EPIDEMIOLOGIC STUDY OF ENDOMETRIAL LESION CHARACTERISTICS BY AGE IN PATHOLOGY DIAGNOSTIC CENTER IN SURABAYA 2015-2017

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ABSTRACT

Background: *The etiology of endometrial lesions varies from benign to malignant. Early detection and management of malignancy give the best prognosis for the patient. While studies in America and Europe report a 3-5% risk of malignancy in women below 50 years and a significant increase up to 75-80% in postmenopausal, the availability of national epidemiologic data is limited, therefore the study is held.* ***Method:*** *A descriptive- retrospective study. Total sampling obtained from endometrial specimens in Pathology Diagnostic Center-Prof JH Lunardhi, Sp.PA(K) from 2015 to 2017, while gestation-related, inadequate sample, and incomplete report are excluded. Data analyzed by IBM SPSS 23.0 version.* ***Result:*** *Data of 560 samples, 90% from curettage, 8% hysterectomy, and 2% hysteroscopy. The majority belonged to the 40-49 age group (44.3%). Secretory phase endometrium is the most common finding in the age group of 20-29 years (26.9%). Proliferative phase endometrium is the most common finding. The highest incidence of endometrial hyperplasia occurred in the age group of 40-49 years, for both typical and non-atypical. Endometrial malignancy was found mostly in the 50-59 years (37.03%).* ***Conclusion****: The prevalence of endometrial lesions differed according to age groups, with physiological changes, endometritis, polyps, and hyperplasia were most common under 50 years old and the risk of malignancy increased 4.39 times (p.00) beyond 50 years old.*

Keyword*: Endometrial Lesion, Hyperplasia, Age, Menopause, Malignancy*

ABSTRAK

Latar Belakang: Etiologi lesi endometrium bervariasi dari kelainan jinak sampai keganasan. Deteksi dan tata laksana dini pada keganasan memberikan prognosis terbaik. Penelitian di Amerika dan Eropa melaporkan 3-5% resiko keganasan pada usia dibawah 50 tahun dan meningkat signifikan sampai 75-80% paska menopause. Data epidemiologi nasional masih terbatas sehingga penelitian ini perlu dilaksanakan. **Metode:** Studi deskriptif retrospektif. Total sampel dari spesimen endometrium di Sentra Diagnostik Patologi Prof. JH Lunardhi, SpPA(K) tahun 2015-2017 dengan kriteria eksklusi lesi terkait gestasi, sampel tidak adekuat

dan laporan tidak lengkap. Data dianalisa dengan IBM SPSS versi 23.0. **Hasil:** Data 560 sampel endometrium, 90% kuretase diikuti dengan histerektomi 8% dan histeroskopi 2%, yang didominasi kelompok usia 40-49 tahun (44,3%). Endometrium fase sekresi merupakan temuan yang terbanyak pada kelompok usia 20-29 tahun (26,9%). Endometrium fase proliferasi merupakan temuan terbanyak pada kelompok usia 30-69 tahun dan usia 80-89 tahun. Pada kelompok usia 70-79 tahun, temuan yang terbanyak adalah hiperplasia endometrium non-atipikal (50%). Kejadian hiperplasia endometrium paling banyak terjadi pada kelompok usia 40-49 tahun, baik pada non-atipikal (55,3%) maupun atipikal (83,3%). Keganasan pada endometrium paling banyak ditemukan pada kelompok usia 50-59 tahun (37,03%). **Kesimpulan:** Prevalensi lesi endometrium berbeda sesuai kelompok umur, pada usia dibawah 50 tahun didapatkan endometritis, polip dan hiperplasia. Pada usia diatas 50 tahun risiko keganasan meningkat 4,39 kali lipat (p=0,00)

***Kata Kunci**: Lesi Endometrium, Hiperplasia, Umur, Menopaus, Keganasan*

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BACKGROUND

Endometrial lesions may occur anytime in a woman's life, which prompts them to visit medical facilities with the chief complaint of vaginal bleeding. The etiology varies from benign changes caused by hormone exposure, endometrial polyps, chronic endometritis, endometrial hyperplasia, and endometrial malignancy. Endometrial hyperplasia is potentially progressed to endometrial malignancy according to clinicopathology and epidemiology past studies [1]. In 2018, the estimated prevalence of endometrial cancers was 33.9/100.000 and becoming the second-largest cancer prevalence worldwide after cervical cancer[2].

