Marichereda V. G., Bykova N. A., Shevchenko I. M., Volyanska A. G., Rozhkovskaya N. M. Assessment of significance and relation between risk factors of endometry cancer development in women with endometry hyperproliferative processes. Journal of Education, Health and Sport. 2018;8(8):891-901. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.1405097
http://ojs.ukw.edu.pl/index.php/johs/article/view/5881

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part b item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eissn 2391-8306 7 ©

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 10.08.2018. Revised: 20.08.2018. Accepted: 28.08.2018.

ASSESSMENT OF SIGNIFICANCE AND RELATION BETWEEN RISK FACTORS OF ENDOMETRY CANCER DEVELOPMENT IN WOMEN WITH ENDOMETRY HYPERPROLIFERATIVE PROCESSES

V. G. Marichereda, N. A. Bykova, I. M. Shevchenko, A. G. Volyanska, N. M. Rozhkovskaya

Odessa National Medical University, Ukraine

e-mail: natalia_bykova@ukr.net

Abstract

A retrospective analysis of 27 patient case histories with pathomorphologically confirmed diagnosis of endometrial cancer (EC) showed that the most common and statistically significant risk factors for the development of uterine body cancer are: age of a woman above 50 years, heredity and genetic predisposition, late menopause, polycystic ovary syndrome, thyroid gland diseases, diabetes mellitus, obesity, infertility of hormonal genesis, arterial hypertension, inflammatory diseases of female genital organs, early menarche. Hereditary non-polypous colorectal cancer (11.68%, 95% CI 0.59-227.89), and hepatobiliary system diseases (2.50%, 95% CI 0.71-8.72) according to our results are not statistically significant. In order to determine the risk of EC development, 3 rules based on the "AssociationRules method" have been developed. They are: the combination of late menopause and heredity can lead to the development of EC with a probability of 59.25% and accuracy of 88.88%, while the correlation coefficient is 88.88%; the presence of obesity or heredity in a woman above 50 years of age can lead to EC with a probability of 59.25% and

accuracy of 80.00% with a correlation coefficient of 84.32%; the development of EC in women above 50 years of age with a late-onset menopause is possible with a probability of 62.96% and accuracy of 94.44%, while correlation coefficient is 89.59% in this case.

Key words: risk factor, endometrial cancer.

Introduction

The study of pathogenesis, early diagnosis and prediction of the development of hyperplastic processes and endometrial cancer (EC) is a topical issue in modern gynecology. Annually around the world about 42 thousand women die from oncopathology of endometrium, and about 150 thousand of new cases are registered [1, 2]. Over the past decade the incidence in EC has increased by about 20%, and resulting in this, EC postures in the first place as a malignant disease of the female reproductive system, and is most often diagnosed [3, 4]. In the developed countries, its incidence is 10 times higher than in the developing ones [5, 6, 7]. According to the bulletin of the National Cancer Registry of Ukraine, the incidence of morbidity in EC (ICD-10 - C54) for 2016-2017 is 33.3 cases per 100 000 among female population [8]. Morbidity peak accounts for perimenopausal women, which is evidenced by the EC diagnosis in about 70% of this age patients. In 20-25% of cases EC is detected in late reproductive age, and 5% of cases it is diagnosed in women under the age of 40 y. o. [1, 2].

According to the data of literature, in 70% of cases, EC develops against the background of hyperproliferative processes of endometrium (HPE), and in 30-79% of cases during 1-3 years atypical endometrial hyperplasia is reborn in cancer [9, 10]. Some scientific articles inform that the HPE are not precancerous diseases [4, 11]. At the same time it is known that in HPE patients combination of gynecological and somatic pathology stipulates a higher risk of endometrium malignant degeneration [3, 4, 11].

In the development and progression of HPE and EC an important role is assigned to the violation of hormonal balance, in particular the predominance of absolute or relative hyperestrogenism [10]. In recent years there have been reports of the influence of molecular genetic aspects on the formation of endometrial carcinoma [5, 12, 13].

One of the main risk factors for EC development is the perimenopausal age of a woman [4]. In this period at the background of the endocrine imbalance and / or molecular genetic disorders, conditions are created for the occurrence of HPE [1, 14].

Analyzing the modern literature data, we found that the development of EC is associated with obesity [6, 7, 13, 15]. The linear relationship between the development of EC

and the increase in body mass index (BMI) is noted [15, 16]. In his reviews, Ali A. T. [6, 17] mentions a positive correlation between the risk of endometrial adenocarcinomas development and a woman's age (especially in the postmenopausal period), early onset of menarche, late menopause, obesity, heredity, infertility, especially associated with polycystic ovary syndrome - PCOS).

