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ENDOMETRIAL LESION'S PATTERN IN DIFFERENT AGE GROUPS

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Background. *Endometrial polyps (EP) take an important part in the structure of intrauterine pathology and could be associated with abnormal uterine bleeding (AUB), infertility and the risk of endometrial cancer (EC) development. The data concerning EP's prevalence and combination with other endometrium pathology's forms in women of different age varies widely. It causes difficulties for understanding the magnitude of the problem and finding solutions for management.*
Aim. *To evaluate the prevalence of EP and other endometrium conditions at different ages.*
Materials and methods. *Based on the study of 4059 histological samples we analysed the EP's prevalence and association with other intrauterine pathology in women of different age groups.*
Results. *EP was diagnosed in 27.4% of samples. It's frequency varied from 21.7 to 27.3% in reproductive age and - 45% in postmenopausal women. 19.8% of EP were concomitant with chronic endometritis (CE), 3.7% with endometrial hyperplasia (EH).*
Conclusions. *EP take 1st place in the structure of intrauterine pathology during all age periods. Their prevalence is 2.7 times higher than CE, and 4.5 times higher than EH.*

Key words: *endometrial pathology, endometrial polyps, the prevalence.*

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Endometrial hyperplastic processes are the most common gynaecological disease. It is one of the main causes of abnormal uterine bleeding (AUB) and is the indication for most intrauterine interventions. It also has to be mentioned that endometrial hyperplasia (EH) is considered to be a risk factor of endometrial cancer; this condition has become more common in recent years and now affects younger people. Therefore, particular attention is being directed to developing programmes that involve timely diagnosis and adequate therapy of background and precancerous endometrial lesions. The risk of malignancy is known to be increased in both EH and EP. These disorders are also associated with a high risk of relapses, which lead to numerous intrauterine interventions resulting not only in decreased quality of life but also in a risk of endometrial damage, formation of intrauterine synechiae, and development of uterine variants of infertility. According to literature data, the prevalence of EP is in the range of 7.6 % to 34.9 % [1—6]. It should be mentioned that a number of publications provide EP prevalence data obtained through analysis of the causes of abnormal uterine bleeding in women hospitalized in gynaecology hospitals [2, 6, 7]. Other publications provide EP occurrence rates based on results of a screening conducted in a population of women many of whom made no complaints of menstrual cycle disorders [3, 8]. This high variability of detection rates can also be explained by the fact that patients of different age groups were enrolled in these studies and by the use of different diagnostic methods. For instance, some of the investigators evaluated data from histology reports obtained after endometrial sampling [7, 9], while others analyzed results of ultrasonography [8, 10], a technique that hasn't got enough sensitivity and specificity compared with sonohysterography and morphological examination of endometrial samples [11]. The ambiguity of the approaches utilized to assess EP prevalence rates pose difficulties for understanding the real scale of this problem and optimizing possible solutions.

The aim of the study is to evaluate the prevalence of EP and the morphological structure of the uterine mucous membrane at different ages.

Materials and methods

We conducted a retrospective analysis of results obtained in 4059 histological studies: endometrial samples (3956) and biopsies (103). The materials of the study were archived data in 2016 from the Department of Pathology of the Federal State Budget Institution «V.I. Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology» Ministry of Healthcare of the Russian Federation. According to the formulated study objective, the primary diagnosis in patients with combined endometrial disorders was recorded as EP or, in their absence, as EH. Statistical analyses were carried out using the statistical application package R, version 3.4.0. Statistical significance was assessed with the help of Pearson's chi-square test with a critical p value of < 0.05.

Results

The endometrial morphology data are presented in Table 1. This table shows that no abnormalities were observed in 52.7 % of the cases: the endometrium was either proliferative or secretory. The most common disorder was EP; their rate was 27.4 %. It should be mentioned that precancerous changes were found in 6 EP cases and an endometrioid adenocarcinoma was found in one observation (0.09 %). In the other samples, EP were benign and characterized by pathologists as glandular fibrous, glandular, or fibrous. CE was diagnosed 2.7 times less commonly, and EH 4.5 times less commonly. The rate of atypical endometrial hyperplasia (AEH) was only 0.3 %, and that of endometrial cancer 0.7 %. (Table 1).

Table 1. The structure of endometrial morphology.