Histopathology abnormalities vary among age groups of women. Endometrial lesion among young women is caused by hormone imbalance, while endometrial hyperplasia and endometrial malignancy occur among older women [3].

Data on the prevalence of endometrial lesions based on age helps the physician in managing patient complaints and stakeholders in establishing policies for screening in high-risk age groups. The epidemiological study regarding the prevalence of endometrial lesions in Indonesia is limited, therefore a thorough report is needed.

METHODS

This research was a descriptive, observational, and retrospective study. The population was women who had undergone pathology examinations of the endometrium from January 2015 to December 2017. The total sampling method includes endometrial examinations obtained from curettage, hysteroscopy, and hysterectomy. The exclusion criteria were gestation-related lesions, inadequate samples, and incomplete reports. The research was carried out from October 1, 2020, to December 31, 2020, at the Anatomical Pathology Clinic run by Prof. JH Lunardhi in Surabaya and analyzed using the IBM SPSS version 23.0 program. The chart of epidemiology distribution is shown in numbers and percentages.

RESULT

560 reports of the endometrial examination met the inclusion criteria, with 90% of specimens obtained by curettage, 2% hysteroscopy, and 8% hysterectomy. Hysteroscopic classifications are presented to demonstrate the use of technology in patient management.

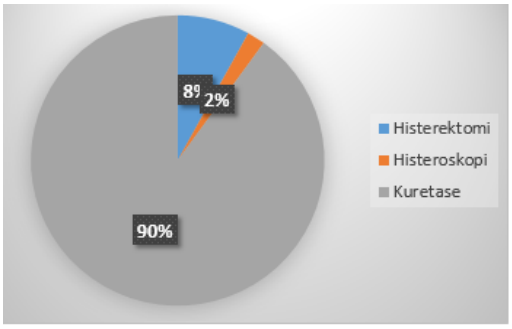

Figure 1. Distribution of Procedures Done to Obtained Endometrial Tissue.

