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Epidemiological analysis of the incidence of endometrial hyperplasia in a large city of Kazakhstan

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ABSTRACT

Endometrial hyperplasia (EH) is an abnormality of uterus, characterized by excessive proliferation of endometrium, and in case of lack of timely diagnostics and treatment, it may rapidly progress to endometrial cancer (EC). According to the World Cancer Research Fund, EC ranks 6th among all female malignancies in the world. EC takes the 3rd place in the Republic of Kazakhstan according to the state statistics. However, there is no determining statistical data on dynamics of EH incidence in our region, which will show the extent of exposure of the population to this disease. Therefore, this research provides assessment and analysis of all registered cases of EH from the Republican Center for Electronic Healthcare for the period from 2012 to 2022 for presentation of accurate and correct information on the trends of EH incidence and its histologic types, taking into account age differences of the female population of our city. The study has showed the increase of indicators of incidence of EH, especially, non-atypical endometrial hyperplasia (NAEH) and atypical endometrial hyperplasia (AEH). It was found that the peak incidence of EH occurred in the age group of 65-69 years, where the main increase was due to an increase in number of cases of NAEH. The age group of 45-49 years is at the peak of the incidence of AEH. The conducted research has identified the trends of EH incidence, reflecting population changes in the EH risk factors, and that requires their comprehensive study for development of strategies of treatment and prevention measures.

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1. INTRODUCTION

Endometrial hyperplasia (EH) is a gynecological disease characterized by pathological overgrowth of the endometrium as a result of the unhindered action of estrogens [1]. The relevance of this disease is determined by the fact that in the lack of timely diagnosis and treatment, EH may rapidly progress to endometrial cancer (EC) [2]. According to the World Cancer Research Fund International, EC ranks 6th

among all female cancers [3]. Global cancer statistics (GLOBOCAN) estimates that in 2022, more than 420,368 new cases of EC were reported worldwide, and 97,723 people died from this disease. Moreover, the incidence of EC is significantly higher in developed countries than in less developed countries. Thus, the highest incidence rates of EC were observed in North America (22.3 cases per 100,000 female population) and Eastern Europe (19.2 cases per 100,000 female population), and the lowest rates were in Central Africa (2.4 cases per 100,000 female population) [4].

The prevalence of EH is related to age and its histological type [5]. In 2014, the World Health Organization (WHO, 2014) has identified two main histological types of EH: non-atypical endometrial hyperplasia (NAEH) and atypical endometrial hyperplasia (AEH) [6]. Both types are rare in women under the age of 30. NAEH is most often diagnosed in women aged 50-54 years, and AEH is diagnosed in women aged 60-64 years [7]. AEH is a highly pre-cancerous condition and in 40% of cases it may be accompanied with EC. The risk of progression of AEH to EC is 60%, and of NAEH-less than 5% [8]. Nevertheless, scientists believe that the incidence of EH is significantly underestimated due to the lack of uniform forms of statistical accounting of this pathology [9]. It should be noted that earlier studies conducted by scientists from various countries were devoted to the study of the pathogenesis, classification, early diagnosis and treatment of EH [2], [5]–[7] and rather modest attention was paid to the analysis of the incidence and frequency of EH. It is known that studies devoted to the epidemiological analysis of morbidity is one of the reliable research methods that allow to determine the exact degree of exposure of a particular disease to a specific population group. The obtained results of these studies clearly show the trends (increase/decrease) of the studied disease over time and serve as important evidence for determining the priorities of medical interventions [10]. Unfortunately, our region also lacks accurate data on the incidence of EH, especially it is histological types. There were previous studies examining the prevalence and incidence of EH in our city [11], [12]. However, these studies were conducted on small samples in a short period of time, and the materials for the study were taken from one or two hospitals when patients urgently sought medical help. Therefore, the lack of completeness and detail of this information does not allow us to present a complete picture of EH burden among the population. Meanwhile, EH, clinically occurring with abnormal bloody discharge, often leads to emergency and outpatient examinations, which require high costs for treatment and rehabilitation from the state [1]. Therefore, it is necessary to continue and expand research aimed at analyzing morbidity based on official statistical reporting data.