Endometrial structure	N=4059	%
Endometrial polyps	1113	27,4%
Endometrial hyperplasia without atypia	233	5,8%
Atypical endometrial hyperplasia	11	0,3%
Chronic endometritis	422	10,4%
Endometrial cancer	30	0,7%
Atrophic endometritis	93	2,3%
Uterine synechiae	18	0,4%
No abnormalities	2139	52,7%

In the overwhelming majority of cases, EP were found against a background of unaltered proliferative or secretory endometrium; they were combined with other uterine mucosa disorders in 23.5 % of cases. The most common comorbidity was CE, which was observed in one out of five patients (Figure 1). Women aged 36 - 45 years were found to have an association between EP and CE - OR 1.58 CI [1.19; 2.10], while no reliable association could be demonstrated in the other age groups. EP were combined with EH in 3.4 % of observations and with AEH in 0.3 % of them.

Apart from studying endometrial samples, we evaluated the state of the cervical canal mucosa. Endometrial pipelle sampling results did not permit a judgement on the state of the endocervix, so we took into account 3956 tissue samples obtained by D&C. Endocervix disorders were observed only in 482 cases (12.2 %). Chronic cervicitis was diagnosed in 240 (6.1 %) patients, polyps of the cervical canal in 237 cases (6.0 %), and cervical cancer in 5 patients (0.13 %). Cervical canal morphology data obtained in patients with EP revealed a combination with polyps of the cervical cancer in 5.5 % of cases and a combination with chronic cervicitis in 4.0 %.

To analyze the rates of endometrial disorders in connection with age, we divided all patients into five groups: 25 years old or younger (n = 198), age 26 - 35 years (n = 1797), 36 - 45 years (n = 1612), 46 - 55 years (n = 290), and over 56 years of age (n = 162). The detection rates of the main endometrial disorders in these groups are shown in Figure 2.

The presented data provide convincing evidence that EP were predominant in all age groups. Their rate was found to be 21.7 % in women aged up to 25 years, whereas CE was 2.4 times less common and EH was 4.7 times less common. Uterine synechiae, a rather rare disorder, was diagnosed in 1 % of patients in this group. There were no cases of AEH or endometrial cancer in patients aged under 25 years. The overall rate of endometrial disorders in this age group was 36.4 %, the proportion of EP was 59.7 %.

In the 26 - 35 years group, we observed a trend towards higher occurrence of EP (up to 26.1 %, $p<0.001$) and CE (up to 12.5 %); intrauterine synechiae were observed in isolated cases (0.5 %). The rate of EH was at the same level. Interestingly, 4 patients in this age group (0.2 %) were diagnosed with AEH, one patient with EP, and 5 subjects (0.3 %) with endometrial cancer.

There were no significant changes in the analyzed rates in the 36 to 45 years group (Figure 2). The rate of EP exceeded that of CE 2.6 times and that of EH 4.2-fold. The overall rate of endometrial disorders in the age groups 26 - 35 years and 36 - 45 years were higher: 44.4 % and 45.6 %, respectively. The proportions of EP were 58.7 % and 60 %, respectively.

As the data presented in Figure 2 show, perimenopausal women (46 - 55 years old) had a higher rate of EP compared with women aged up to 25 years ($p<0.001$). EP were diagnosed in one out of three endometrial samples, accounting for 57.9 % of all diagnosed disorders. The rate of EH without atypia was almost twice higher than in women aged up to 35 years, reaching 8.3 %. The rate of AEH was 7 times higher, and that of endometrial cancer 3.7 times higher. Compared with the 36 - 45 years group, we also observed a significantly higher rate of endometrial cancer (1.4 % vs. 0.4 %, more than 3.5 times higher) and AEH (1.4 % vs. 0.2 %, 7 times higher). The proportion of CE was, on the contrary, 2 times lower; there were no cases of endometrial synechiae. The endometrium was found to be atrophic in 6.5 % of cases. The overall rate of endometrial disorders in this age group was 52.8 %, and the proportion of EP was 56.8 %, which was significantly higher than in women aged 26 - 35 years ($p<0.001$).