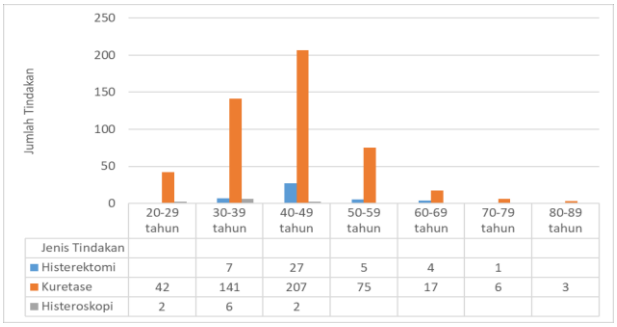

Figure 2. Distribution of procedures done based on age group

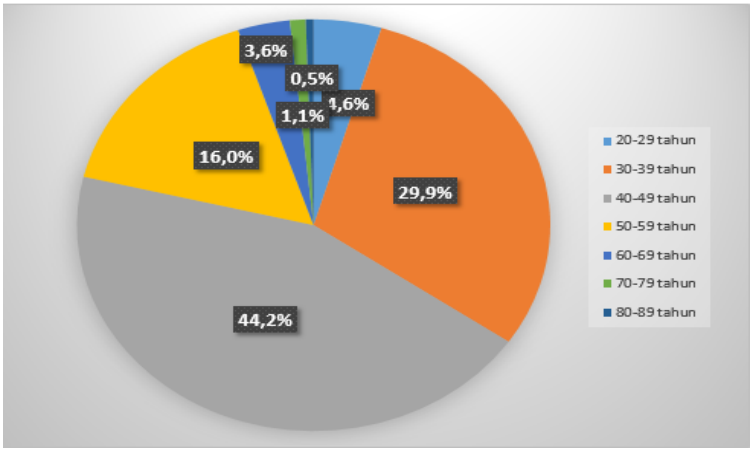

Figure 3. Distribution of age underwent sampling procedures

Table 1. Result of Biopsy Based on Age

	Age Group							Total
	20-29	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-89**	
Irregular Shedding	1 (3,8%)	10 (6,0%)	16 (6,4%)	4 (4,4%)	0 (0%)	0 (0%)	0 (0%)	31 (5,5%)
Endometrial polyp	6 (23,1%)	34 (20,2%)	27 (10,8%)	10 (11,1%)	1 (5,0%)	0 (0%)	0(0%)	78(13,9%)
Long Standing Progesterone Effect	2 (7,7%)	7 (4,2%)	4(1,6%)	0(0%)	0(0%)	0(0%)	0 (0%)	13(2,3%)
Undifferentiated Carcinoma	0 (0%)	1 (0,6%)	0 (0%)	1 (1,1%)	0 (0%)	0(0%)	0 (0%)	2 (0,4%)
Atrophic Endometrium	0 (0%)	0 (0%)	0 (0%)	2 (2,2%)	1 (5%)	0 (0%)	0 (0%)	3 (0,5%)
Atrophic Endometrium with Cystic Changes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (0,2%)
Proliferative Phase Endometrium	6(23,1%)	45(26,8%)	65(26,1%)	37(41,1%)	9 (45%)	2 (33,3%)	2(66,7%)	166 (29,5%)
Secretory Phase Endometrium	7 (26,9%)	31 (18,5%)	41(16,5%)	4 (4,4%)	0(0%)	0(0%)	0(0%)	83 (14,7%)
Nonatypical Hyperplasia	1 (3,8%)	27 (16,1%)	68 (27,3%)	21 (23,3%)	3 (15%)	3 (50%)	0(0%)	123 (21,8%)
Atypical Hyperplasia	1 (3,8%)	0 (0%)	10 (4%)	1 (1,1%)	0 (0%)	0 (0%)	0 (0%)	12 (2,1%)
Chronic Endometritis	1 (3,8%)	7 (4,2%)	11 (4,4%)	1 (1,1%)	1 (5%)	1 (16,7%)	1 (33,3%)	23 (4,1%)
Grade 1 Endometrioid Carcinoma	0 (0%)	2 (1,2%)	0 (0%)	2 (2,2%)	0 (0%)	0 (0%)	0 (0%)	4 (0,7%)
Grade 2 Endometrioid Carcinoma	1 (3,8%)	0 (0%)	4 (1,6%)	2 (2,2%)	3 (15%)	0 (0%)	0 (0%)	10 (1,8%)
Grade 3 Endometrioid Carcinoma	0 (0%	1 (0,6%)	0 (0,0%)	1 (1,1%)	0 (0%)	0 (0%)	0 (0%)	2 (0,4%)
High grade endometrial Adenocarcinoma	0 (0%)	0 (0%)	0 (0%)	1 (1,1%)	0 (0%)	0 (0%)	0 (0%)	1 (0,2%)
Moderately differentiated adenocarcinoma	0 (0%)	1 (0,6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,2%)
Papillary Adenocarcinoma	0 (0%)	0 (0%)	0 (0%)	1 (1,1%)	0 (0%)	0 (0%)	0 (0%)	1 (0,2%)
Endometrial Stromal Sarcoma DD Malignant Mixed Müllerian Tumor	0 (0%)	0 (0%)	0 (0%)	1 (1,1%)	0 (0%)	0 (0%)	0 (0%)	1 (0,2%)
Endometrial Stromal Tumor	0 (0%)	1 (0,6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,2%)
Endometrioid Adenocarcinoma with squamous metaplasia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (0,2%)
Endometrioid Adenocarcinoma, Well differentiated	0 (0%)	0 (0%)	0 (0%)	1 (1,1%)	0 (0%)	0 (0%)	0 (0%)	1 (0,2%)
Nonkeratinizing Squamous Cell Carcinoma, intermediate cell type	0 (0%)	1 (0,6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,2%)
Polypoid Adenocarcinoma, well differentiated	0 (0%)	0 (0%)	1 (0,4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0,2%)
Total	26 (100%)	168 (100%)	248 (100%)	90 (100%)	20 (100%)	6 (100%)	3 (100%)	560 (100%)

