Endometrial Histology in Abnormal Uterine Bleeding with Risk Factors

Gambaran Histologi Endometrium PUA dengan Faktor Risiko

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Abstract

Objective: To determine the endometrial histology in abnormal uterine bleeding (AUB) patients with risk factors.

Method: This study involved 30 patients with complaints of AUB, aged over 35 years with associated risk factors of parity, obesity and fasting blood glucose in the outpatient clinic at Prof. Dr. R. D. Kandou General Hospital Manado, from July 2013 until October 2013. Patients who agreed to be involved in this study, underwent dilatation and curettage (D&C) to assess the endometrial histology that was grouped as the hyperplasia and non-hyperplasia groups.

Result: From the results of the study, 7 patients were in the 35-40 years age group (23.3%) and in the 41-50 years age group were 23 patients (76.7%). Based on parity, 11 patients (36.7%) were nulliparous and 19 patients (63.3%) were multiparous. Based on the BMI, 16 patients (53.5%) were obese and 14 patients (46.7%) were non-obese. And based on the results of fasting blood sugar, similar results was obtained in normal and abnormal fasting blood glucose with the results of 15 patients in each groups (50%). And from all of patients who underwent D&C, endometrial hyperplasia was shown in 21 patients (70%) and non-hyperplasia endometrium in 9 patients (30%). From the results of Fischer exact test, a significantly high association was obtained between BMI and fasting blood glucose with the occurrence of endometrial hyperplasia.

Conclusion: There is a significant relationship between BMI and high fasting blood glucose with endometrial hyperplasia.

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Keywords: age, AUB, BMI, endometrial hyperplasia, fasting blood sugar, parity

Abstrak

Tujuan: Untuk mengetahui gambaran histologi endometrium pada penderita PUA dengan faktor risiko.

Metode: Penelitian ini melibatkan 30 pasien dengan keluhan PUA yang berusia di atas 35 tahun dan dihubungkan dengan faktor risiko paritas, obesitas dan gula darah puasa di poliklinik RSUP Prof. Dr. R. D. Kandou Manado, sejak Juli 2013 sampai Oktober 2013. Pasien yang telah setuju untuk terlibat dalam penelitian ini dilakukan D&C untuk mengetahui gambaran endometrium yang dikelompokkan dalam kelompok hiperplasia dan non-hiperplasia.

Hasil: Dari hasil penelitian terhadap 30 pasien yang datang dengan keluhan PUA dan setuju dilakukan D&C didapatkan hasil pada kelompok usia 35-40 tahun sebanyak 7 pasien (23,3%) dan kelompok usia 41-50 tahun sebanyak 23 pasien (76,7%). Berdasarkan paritas didapat 11 pasien (36,7%) nullipara dan 19 pasien (63,3%) multipara. Berdasarkan BMI didapatkan 16 pasien (53,5%) dengan obesitas dan pasien non-obese sebanyak 14 pasien (46,7%). Dan berdasarkan hasil gula darah puasa didapatkan hasil yang sama pada gula darah puasa normal dan gula darah puasa yang tidak normal dengan hasil masing-masing 15 pasien (50%). Dari semua pasien yang dilakukan D&C didapatkan hasil hiperplasia endometrium sebanyak 21 pasien (70%) dan non-hiperplasia endometrium sebanyak 9 pasien (30%). Dari hasil uji statistik Fischer exact test didapatkan hubungan yang bermakna antara BMI dan gula darah puasa yang tinggi dengan terjadinya hiperplasia endometrium.

Kesimpulan: Terdapat hubungan bermakna antara BMI dan gula darah puasa yang tinggi dengan hiperplasia endometrium.

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Kata kunci: gula darah puasa, hiperplasia endometrium, IMT, paritas, PUA, usia

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INTRODUCTION

Abnormal uterine bleeding (AUB) consists of all menstrual abnormalities, both in the amount and duration. Clinical manifestations may include bleeding, prolongation of menstrual cycle or irregular cycle.[1,2] AUB is a disorder most commonly encountered in daily practice in gynecology and a part of the largest problems in women. It is often present with varied clinical picture and is considered a complicated problem.[3] Its incidence amounts to 19.1% of all clinical visits for gynecological cases. In addition, it was reported that approximately 25% of all gynecologic surgery is related to abnormal uterine bleeding.[4]

AUB affects women by causing a decrease in productivity. This is due to a disturbance in the menstrual cycle and the amount of blood lost that can lead to anemia if not treated in a comprehensive manner. Given the high number of women of reproductive age in the population in Indonesia, and

the higher life expectancy in premenopausal and menopausal patients compared to the past, the negative impact of AUB will unconsciously decrease the productivity of Indonesia in the medium and long term.