An analysis of the results of our study conducted from 2012 to 2022 revealed the dynamics of morbidity rates based on officially registered cases of EH and its histological types, and also showed the most vulnerable age groups of the population of a large city in our country. In our opinion, the data obtained on the growth trend in the incidence of EH over the past 11 years will provide an understanding of the health status of the population and the activities of medical organizations. According to the latest data from the statistical and analytical collection “Indicators of the oncological support service of the Republic of Kazakhstan”, EC ranks 3rd among all female cancers in our country [13]. Therefore, conducting an epidemiological analysis of the incidence of EH in our region is relevant for the development of preventive programs that help reduce the risks of degeneration of EH into EC and improve diagnostic and treatment protocols as well as making managerial decisions at different levels of medical care. The purpose of the study: to analyze the incidence of EH and it is histological types among the female population of Almaty in 2012-2022.

2. METHOD

2.1. Materials and data collection

The data from the healthcare information system “Electronic register of inpatient patients” (“ERIP”), provided by the Republican Center for Electronic Healthcare (RCEH) of the Republic of Kazakhstan. RCEH is the official leading center for the management and enforcement of a unified methodology and technology for the formation of medical databases in the healthcare system and contains all cases of diseases treated in medical institutions at the expense of the republican budget. This provides comprehensive information on incidence statistics. The researchers extracted all newly identified cases with histologically confirmed diagnoses according to the International Statistical Classification of Diseases and Related Health Problems, WHO 10 revision, N85.0-Glandular endometrial hyperplasia (non-atypical endometrial hyperplasia), N85.1-Adenomatous endometrial hyperplasia (atypical endometrial hyperplasia) for the period from January 1, 2012 to December 31, 2022 from the healthcare information system “ERIP”. A retrospective, descriptive epidemiological study was conducted.

2.2. Calculation of incidence indicators

The researchers calculated the overall incidence rate (crude rate) of EH and its histological types, as well as the incidence rate, taking into account the age differences of the female population of Almaty. The age groups were divided into 10 groups (under 29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69,

70 and older). Formulas approved by the Order of the Minister of Healthcare of the Republic of Kazakhstan "On approval of the methodology for the formation of indicators in the field of healthcare" dated November 30, 2020 No. RK DSM-212/2020 were used for the calculation [14]. Initially, the researchers calculated incidence rate of EH and its histological types, where a number of cases with newly diagnosed diseases per a certain year was divided by the total female population of Almaty, then multiplied by 100,000. Then, the incidence rate of EH and its histological types was calculated in age groups, where a number of cases with newly diagnosed diseases per a certain year in the age group under study was divided by the total female population of the studied group, and then multiplied by 100,000. The researchers retrieved the data on the total female population for 2012-2022, necessary for calculating the incidence of EH and its histological types, from the official website of the National Bureau of Statistics of the Agency for Strategic Planning and Reforms of the Republic of Kazakhstan [15].

2.3. Data analysis

The patterns of changes for each year and age group regarding the incidence rate EH and its histological types are presented in this study illustratively. Database was formed with the use of the Microsoft Excel software package. A linear graph was used to determine the dynamics of incidence rates (crude rates) of EH of female population of Almaty in 2012-2022, and a table was used for histological types of EH. A bar chart was used for the trends in the incidence of EH and its histological types among age groups. The statistical package of the SPSS Statistics 26 program was used to calculate the average annual incidence rate (M), average error (m), 95% confidence interval (95% CI) of EH, and it is histological types in general and age groups. The study was approved by the Ethics Committee of the Kazakhstan Medical University "KSPH" (Minutes No. IRB-335 dated 05.01.2023).

3. RESULTS AND DISCUSSION

3.1. The dynamics of incidence rates of EH in the female population of Almaty from 2012 to 2022

During the follow-up period (2012-2022), 1,308 new cases of EH were registered among the female population of Almaty, of which 1,241 cases (94.9%) of NAEH, and 67 (5.1%) of AEH. The dynamics of incidence rates (crude rates) of EH in the female population of Almaty for 2012-2022 is shown in Figure 1. There was an increase in the incidence rates (crude rates) of EH from 0.51 cases in 2012 to 14.67 cases per 100,000 female population in 2022, i.e. 28.8 times. The analysis of the incidence of EH in the female population of Almaty showed that there was a sharp increase in the indicator from 0.51 to 17.75 cases per 100,000 female population in 2012-2016. In 2016, the peak incidence of EH was recorded (17.75 cases per 100,000 female population). In the next two years (2017-2018), the indicator decreased to 15.11 cases per 100,000 female population, and by 2020, the level of the incidence of EH was stabilized in the range of 15.11-15.33 cases per 100,000 female population. However, in 2021, the indicator increased again to 17.19 cases per 100,000 female population, followed by a decrease in 2022 to 14.67 cases per 100,000 female population.