RESULT

The prevalence of endometrial lesions is listed in Table 1. Based on this table, the endometrial secretion phase was the most common finding in the 20-29 year age group (26.9%). Proliferation phase endometrium was the most common finding found in the age group 30-39 years (26.8%), 50-59 years (41.1%), 60-69 years (45%). and aged 80-89 years (66.7%). In the 40-49 years and 70-79 years age group, the most common finding is non-atypical endometrial hyperplasia (27,3% and 50% respectively).

The result of endometrial irregular shredding was most commonly found in the 40-49 age group (n=16/31;51.6%). Endometrial polyps were found mostly in the 30-39 age group (n=34/78;43.6%). Chronic endometritis was also found mostly in the 40-49 age group (11/23;47.8%), and endometrial lesions caused by prolonged progesterone exposure were commonly found in the 30-39 age group (n=7/13;53.8%). In the 50-59 age group, most findings were endometrial atrophy (n=2/3;66.7%) while in the 60-69 age group, most of the findings were endometrial atrophy cystic changes (n=1/1;100%).

Table 2. Age group domination for endometrial lesion

Endometrial lesion	Age group	Percentage of most common age group in a finding *
Long-standing progesterone effect	30-39 y.o	53.8% (7/13)
Endometrial polyp	30-39 y.o	43.6% (34/78)
Irregular shedding	40-49 y.o	51.6% (16/31)
Chronic Endometritis	40-49 y.o	47.8% (11/23)
Non-atypical and typical endometrial hyperplasia	40-49 y.o	83.3% (10/12) – Atypical** 55.3% (68/123) – Typical***
Endometrial atrophy	50-59 y.o	66.7% (2/3)
Endometrial malignancy	50-59 y.o	37.0% (10/27)

- For example:7 out of 13 cases of long-standing progesterone effects were found in 30-39 y.o
  ** 10 out of 12 cases of atypical hyperplasia found in 40-49 y.o
  *** 68 out of 123 cases of typical hyperplasia found in 40-49 y.o