In [13, 18, 19] they report that the development of EC may be linked to hereditary tainted, diabetes mellitus presence, hereditary non-polyposis colorectal cancer (HNPCC).

Consequently, HPE combined with gynecological and somatic pathology increases the risk of EC nascency. In order to increase the possibilities of early diagnostics, prognosis, and thus prevention of HPE oncotransformation, detection and, if possible, timely prevention or treatment of identified risk factors is important.

The objective. To identify and analyze the patients' case histories, as well as to formulate associative rules based on the determination of the relationship between the most statistically significant for EC nascency risk factors.

Materials and methods. A retrospective analysis of case histories of 27 patients aged 38-79 y. o. with a pathomorphologically-verified diagnosis of EC was conducted. The patients urgently turned to for medical assistance to the gynecological department of the Multidisciplinary Medical Center (University Hospital No. 1) of the Odessa National Medical University for abnormal uterine bleeding, either they accessed electively for conducting endometrial biopsy (hysteroscopy, fractional diagnostic curettage) in cases of HPE ultrasound detection for the period 2013-2017. Further examination and treatment of the patients took place in the oncological clinics at their places of residence.

The control group consisted of 30 women of reproductive age (21-42 y. o.) without gynecological pathology, who were preparing for the program of extracorporal fertilization because of male infertility. In 2 (6.7%) control group women BMI was > 30, 5 (16.7%) of them had liver and gall bladder disease, 1 (3.3%) had arterial hypertension and inflammatory diseases of female genital organs.

We estimated and statistically evaluated the risk factors for EC in women with HPE: age above 50 years, early menarche (up to 12 years), late menopause (after 50 years), infertility of hormonal genesis, obesity, diabetes, PCOS, HNPCC, inflammatory diseases of genitals (IDG), thyroid gland disease (TGD), arterial hypertension (AH), heredity and genetic predisposition, diseases of hepato-biliary system (DHBS).

The statistical evaluation of the results was carried out with the use of STATISTICA 10.0, MedCalc 14.8.1 and Microsoft Excel 2010 with the AddStat 12.5 add-on. The

calculations were carried out by Simulator Interactive Statistical Analysis (http://www.quantitativeskills.com/sisa/) and Web Pagestat Perform Statistical Calculations (http://statpages.info). The odds ratio (OR) was calculated by MedCalc 14.8.1. The average sample values of the quantitative attributes are given in the text in the form $M \pm m$, where M is the mean selective, m is the mean error. Parcels (percentages) are presented at 95% confidence intervals. In all procedures of statistical analysis, when checking null hypotheses, the critical significance of "p" was taken to be 0.05. Investigation of the relationship (communication rules) between pairs of discrete qualitative characteristics was carried out using the analysis of paired tables of conjugacy, where the value of Pearson's Chi-square statistics ($\chi 2$) was evaluated, the level of significance (p), relative risk (RR) with 95% confidence intervals. In order to detect common factors between large number of qualitative features, modules of intellectual data analysis (Datamining) - "Association Rules" and "Feature Selection and Variable Filtering" were used.

***Results and their discussion.** To assess the risk factors of EC, we have identified and analyzed the disease histories data.

Statistical data processing by calculating the OR of the aforementioned risk factors showed (Table 1, Fig. 1) that the women's age > 50 y. o. is the main feature in the cohort of risk factors for the development of EC and equals 139.94% (95% CI 7.63 -2564.46). This means that in women aged above 50 y. o. the risk of EC developing is almost 140 times higher than that of women under this age. The second factor in significance is heredity and genetic predisposition - 118.78% (95% CI 6.52-2163.06). In the third place is late menopause - 58.00% (95% CI 6.76-496.97). This factor is almost 2 times lower than the age indicator. The fourth feature of the frequency is the PCOS, which is equal to 42.51% (95% CI 2.35-768.16). The risk of uterus body cancer development in the presence of TGD is 36.6% (95% CI 2.01-663.40), with diabetes mellitus it is 31.32% (95% CI1.72-570.39), and with obesity - 28, 00% (95% CI 5.41-144.72). The following statistically significant risk factors are IHG: - 22.31% (95% CI 1.20-412.53) and AH - 15.07% (95% CI 2.98-76.26). The risk of endometrial adenocarcinoma in women with HPE is 13.00% (95% CI 2.57-65.76) if IHG is diagnosed and it accounts 5.81% (95% CI 1.79-18.91) for early menarche.