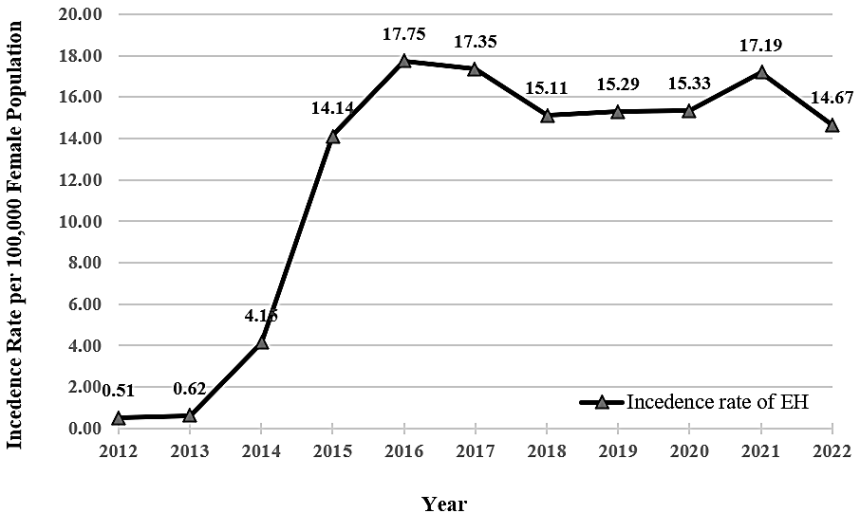

Figure 1. Dynamics of incidence rates (crude rates) of EH in the female population of Almaty in 2012-2022 (per 100,000 female population)

In our opinion, the reason for the increase in the levels of incidence rates (crude rates) among the female population in our region during the study period (2012-2022) may be closely related to the implementation of the Healthcare Development State Program in the Republic of Kazakhstan "Salamatty Kazakhstan" for 2011-2015, where the main task was to improve the prevention and management of diseases based on screening the population, as well as the modernization of primary health care services. This is confirmed by a sharp increase in the incidence of EH in 2012-2016. From the other perspective, the trend of increase in EH incidence rates under conditions of large city may be partially be attributed to impact of the diet with a high content of fats, sugar, and calories, as well as low activity life style, on the female body. Researchers Wise *et al.* [16] state that increase in EH cases in large cities is related to unhealthy life style and increase in obesity prevalence. As known, obesity is one of the EH risk factors, as hydroforming process in fat tissues leads to hyperestrogenism, which, in turn, causes intensive endometrium proliferation [17].

3.2. The dynamics of incidence rates of histological types of EH in the female population of Almaty from 2012 to 2022

Table 1 shows the dynamics of incidence rates (crude rates) of the main two histological types of EH in the female population of Almaty separately. There was an increase in the incidence of both NAEH from 0.51 in 2012 to 13.85 cases in 2022, and AEH from 0.0 in 2012 to 1.16 cases in 2022. The average annual incidence rate of EH was 12.01±2.03 cases per 100,000 female population (95% CI: 7.48-16.54) with: NAEH-11.42±1.94 cases per 100,000 female population (95% CI: 7.10-15.73), AEH-0.59±0.16 cases per 100,000 female population (95% CI: 0.23-0.96), respectively. Moreover, the increase in the incidence of EH occurred mainly due to requests for medical help from the female population due to NAEH, the average annual incidence of which exceeded the AEH indicators by 19.4 times. Our data correlate with the results of studies from an earlier period, where the incidence rates of NAEH exceeded the rates of AEH. Thus, in a study conducted by Korean scientists, the incidence of EH in female population of South Korea in 2009-2012 was 37 cases per 100,000 female population, where 30 of them were cases of NAEH, and 7 cases of AEH [18].