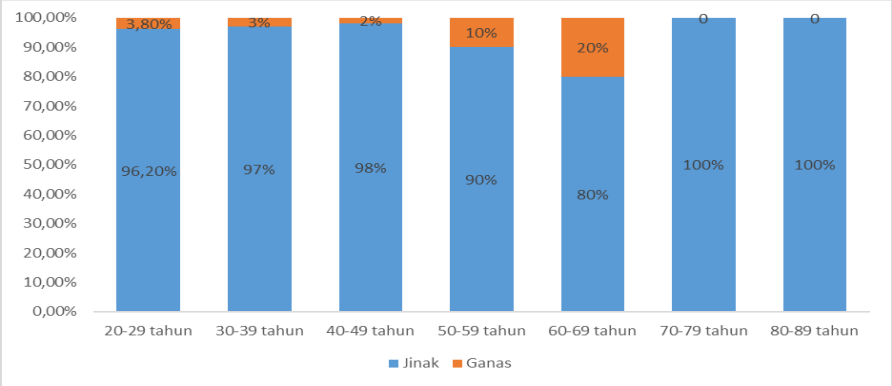

Figure 4. Prevalence of Benign and Malignant Lesions across Age Group

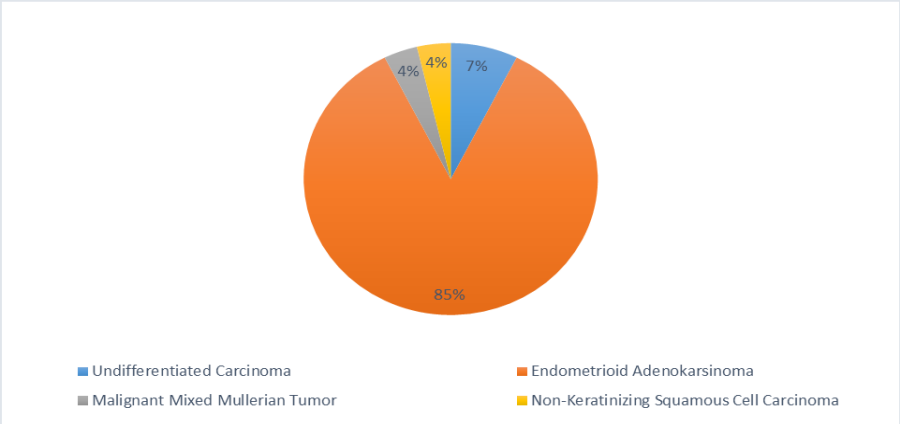

Figure 5. Endometrial Malignancy Distribution

Endometrial malignancy were commonly found in 50-59 y.o (n=10/27;37.03%). Malignancies found in this research dominated by endometrioid adenocarcinoma (n = 23/27; 85.1%) followed by undifferentiated carcinoma (n=2/27;7.4%), non-keratinizing squamous cell carcinoma (n=1/27;3.7%), and endometrial stromal sarcoma tumor with Mixed Mullerian Tumor as its differential diagnosis (n=1/27;3.7%). Endometrioid carcinoma was mostly found in grade II (n=10/16;62.5%).

Tabel 3. Rissygk of Malignancy

			Findings		Total	**Odds Ratio**	**P-Value**
			Malignant	Benign			
Risk	< 50 years old	Count	13	428	441	**4.39**	**0.000***
		% within Risiko	2.9%	97.1%	100.0%		
	≥ 50 years old	Count	14	105	119		
		% within Risiko	11.8%	88.2%	100.0%		
	Total	Count	27	533	560		
		% within Risiko	4.8%	95.2%	100.0%		

Women at 50 years old and above have a 4.39 times higher risk of malignancy than their peers. This finding was statistically significant p = 0.000.

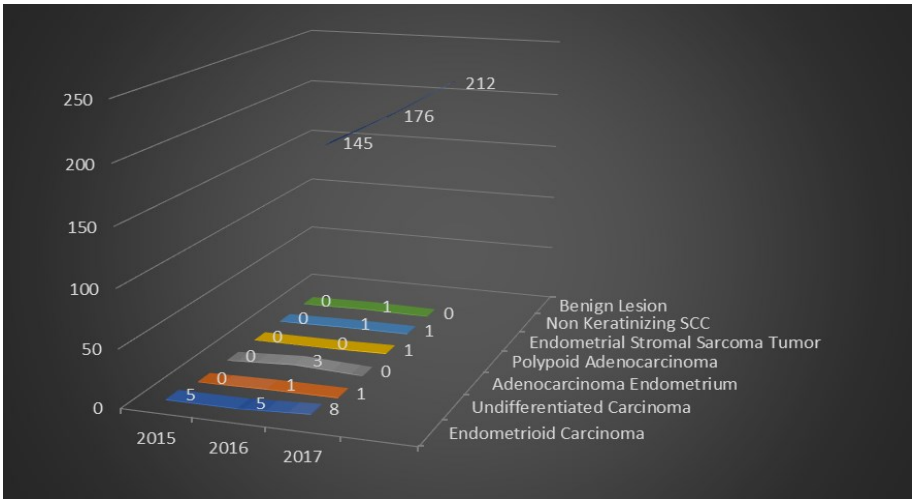

Figure 6. The trend of cases found from 2015-2017

Prevalence of malignancy was unchanged in 3 years, while the benign lesion increased rate by 20% annually from 145 cases in 2015, 176 cases in 2016, and 212 cases in 2017.