Interesting data were obtained in the postmenopausal group. The overall rate of endometrial disorders did not differ significantly (58 %); however, the proportion of EP was as high as 77.7 %. EP were observed in almost every second endometrial sample (45 %). Two of these cases were AEH, and one was an adenocarcinoma. The rate of EH was lower, 3.1 % vs. 8.3 %; there were almost no cases of CE (0.6 %). The rate of endometrial cancer in postmenopausal women was as high as 9.3 %, 6.6 times higher than in the 46 - 55 years group.

Discussion

We evaluated the EP detection rates at different ages based on histology results obtained in 4059 endometrial samples. EP were shown to be the most common endometrial disorder, with a proportion of 27.4 %. Similar data were reported in a number of foreign studies. In particular, Mariam Abid et al. (2014) revealed that the rate of EP in women with AUB was 21 % based

on histology reports [7]. A retrospective analysis by P. Capmasa et al. (2016) yielded a 27 % proportion for EP. It has to be mentioned that this study assessed the prevalence of EP using only hysteroscopy, without morphological confirmation, and without taking patient age into account [6]. Literature data also indicate lower rates of EP: in particular, a publication by Ozturk Inal et al. (2017). The prevalence of EP, based on 4247 histology reports, was only 10.4 % [9]. In a study by E. Dreisler, which enrolled 686 women aged 20 - 74 years, the rate of EP was still lower, 7.8 % [8]. This can be explained by the fact that this analysis used data of randomly selected female patients in the Danish Civil Registration System and that a diagnosis of EP was made using only ultrasonography findings. In our study, we evaluated the occurrence of EP based on patient's visits and histological reports.

The second most common uterine disease was CE detected in 10.4 % of endometrial samples. According to domestic and foreign literature data, the prevalence of CE varies from 3 % to 60 % [9, 12, 13, 14]. In patients undergoing hysteroscopy for AUB, the prevalence of CE is in the range of 9.1 % to 12 %, not differing significantly from our own data [7, 15].

The reported study yielded a 5.8 % rate for EH and a 0.3 % rate for AEH. These data are practically the same as the results of an earlier study conducted in our clinic. Morphological results obtained for 11219 endometrial samples revealed a 4.8 % rate for EH without atypia and a 0.6 % rate for AEH [16]. Other sources, however, provide higher rates of EH, in the range of 8.6 % to 26.4 % [9, 14, 17]. EH is conventionally seen as a background disease for endometrial cancer, which is one of the most common cancers of the female reproductive system. The highest rate of endometrial cancer is observed in the postmenopausal period [9, 18]. Our data revealed that the prevalence of endometrial cancer in this age group was 9.3 %, i. e. 6.6 times higher than in premenopausal women. It is essential to mention that isolated cases of endometrial cancer (0.3 %) were documented in women under 35 years of age. These findings show that endometrial morphology is important not only in postmenopausal women but in younger patients as well.

Of note is the fact that no endometrial abnormalities were observed in one out of two endometrial scrapings (52.7 %): the endometrium was either proliferative or secretory. Some literature sources provide similar data, i. e. a high percentage of normal endometrial scrapings (including patients with AUB), up to 63—72 % [9, 15, 17]. One possible explanation of the absence of endometrial abnormalities in examined samples is that diagnostic curettage is performed in most laparoscopic surgical interventions, following failed in vitro fertilization attempts, as well as to monitor endometrial morphology after treatment for EH or CE. From our point of view, the obtained data reveal a need for more accurate endometrial assessment at the pre-hospital stage and to define clear indications for endometrial curettage during laparoscopic surgeries, as this procedure is associated with an additional risk of intraoperative complications and endometrial injury. It appears that the spectrum of indications for minimally invasive intrauterine surgical procedures (such as suction biopsy) should be broadened.

The results of the reported study demonstrated that the endometrial pathology detection rate progressively increased with age, from 36.4 % in women aged 25 years or younger to 58 % in postmenopausal patients. Polyps are the most common endometrial abnormality regardless of age. Its detection rate was 21.7 % in women aged 25 years or younger, increasing to 30 % and 45 % in perimenopausal and postmenopausal women, respectively. Other studies have also shown an increase in EP occurrence from reproductive age to menopause, although with lower rates in the age groups. According to some authors, this rate is 1 % to 5 % in the age interval from 20

