** *	2,81±0,08* ** *** *****
AC, conv. unit	4,04±0,13	4,44±0,16	4,53±0,36	4,21±0,10	2,91±0,14* ** *** *****
Glucosa,	5,59±0,08	5,52±0,09	6,1±0,26**	5,79±0,06* **	4,43±0,05* ** *** *****

mmol /l					
---------	--	--	--	--	--

*P≤0.05 compared with group MS I
 ** P≤0.05 compared with group MS II
 *** P≤0.05 compared with group MS III
 ****P≤0.05 compared with the General MS group

Comment [M9]: Incorporate exact P values

152

153 Of the examined 256 women aged 35 to 70, formed menopausal metabolic
 154 syndrome (MMS) was observed in 81 (30.6%). The most vulnerable period was
 155 the menopausal transition - MMS was diagnosed in every third woman - 40
 156 (33.9%), whereas in women in the late reproductive period and postmenopausal
 157 women it was less common - in 14 (27.5%) and in 27 (28.1%), respectively. In the
 158 presence of the clinic of the MS, the chances of developing MMS increased almost
 159 4 times. 74 out of 208 (35.6%) women with MS had MetS, whereas among women
 160 without manifestations of MS, it was less common 3 times less - only 7 out of 57
 161 (12.3%). Most often, menopausal MMS was diagnosed in women with moderately
 162 severe MS - almost every second - 48 (54.5%), with MS 1 degree - in 23 (20.5%),
 163 and in MS 3 degree - in 3 (37.5%).

164

165 **DISCUSSION**

166 The analysis of the course of pre-, peri- and post-menopause showed a
 167 significant influence of social factors on the development of pathological
 168 menopause. Thus, the MS was noted significantly more often among the residents
 169 of the city - 72.0 against 54.8% without a clinic of the MS (OR = 2.1), women with
 170 higher education - 48.4 against 33% (OR = 1.9). The protective factors behind the
 171 development of a clinic at the MS are the absence of the fact of marriage (single) -
 172 1.5 versus 5.2% (OR = 0.3) and medical education - 69.6 versus 79.1% (OR = 0.6),
 173 which is the most likely associated with access to health care and awareness. A
 174 significant factor in the development of MS with the formation of MetS is the
 175 presence in the history of somatic and gynecological diseases, such as components
 176 of MetS - diabetes - 7.4 against 0.9% (OR = 9.1), hypertension - 20.5 against
 177 10.4% (OR = 2.2); as well as surgical menopause - 6.5 versus 0.9% (OR = 7.9),
 178 uterine mioma - 12.3 versus 3.5% (OR = 3.9), overweight and obesity - 22.2

179 against 26.8% (OR = 2.3). Waist circumference <80 cm is the protective factor for
180 the development of the MS (OR = 0.5). With the progression of symptoms of the
181 MS increases both the frequency and severity of the components of MetS, which
182 proves the validity of the existence of the fact of MMS. The glycemic profile is
183 exacerbated by the severity of the MS, rather than increasing age.

184 The most significant predictors of MS development (BMI \geq 25 and higher),
185 which is consistent with the literature data [16], (OR = 7.0), the presence of MetS
186 (OR = 3.9), a high AC (OR = 6.9), due to dyslipidemia ((OR = 2.2).

187

188 CONCLUSION

189 The premorbid background for the development of the pathological course
190 of menopause is a burdened somatic and obstetric-gynecological anamnesis. An
191 eEarlier onset of menopause (46.7 \pm 0.2 years) in women in the region was
192 identified, in contrast to global data (50 \pm 2 years) [17, 18]. The question of
193 premature and early onset of menopause in almost every tenth woman in the region
194 remains relevant. The presence of indicators of MetS significantly aggravates the
195 course of menopause, causing a high comorbidity and the development of thea MS
196 clinic.

197

198 REFERENCES

- 199 1. Plaksina N. D., Simonovskaya H.Yu. Possibilities of non-hormonal
200 correction of vasomotor paroxysms in postmenopausal // StatusPraesens.
201 Gynecology. Obstetrics. Barren marriage. 2014. № 2 (19). Pp. 60-65.
202 [Plaksina N.D., Simonovskaya Kh.Yu. Vozmozhnosti negormonal'noy
203 korrektsii vazomotornykh paroksizmov v postmenopauze // StatusPraesens.
204 Ginekologiya. Akusherstvo. Besplodnyy brak. 2014. № 2 (19). S. 60-65. (in
205 Russian)].
- 206 2. Healthy aging should be a global priority. News release // WHO.
207 11/06/2014. [Zdorovoye starenie dolzhno stat 'global'nym prioritetom.
208 Vypusk novostey // WHO. 11/06/2014. (in Russian)].