According to the results of our statistical analysis, the HNPCC (11.68%, 95% CI 0.59-227.89) and DHBS (2.50%; 95% CI 0.71-8.72) are not statistically significant factors (Fig. 1). The results of the control group did not exceed the average statistics.

Table 1.

Results of the analysis of risk factors for the development of EC by determining OR

Predictor	Odds ratio	95%CI
> 50 years old	139.94	7.63-2564.46
Late menopause	58.00	6.76-496.97
Early menarche	5.81	1.79-18.91
HG infertility	22.31	1.20-412.53
Obesity	28.00	5.41-144.72
Diabetes mellitus	31.32	1.72-570.39
PCOS	42.51	2.35-768.16
HNPCC	11.68	0.59-227.89
IDG	13.00	2.57-65.76
TGD	36.60	2.01-663.40
AH	15.07	2.98-76.26
Heridity	118.78	6.52-2163.06
DHBS	2.50	0.71-8.72

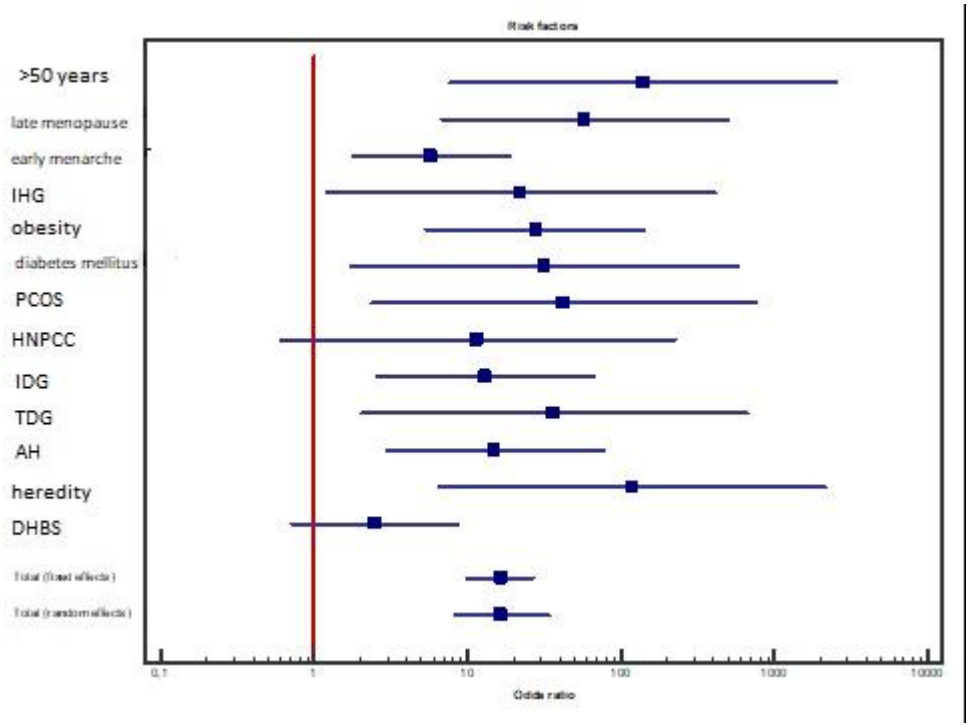

Fig. 1. Graphic representation of the risk factors for the development of EC by calculating OR

The results of statistical analysis of the data by calculating OR of the selected case histories allowed us to select 13 factors for the further statistical treatment. These factors are most commonly found in EC patients aged more than 50 years, had early menarche, late menopause, infertility, obesity, diabetes mellitus, PCOS, HNPCC, IDG, TGD, AH, heredity and genetic predisposition, DHBS.

Multifactor analysis of qualitative indicators with the use of "Feature Selection and Variable Filtering" technique helped to build "pyramid" of f risk factors for EC development sequence starting from the most to the least significant indicator (Table 2, Fig. 2). Patients' age > 50 years ($\chi 2 = 34.23423$, $p = 0.000000$) is the leading indicator. Late menopause is in the second place - ($\chi 2 = 25.65000$, $p = 0.000000$) and the third in order of importance is obesity ($\chi 2 = 22.46108$, $p = 0.000002$).