Table 1. Incidence rate of histological types of EH in 2012-2022

Year	Incidence rate (crude rate) of EH, per 100,000 female population	Incidence rate (crude rate) of NAEH, per 100,000 female population	Incidence rate (crude rate) of AEH, per 100,000 female population
2012	0.51	0.51	0.00
2013	0.62	0.62	0.00
2014	4.15	4.02	0.12
2015	14.14	13.58	0.56
2016	17.75	17.32	0.43
2017	17.35	17.14	0.21
2018	15.11	14.29	0.82
2019	15.29	14.89	0.40
2020	15.33	13.98	1.35
2021	17.19	15.70	1.50
2022	14.67	13.51	1.16
The average annual incidence rate, M±m (95% CI)	12.01±2.03 (7.48-16.54)	11.42±1.94 (7.10-15.73)	0.59±0.16 (0.23-0.96)

Note: M: the average annual incidence rate; m: average error; CI: confidence interval.

3.3. Dynamics of the incidence rates of EH and its histological types in the age groups of female population in Almaty for 2012-2022

Figure 2 shows the distribution of indicators of the average annual incidence of EH and its histological types per 100,000 female population for each age group from 2012 to 2022. An analysis showed that the peak incidence of EH occurred in the age group of 65-69 years (36.3 cases per 100,000 female population), where the main increase was due to an increase in cases of NAEH (35.9 cases per 100,000 female population), whereas the incidence rate was only 0.44 cases per 100,000 female population for AEH in this age category. On the contrary, the age group 45-49 years old (2.66 cases per 100,000 female population) was at the peak of the incidence of AEH, where the incidence of NAEH was 31.7 cases per 100,000 female population).

It should be noted that women in the age group of 60-64 years (34.6 cases per 100,000 female population), 45-49 years (31.7 cases per 100,000 female population) and 50-54 years (30.8 cases per 100,000 female population) were also more susceptible to NAEH. The prevalence of NAEH was slightly lower in the age groups 55-59 years (28 cases), 40-44 years (19.3 cases), 70 years and older (12.4 cases). It was even less common in the age groups of 35-39 years (8.9 cases), 30-34 years (3.67 cases). The lowest incidence rates occurred in the group of 29 and younger years (1.05 cases). Whereas women in the age group of 50-54 years

(1.53 cases), 35-39 years (1.23 cases), 60-64 years (1.2 cases) were more vulnerable to AEH. AEH was observed even less frequently in the age group of 55-59 years (1.06 cases), 70 and older years (0.68 cases), 30-34 years (0.47 cases) and 65-69 years (0.44 cases). The lowest incidence rates were observed in the age group of 29 years and younger. The incidence of AEH in the age group of 40-44 years was completely absent.

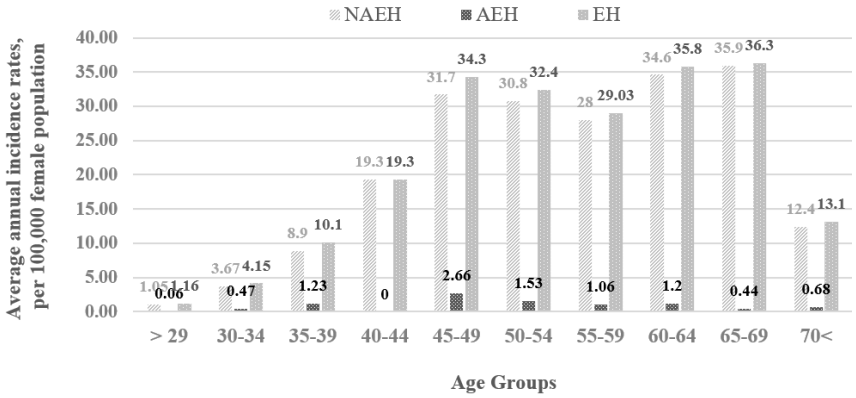

Figure 2. The average annual incidence rates (crude rates) of EH and its histological types in the age groups of women in Almaty for 2012-2022 (per 100,000 female population)

The available scientific literature data demonstrate that the prevalence of EH varies in a significant range, and the results of studies vary, which is more often explained by a different combination of risk factors for the development of EH. Thus, the systematic review by Petersdorf *et al*. has identified that EH incidence rate increases with the age, and the most cases are observed in the USA and South Korea. Maximum concentration of EH was observed in age group of 45-49 among female population in the USA (270 cases per 100,000 female population), and in age group of 46-50 among female population in the South Korea (121 cases per 100,000 female population). In addition, the EH prevalence was highly dependent on the specifics of the population under study [19]. A study conducted by Indian scientists Sandeepa *et al.* should be noted, according to which NAEH among women aged 20 to 83 years was more common in the age group of 41-50 years (24%), and less in the group of 21-30 years (6%), while an increase in the prevalence of AEH was observed in the age group of 51-60 (11%) and 31-40 years (10%) and, on the contrary, it was not observed at all in the age group of 21-30 years [20].