- 209 3. Baber R.J., Panay N., Fenton A. IMS Writing Group. 2016 IMS
210 Recommendations on women's midlife health and menopause hormone
211 therapy. //Climacteric. 2016; 19(2): 109-150.
- 212 4. Avis NE, Crawford SL, Greendale G, the Study of Women's Health Across
213 the Nation (SWAN). Duration of menopausal vasomotor symptoms over the
214 menopause transition. //JAMA Intern Med. 2015;175(4):531-539
- 215 5. Dvoryansky SA, Emelyanova D.I., Yagovkina N.V. Climacteric syndrome:
216 the current state of the issue (Literature review) // Vyatka Medical Bulletin
217 2017 №1 (53) 7-16. Dvoryanskiy S.A., Yemel'yanova D.I., Yagovkina N.V.
218 [Klimaktericheskiy sindrom: sovremennoye sostoyaniye voprosa (Obzor
219 literatury) // Vyatskiy med vestnik 2017 №1 (53) 7-16. (in Russian)].
- 220 6. Randolph J.F. Jr, Sowers M., Bondarenko I. et al. The relationship of
221 longitudinal change in reproductive hormones and vasomotor symptoms
222 during the menopausal transition // J Clin Endocrinol Metab. 2005. Vol. 90.
223 P. 6106–6112.
- 224 7. Kasyan VN. Pathophysiology of hot flushes. Focus on neurohormonal
225 regulation Review of literature) // Problems of reproduction. - 2017.- №1. -
226 p. 115-121. [Kasyan V.N .. Patofiziologiya prilivov zhara. Fokus na
227 neyrogormonal'nuyu regulyatsiyu Oobzor literatury) // Problem reproduksii.
228 - 2017.- №1. - S. 115-121. (in Russian)].
- 229 8. Torrén JI, Sutton-Tyrrell K, Zhao X, et al. Relative androgen excess
230 during the menopausal transition predicts incident metabolic syndrome in
231 midlife women: Study of Women's Health Across the
232 Nation. //Menopause 2009;16(2):257-264.
- 233 9. Borovkova E.I. Clinical manifestations, diagnosis and management of
234 patients in peri-and menopause // Russian Bulletin of the obstetrician-
235 gynecologist. 2017. No. 3. P. 112–117 [Borovkova E.I. Klinicheskie
236 javleniya, diagnostika i vedenie pacientok v peri- i menopauze //
237 Rossijskiy vestnik akushera-ginekologa. 2017. No. 3. S. 112–117 (in
238 Russian)].

- 239 **10.**Lee SW, Jo HH, Kim MR. Association between menopausal symptoms and
240 metabolic syndrome in postmenopausal women. //Arch Gynecol Obstet.
241 2012;285:541-548
- 242 **11.**Agababyan L. R., Akhmedova A. T. Possibilities of correcting menopausal
243 disorders in women with contraindications to hormone replacement therapy
244 // Problems of reproduction. 2017; 23 (3): 108-110 [Agababyan L. R.,
245 Akhmedova A. T. Vozmozhnosti korrektsii klimaktericheskikh rassstroystv u
246 zhenshchin s protivopokazaniyem k zamestitel'noy gormonal'noy terapii //
247 Problemy reproduktivnoy. 2017; 23 (3): 108-110. (in Russian)].
- 248 **12.**Asrankulova DB, Akhmedova N.M., Yunusova D.Kh. Evaluation of the
249 effectiveness of the use of femoston in women with menopausal problems /
250 Jubilee All-Russian Congress with international participation “Outpatient
251 care is at the epicenter of women's health” Abstracts collection M., 2014–
252 383 p. C 159-160. [Asrankulova D.B., Akhmedova N.M., Yunusova D.KH.
253 Otsenka effektivnosti primeneniya preparata "Femoston" and zhenshchin s
254 klimaktericheskimi problemami / Yubileynyy C 159-160. (in Russian)]
- 255 **13.** Sandakova E. A., Elkin V. D., Kobernik M. Yu. Predictors of the
256 pathological course of menopause // Perm medical journal. -2014. -Tom
257 XXXI-№ 3. - p. 23-27. [Sandakova E. A., Yel'kin V. D., Kobernik M. Yu.
258 Prediktory patologicheskogo techeniya klimakteriya // Permskiy
259 meditsinskiy zhurnal. -2014. -Tom XXXI -№ 3. - S. 23-27. (in Russian)].
- 260 **14.**Alberti K.G.M.M., Eckel R.H., Grundy S.M., Zimmet P.Z., Cleeman J.I.,
261 Donato K.A. et al. Harmonizing the metabolic syndrome: A joint interim
262 statement of the International Diabetes Federation Task Force on
263 Epidemiology and Prevention; National Heart, Lung, and Blood Institute;
264 American Heart Association; World Heart Federation; International
265 Atherosclerosis Society; and International Association for the Study of
266 Obesity. //Circulation. 2009; 120: 1640—1645.

- 267 **15.**Liu J, Grundy SM, Wang W, Smith SC, Jr., Vega GL, Wu Z et al. Ethnic-
268 specific criteria for the metabolic syndrome: evidence from China.
269 //Diabetes Care 2006;29:1414-6
- 270 **16.**Metabolic syndrome in postmenopausal patients Dobrokhotova Yu.E., Ilina
271 I.Yu. , Narimanov M.R. , Ibragimova D.M. // breast cancer. Mother and
272 child - 2018. -№1 - C.33-38.
- 273 **17.**DOI: 10.32364 / 2618-8430-2018-1-1-33-38 [Dotabrokhotova Yu.E., Il'ina
274 I.Yu., Narimanova M.R., Ibragimova D.M. // rmzh. Mat 'i ditya - 2018. -№ 1
275 - S.33-38. DOI: 10.32364 / 2618-8430-2018-1-1-33-38. (in Russian)].
276 Metabolic syndrome in postmenopausal patients Dobrokhotova Yu.E., Ilina
277 I.Yu. , Narimanov M.R. , Ibragimova D.M. // breast cancer. Mother and
278 child - 2018. -№1 - C.33-38.
- 279 **18.**Schoenaker DA, Jackson CA, Rowlands JV, Mishra GD. Socioeconomic
280 position, lifestyle factors and age at natural menopause: a systematic review
281 and meta-analyses of studies across six continents. //Int J Epidemiol
282 2014;43:1542–1562.