They are followed by DHBS and AH with the same indices ($\chi 2 = 16.22824$, $p = 0.000056$). The next in importance indicator is PCOS ($\chi 2 = 15{,}14493$, $p = 0.000100$). Heredity ($\chi 2 = 14{,}76023$, $p = 0{,}000122$) and IDG ($\chi 2 = 14{,}36972$, $p = 0{,}000150$) are recorded at almost the same level. The last place among the risk factors is shared by diabetes and TGD ($\chi 2 = 13.47518$, $p = 0.000242$).

Table 2

Significance of EC risk factors by the results of the "Feature Selection and Variable Filtering" of intelligent data analysis module (Data Mining)

Predictor	**Xi2**	**P**
> 50 y.o.	34.23423	0.000000
Late menopause	25.65000	0.000000
Obesity	22.46108	0.000002
DHBS	16.22864	0.000056
AH	16.22864	0.000056
PCOS	15.14493	0.000100
Heredity	14.76023	0.000122
IDG	14.36972	0.000150
Diabetes mellitus	13.47518	0.000242
TGD	13.47518	0.000242

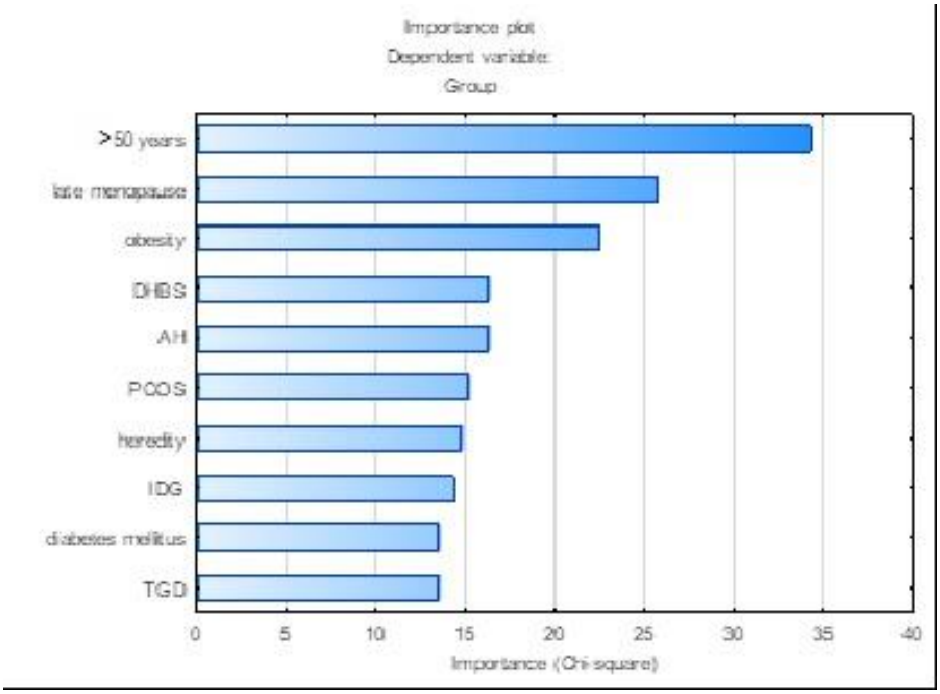

Fig. 2. Significance of EC risk factors by the results of the "Feature Selection and Variable Filtering" of intelligent data analysis module (Data Mining) in graphic representation

Using the "Association Rules" method of module “Data Mining” intelligent data analysis we conducted the second stage of sequential analysis. Its aim was to formulate associative rules based on 10 selected statistically significant risk factors. The data analysis done resulted in 3 communication rules to determine EC risk factors (Table 3, Fig. 3).

Table 3

Associative rules of the most significant risk factors for EC development

N	cause	==>	consequence	Support,%	Probability,%	Correlation,%
1	Late menopause	==>	Age>50 y.o.	62.96	94.64	89.54
2	Age>50 y.o.	==>	BMI	59.25	80.00	84.32
3	Age>50 y.o.	==>	Heredity	59.25	80.00	80.00
4	Late menopause	==>	Heredity	56.25	88.88	88.88