DISCUSSION

Irregular shedding of endometrium occurs due to regression failure of the corpus luteum lead to prolonging progesterone exposure. Irregular endometrial shedding was found across ages, mostly in the 40-49 year age group (n = 16/31; 51.6%). The results are similar to research conducted at the Kandou Manado General Hospital which stated that most irregular shedding cases were at 41-50 years old (33.87%) [4]. Also, research in Nigeria states that irregular shedding was found most frequently in the fourth decade as 43.3% [3]. However, another study states that the age of irregular shedding occurs in the fifth decade as much as 35.9% [5]. This difference might happen due to multifactorial influences such as genetics, ethnics or environmental such as diet, nutrition, and activities.[6].

This study reported proliferation phase of the endometrium was 29.5%and secretory 14.7% with the age range of the endometrium in the proliferation phase varying at the age of 20-89, while the endometrium in the secretion phase was mostly found in the 20-29 year age group. Proliferative endometrium can be caused by contraceptive use and medications for abnormal uterine bleeding before curettage. Another study in Nigeria also found that the proliferation phase endometrium also dominates (21.7%) and secretion phase endometrium (12.4%) [3]. Research in Italy on women aged 30-40 years stated that the endometrium does not age, but only

changes when there is hormonal administration or the menstrual cycle [7].

The most commonly used low-dose oral contraceptive is progesterone, which inhibits proliferative changes in the endometrium's normal cycle [8]. In this study, it was found that endometrial lesions due to the effects of prolonged progesterone were mostly found in the 30-39 year age group (n = 7/13; 53.8%). This might be related to the age of women who use contraception, especially hormonal contraceptives that contain progesterone such as birth control pills, injection contraceptives, or IUD with progesterone. Prolonged progesterone exposure can also be caused by abnormal uterine bleeding treatment.

In this study, it was found that the prevalence of endometrial polyps was 13.9%. The results of this study were higher than other studies in Nigeria, which only included 3.1% [3]. This difference could be due to differences in racial and ethnic characteristics in each population. In previous studies, it was found that menopause, the elderly (> 60 years), obesity, and diabetes mellitus are clinical parameters that can increase the risk of developing benign and malignant endometrial polyps. The highest number of cases of endometrial polyps in this study was found in the 30-39 year age group. This result is inconsistent with previous studies in which endometrial polyps were found to be the largest in the perimenopausal age group. The low number of cases in the younger age group may be due to the spontaneous regression mechanism of polyps, which are characteristic of changes in the endometrial cycle in women of reproductive age.

The number of endometrial polyps cases continued to decline, starting in the perimenopausal age group. Other studies have listed an increase in the prevalence of endometrial polyps with age due to prolonged exposure to estrogen and progesterone, which affects the proliferation and differentiation of the endometrium [9]. The results of another study in Denmark also stated that the prevalence of endometrial polyps would continue to increase with age [10].

The prevalence of endometrial atrophy was found to be 0.5% and was found mostly in the 50-59 years age group. The prevalence of endometrial atrophy accompanied by cystic changes is only found in the 60-69 years age group. Our study was consistent with previous studies stating that atrophy in the endometrium was found mostly in post-menopausal women. This is due to the loss of endometrial stimulation by estrogen either externally or internally after menopause, which causes the endometrial walls to become thin and

eventually atrophy [11]. Endometrial walls that experience atrophy will cause minor injury to occur and are the most common cause of postmenopausal bleeding [12].