Our study demonstrates clearer differences in the age groups of patients with EH compared to the above-mentioned studies, which may be due to the demographic characteristics of the female population of our city, as well as various risk factors contributing to the progression of EH. The increase in the incidence of NAEH in women over the age of 60 may be due to the demographic situation caused by the aging of the population and a larger number of women over the working age. According to the census of the population of Kazakhstan in 2019, the transformation of the age structure of the population compared to the population census of 2009 is noted, which manifests in a reduction in the share of the working age population with a simultaneous increase in the share of older population (especially 65-69 years and 70 years and older) and younger working age, which is associated with an increase in natural growth of the population due to some increase in fertility and decline in mortality [21]. The results of several recent studies [22]–[24] showed that the high vulnerability of older women to EH is due to the presence of a greater number of concomitant diseases such as diabetes mellitus, hypertension, thyroid disease, metabolic the syndrome. As known, these diseases are one of the main risk factors leading to the progression of EH [25].

Our study also showed that the maximum concentration of AEH was observed in the age group of 45-49 years. This age period falls at the beginning of the perimenopausal transition, when various hormonal changes occur, an irregular menstrual cycle is noted, and the follicular activity of the ovaries decreases, leading to the progression of various menopausal disorders [26]. It should be noted that during the study period (2012-2022), an increase in the incidence of AEH was observed not only in women of perimenopausal age, but also in women in the 35-39 age group. The probable reasons for the shift in the incidence of AEH towards a younger age is the tendency of young women to postpone their first pregnancy and childbirth to a later age in order to achieve career growth and improve their economically independent status in a large city. Our opinion is shared with Jang and Hwang [27] which determined in their research that one of the AEH risk factor among females of active reproductive age is the nulliparity. Also, the meta-analysis, conducted by

Zhao *et al.* [28] has confirmed that the most important risk factor for the progression of EH in women of reproductive age is the absence of pregnancy for a long time. On the other hand, this may be due to an increase in the growth of chronic endometrial diseases caused by sexually transmitted diseases in sexually active young women. According to research data in China on study of uterus cavity microbiota of women of reproductive age with EH, the long-term chronic inflammation causes disruption of epithelial barrier and development of dysbiosis, which leads to cellular proliferation and genomic instability of endometrium [29]. In addition, other researchers note that against the background of a long-term inflammatory process, EH progresses rapidly in EC [30].

The advantage of our study is that we analyzed intensive incidence rates based on officially registered cases of EH, as well as its histological types, in age groups, which provides a scientific basis for understanding the prevalence of EH in our region and forms the basis for targeted disease prevention and control strategies. Our study has some deficiencies due to use of the official statistics, and we have not analyzed the medical histories of patients from all clinics in our city. In this regard, we were limited in understanding exactly which factors contributed to the progression of EH, and, consequently, to the increase in morbidity in certain age groups. We intend to study the medical history and conduct a sociological survey among patients with EH in our further studies for thorough examination of the risk factors contributing to the progression of EH.

4. CONCLUSION

Our epidemiological analysis showed the increase in incidence rates of EH and it is main histological types in the female population of Almaty for the period 2012-2022. It was found that the peak incidence of EH occurs in the age group of 65-69 years, where the main increase was due to an increase in number of cases of NAEH. There was an increase in the incidence of AEH among women of active reproductive age, as well as women of peri- and postmenopausal age. The revealed trends in the incidence of EH and it is histological types among age groups provided the obstetrician-gynecologists with information on the age requiring special attention for a targeted approach to controlling the prevalence of EH. It is also necessary to continue research for an in-depth study of the risk factors contributing to the development of EH in order to clarify the patterns identified and develop strategies and programs for therapeutic and preventive measures.

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