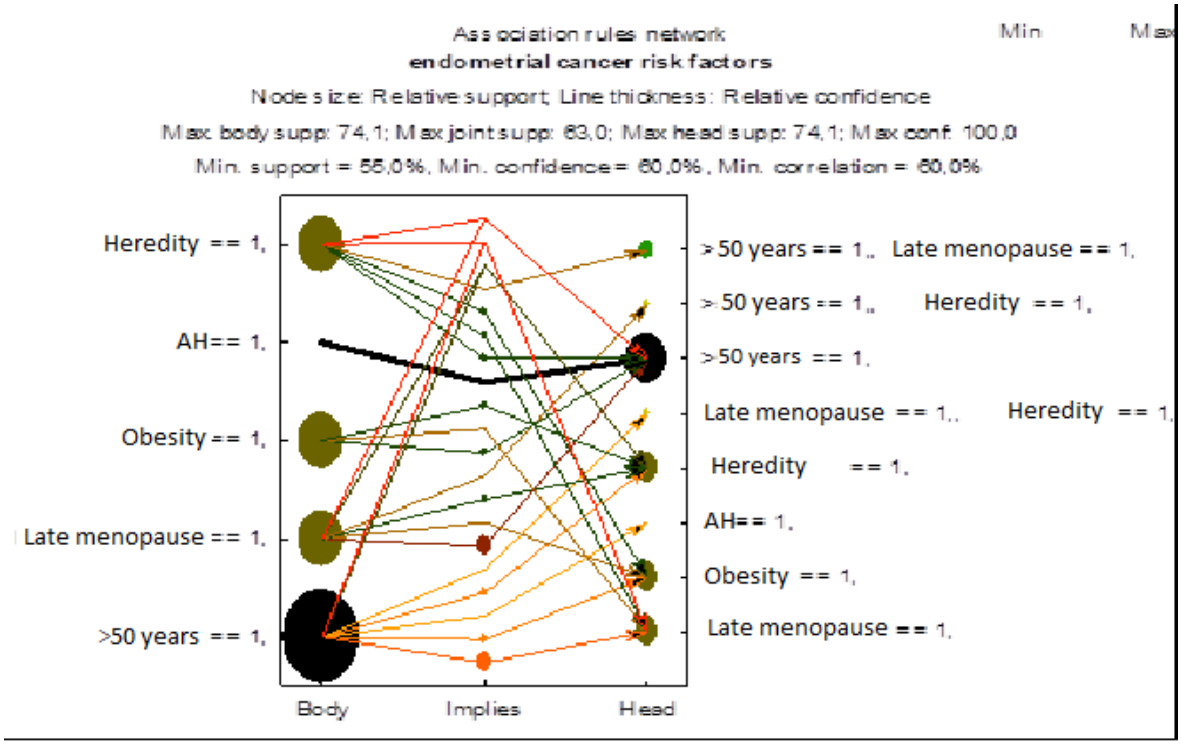

Fig. 3. Rules of relationships of risk factors for the development of EC in graphic representation

1. Risk of EC development in women above the age of 50 years in combination with late menopause. In this case EC probability is 62.96% and accuracy is 94.44% with coefficient of correlation 89.59%.

2. Late menopause and heredity may lead to the emergence of EC with probability of 59.25% and accuracy of 88.88%, coefficient of correlation is 88.88%.

3. Age > 50 years and obesity / age > 50 years and heredity indicate the possibility of EC development with probability of 59.25% and 80% of accuracy, coefficient of correlation is 84.32%.

Conclusions

1. Determination of OR to assess the significance of 13 selected risk factors of EC development has demonstrated that 11 of them are statistically significant. They are: a woman's age above 50 years, heredity and genetic predisposition, late menopause, PCOS, TGD, diabetes mellitus, infertility of HG, AH, IDG and early menarche.

2. According to the statistical analysis of the data, the risk factors related to the HNPCC (11.68%, 95% CI 0.59-227.89) and DHBS (2.50%, 95% CI 0.71-8,72) are not statistically significant.

3. Sequence of statistically significant risk factors of EC development in multivariate analysis with the use of "Feature Selection and Variable Filtering" method of the data analysis module (Data mining) from the most to the least significant are: age > 50 years ($\chi 2$ = 34,23423, p = 0,000000) → late menopause ($\chi 2$ = 25.65000, p = 0.000000) → obesity ($\chi 2$ = 22.46108, p = 0.000002) → DHBS ($\chi 2$ = 16.22824, p = 0.000056), AH ($\chi 2$ = 16.22824, p= 0.000056) → PCOS ($\chi 2$ = 15.14493, p = 0,000100) → heredity ($\chi 2$ = 14.76023, p = 0.000122) → IDG ($\chi 2$ = 14.36972, p = 0. 000150) → diabetes mellitus ($\chi 2$ = 13.47518, p = 0.000242), TGD ($\chi 2$ = 13.47518, p = 0.000242).

4. Associative rules of relationships have shown that in EC patients the most often noted risk factors are: late menopause, age > 50 years, heredity and genetic predisposition, obesity.