Figure 1. Endometrial morphology in patients with endometrial polyps

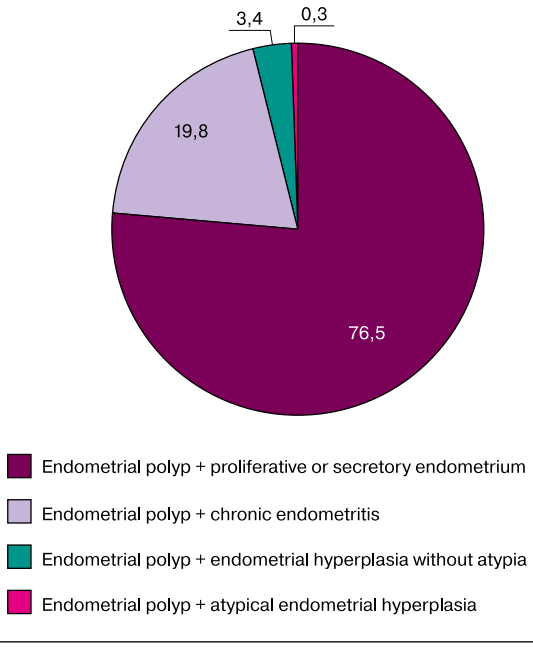
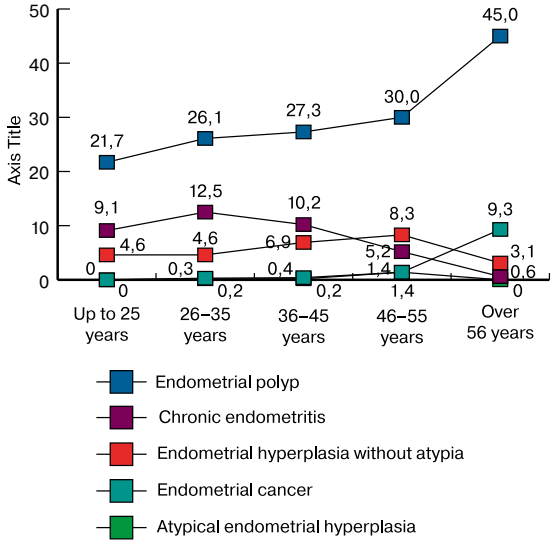


Figure 2. Endometrial disorders in different age periods



to 29 years and grows to 8 % - 9.3 % after 30 years and to 16 % - 35.5 % in perimenopausal women [2, 3, 7, 8, 19].

It should be underlined that precancerous and malignant changes were found in 0.6 % of EP. In foreign literature sources, this rate lies in the range of 0.3 % to 4.8 %, reaching its maximum in the postmenopausal period [20 - 24]. In the reported study, all groups above 25 years of age had approximately the same rate of precancerous changes. The obtained results confirm the need to remove EP at any age.

We were able to find only a few publications on combinations of EP with other endometrial and endocervical abnormalities in available literature. In particular, Topcu et al. found a combination of EP with EH without atypia in 5.9 % of endometrial samples and a combination with AEH in 0.5 % of cases [25]. In the Danish Civil Registration System, 9.4 % of premenopausal women have a combination of EP and cervical canal polyps [8]. Carvalho et al. found that 27.4 % of all EP had developed against a background of CE [26]. According to the obtained results, EP were combined with CE in 19.8 % of cases and with EH in only 3.7 % of them (including combinations with AEH in 0.3 % of patients). These data may be an indirect indication of a role of inflammation in the pathogenesis of EP, although a reliable association between polyps and CE was demonstrated only in women aged 36 to 45 years. Inflammation may cause epigenetic changes, including those in the genes regulating proliferation and apoptosis in the endometrium, which can promote the development of EP [27]. EP are known to frequently relapse. According to literature data, the relapse rate is 13.3 % to 21.5 % for a 2-year period, regardless of the used surgical treatment [28, 29]. The recurrence rate is high because polypectomy does not result in elimination of the aetiological factor and does not affect the mechanisms underlying the development of EP, which have not been established to date.

In general, we can conclude that EP are the most common uterine disorder and the main indication for diagnostic dilation and curettage procedures, which result in endometrial injury and decrease the patient's quality of life. These findings highlight the topicality of this problem and warrant further investigation of EP's pathogenesis to define the predictors of recurrence and principles of secondary prevention.

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