The prevalence of chronic endometritis in this study was found to be 4.1% and was mostly found in the 40-49 year age group. Our study was consistent with a previous study in India, which stated that chronic endometritis was found mostly in perimenopausal age [13]. Transvaginal infection, intrauterine devices (IUD), submucosal leiomyoma, and endometrial polyps are the most common causes of chronic irritation of the endometrium, leading to chronic inflammatory reactions in the endometrium [11]. Chronic endometritis is mostly found in women of perimenopausal age, probably due to menstrual cycle irregularities during perimenopause. The endometrial proliferation phase has been associated with the incidence of plasma cell endometritis. The longer the duration of the proliferation phase during perimenopause increases the risk of developing endometritis [14].

The incidence of endometrial hyperplasia prevalence was highest in the 40-49 years age group, those with and without atypia. This result was following the theory that endometrial hyperplasia occurs mostly in the perimenopausal age due to intermittent anovulation. With intermittent anovulation, there will be an absence of progesterone to counteract estrogen effects so that glandular proliferation continues [15]. However, the age at which endometrial hyperplasia occurs in Indonesia are younger if compared to the 2009 prevalence study in the United States with 63,688 samples who found that non-atypical endometrial hyperplasia was most prevalent at the age of 50-54, and atypic endometrial hyperplasia occurred mostly at the age of 60-64 [16]. Apart from the risk factors for endometrial hyperplasia, the younger occurrence of endometrial hyperplasia in this study might be explained because of sample size at the age of 40-49 is three times larger at the age of 50-59.

Most endometrial malignancies occurred at the age of 50-59, with the number of cases as much as 4.7% of all samples in this study. Previous studies on the prevalence of gynecological cancer in Indonesia in 2009 showed that the prevalence of endometrial cancer was mostly at the age of 45-54 years [17]. Another prevalence study of endometrial cancer at Dokter Sutomo Hospital with a sample of 95 people showed that endometrial cancer occurred mostly in the age of 51-60 years [18]. The population of patients with endometrial cancer in Indonesia is younger than patients in the United States. The number of endometrial

cancer prevalence in the United States is highest in the 55-64 years age group (median 63 years) [19]. There are several probable reasons to explain this phenomenon. The first possibility is that the sample size in our study and the past prevalence study in Indonesia was still smaller than the sample size in the United States study. The second possibility is the existence of special risk factors that are owned by the population in Indonesia. The most common type of malignancy in the endometrium is endometrioid carcinoma. In theory, endometrioid carcinoma accounted for 83% of cases of endometrial malignancies [20]. However, our study found that endometrioid carcinoma only made 37.03% of all malignancies were present in this study. This may be due to the small sample of endometrial malignancy.

The risk factors for endometrial hyperplasia and endometrial cancer are chronic estrogen exposure and a relative progesterone deficiency. This can occur due to increasing age, genetics, early menarche, late menopause, obesity, diabetes mellitus, PCOS, estrogen-producing tumors, and immunosuppression. [21], [22]. Several genetic mutations cause endometrial malignancies, including PTEN Tumor Suppressor Gene, PIK3CA, KRAS, ARID1A, and TP53 [23]. The prevalence of this gene mutation is unknown in Indonesia.

LIMITATION

There were some limitations in this study. The insufficient sample size of women aged 60 years and over may affect the prevalence rate of endometrial disease, particularly endometrial cancer. However, the sample size in this study was relatively superior compared to other studies in Surabaya. It is hoped that, with this large sample, the numbers obtained can be more representative of the actual situation.

For further research, studies with larger sample sizes, more even age distribution, and detail clinical and epidemiological profiles are needed. Research is also necessary to investigate the prevalence of gene mutations or other factors which cause the younger occurrence of endometrial hyperplasia and cancer in Indonesia.

CONCLUSION

There were differences in the etiology of endometrial lesions based on age groups. At a younger age, causes of endometrial lesions include inflammatory lesions, hormonal influences, polyps, and hyperplasia. The risk of endometrial malignancy increased 4.39 times at the age above 50 years significantly ($p = 0.00$). The type of malignancy in the endometrium was dominated by endometrioid

adenocarcinoma The trend in the prevalence of malignancy did not increase in 3 years (2015 - 2017) while cases of benign lesions increased by 20% per year.

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