5. In order to determine the risk of EC development, 3 rules based on the "Association Rules" method have been derived:

- combination of late menopause and heredity can lead to EC development with probability of 59.25% and accuracy of 88.88%, while correlation coefficient is 88.88%;

- the presence of obesity or heredity in women aged above 50 years can lead to EC emergence with probability of 59.25% and accuracy of 80.00% and correlation coefficient of 84.32%;

- EC development in women aged above 50 years and late - onset menopause is possible with probability of 62.96% and accuracy of 94.44% and correlation coefficient 89.59%.

References:

1. Tkachenko L. B., et al. Risk prognostic factors of endometrial hyperplasic processes development under menopause // Volgograd Scientific-Med. J. – 2013. - № 4. – P. 43 - 47.

2. Chernukha G. E. Hyperplasia of endometrium: perspectives of the problem development // Obstetrics & Gynecology. – 2009. – № 4. – P. 11–15.

3. Sorosky J. I. Endometrial cancer / J. I. Sorosky // Obstet. Gynecol. – 2012. – Vol. 120. – P. 383–397.

4. Kornienko S. M. Endometrial hyperplasic processes in women at late reproductive and premenopausal period // Herald for Soc Hygiene and Health Care management in Ukraine. - 2017. - № 2 (72). - P. 39-47.

5. Nachajova M, Mersakova S, Sivakova J, Krivus S, Szepe P, Hatok J, Adamkov M. New molecular aspects of endometrial carcinoma //Neuro Endocrinol Lett.- 2015;36(7):638-43.

6. Ali A. T. Reproductive factors and the risk of endometrial cancer // Int J Gynecol Cancer. - 2014;24(3):384-93.

7. Uchikova E, Uchikov P, Parahuleva P. Obesity and endometrial carcinogenesis // Akush Ginekol (Sofiia).- 2015;54(9):34-7.

8. Fedorenko Z. P., et al. Cancer in Ukraine, 2016–2017: morbidity, mortaliyu, indexes of oncological service // Bull Nat Cancer-register Ukr. — Kiev, 2018. — № 19. — 136 p.

9. Clinical and pathogenic features of endometrium hyperplastic processes in women of premenopausal period // Rus Med J “ Med Review”.- 2018.- N1 (I) .- P. 67-71.

10. Vlasov P. C. Clinical meaning of methylate genes-suppressors of tumor growth at pathological prosesses of endometrium in reproductive age women: synopsis of a candidate thesis: specialty 14.01.01 «Obstetrics & Gynecology. – Moscow, 2011. – 21 p.

11. Vdovichenko Yu. P. Modern management of diagnostics and treatment of hyperplastic processes of endometrium (review of literature // Health of a Woman. – 2012. – № 9. – P. 45–53.

12. Unanian A. l. Prognosis of uterus body cancer in women with hyperplastic prosesses of endometriamin premenopausal period Прогнозирование рака тела матки у женщин с гиперпластическими процессами эндометрия в пременопаузальном возрасте // Obstetrics and Gynecology. Reproduction. - 2012. - №2 - P. 18-24.

13. Senechal C, Cottereau E, de Pauw A, Elan C, Dagousset I, Fourchotte V. Environmental and genetic risk factors for endometrial carcinoma.Bull Cancer.2015;102(3):256-69.

14. Sheshukova N.A., et al. Hyperplastic processes of endometrium: etiology, pathogeneses, clinics, diagnostics, treatment // Obst & Gynecol. – 2011. – № 4. – P. 16–21.

15. Shaw E, Farris M, McNeilJ, Friedenreich C. Obesity and Endometrial Cancer. Recent Results // Cancer Res. - 2016;208:107-136.

16. Zhang Y, Liu H, Yang S, Zhang J, Qian L, Chen X. Overweight, obesity and endometrial cancer risk: results from a systematic review and meta-analysis. Int J Biol Markers. 2014;29(1):e21-9.

17. Ali AT. Risk factors for endometrial cancer.// Ceska Gynekol. 2013;78(5):448-59.

18. Ketabi Z, Mosgaard BJ, Gerdes AM, Ladelund S, Bernstein IT. Awareness of endometrial cancer risk and compliance with screening in hereditary nonpolyposis colorectal cancer. Obstet Gynecol. 2012;120(5):1005-12.

19. Gao J, Yang G, Wen W, Cai QY, Zheng W, Shu XO, Xiang YB. Impact of known risk factors on endometrial cancer burden in Chinese women. Eur J Cancer Prev. 2016;25(4):329-34.