Abnormal uterine bleeding can occur at any age between menarche and menopause, more commonly in the early years after menarche and at the end of the ovarian cycle. At perimenarche age, the most likely cause is a disorder of blood clotting factors and psychological causes.[4] At puberty and after menarche, abnormal uterine bleeding is caused by impaired or delayed maturation in the hypothalamus, which interrupts the gonadotropin hormone releasing factor and gonadotropin hormone. In particular, in adult women of reproductive age and in premenopausal period with abnormal uterine bleeding, curettage is necessary to determine the presence or absence of endometrial abnormalities. Endometrial curettage is also a procedure that is effective in confirming any endometrial abnormalities.[5]

Schröder, in 1915, conducted a histopathological study on the uterus and ovaries at the same time, drawing the conclusion that a bleeding disorder called hemorrhagic metropathy happens due to the persistence of follicles which is not broken, so there is no ovulation and corpus luteum formation. As a result, endometrial hyperplasia occurred due to excessive and continuous estrogen stimulation. This explanation is still acceptable for most cases of AUB.[6]

Endometrial hyperplasia is a condition in which the endometrium grows excessively. These abnormalities are benign, but in some cases can progress toward uterine malignancies. The histologic features of endometrial hyperplasia are glandular proliferation with changes in the shape and size, as well as an increase of glandular and stromal ratio.[7,8] In general, endometrial hyperplasia is divided into 4 types, namely simple, complex, simple with atypia and complex endometrial hyperplasia with atypia. Simple and complex endometrial hyperplasia is distinguished by changes in the structure of the complexity and amount of stroma between the glands, regardless of the existence of atypic cells.[8]

The diagnosis of atypical hyperplasia is based on the description of a specific core, the core is large, round, have irregular nuclear membrane, and is often accompanied by stratification of 2-4 cells with loss of polarity associated with the basement membrane. Chromatin is dispersed and clustered along

the nuclear membrane to form a vesicular picture. These vesicular nuclei are characteristic of atypic hyperplasia.[9] Aiza Saadia et al found that 40 percent of endometrial hyperplasia was identified from the results of endometrial curettage and that endometrial curettage had 100 percent specificity in the diagnosis of endometrial abnormalities and endometrial cancer.[5]

Treatment with progesterone is an ideal treatment for simple or complex endometrial hyperplasia without atypia. Considering that both simple and complex atypical endometrial hyperplasia has the potential towards malignancy, the best treatment is hysterectomy.[9]

Some women are at higher risk of endometrial hyperplasia and endometrial cancer. Furthermore, endometrial hyperplasia is a precursor of endometrial cancer.[10,11] Patients with endometrial hyperplasia usually present with abnormal bleeding, which can include menorrhagia, metrorrhagia, menometrorrhagia, or postmenopausal bleeding. We must be cautious of endometrial cancer for people aged over 35 years who present with bleeding.[10]

Endometrial hyperplasia often occurs in some women who are at high risk.[11,12] This includes patients aged over 35 years, preceded by missed period or amenorrhea, obesity (causing peripheral conversion of androgens to estrogen in fat tissue), patients with diabetes mellitus, nulliparous, long-term users of estrogen without progestin administration in postmenopausal cases, PCOS, and patients with ovarian tumors of granulose theca cell types.

Endometrial cancer is still not familiar for the public. The type of cancer that is popular among women is breast cancer, cervical cancer, or uterine cancer. Although the likelihood of mortality or death rate of patients is smaller than that of other cancers, endometrial cancer still carries its own risks.[13]

When viewed in descriptive epidemiology, in Indonesia there is no data on the number of cases of endometrial cancer. RSCM Jakarta found 72 new cases during the year 1993-2004 and found that 63.9% of patients were aged >50 years. The incidence of endometrial cancer is increasing in Indonesia, because the majority of people are living longer and the presence of more accurate reporting. Approximately 32,000 cases are estimated to occur each year resulting in 5900 deaths. One third of

women with postmenopausal bleeding have uterine cancer. The average age of patients with endometrial cancer was 61, and most patients are at least 55 years old.[13]

Since the cervical cancer death rate has decreased by more than 50% due to the progress in screening and early detection, the incidence of endometrial cancer is found to be second in gynecologic malignancies. The number of people diagnosed with endometrial cancer each year continues to rise.[14]

In this study, patients with AUB accompanied by risk factors of over 35 years of age, obesity, high blood sugar and nulliparity, had their endometrial histology examined to determine the possibility of endometrial hyperplasia occurrence, which is a precursor of endometrial cancer. Endometrial sampling can be performed by dilatation and curettage, hysteroscopy, and endometrial aspiration. Dilatation and curettage is still regarded as the most effective method because other than as a diagnostic tool, it can also simultaneously control bleeding in patients with AUB without abnormalities in the uterus or systemic abnormalities.[15,16] Histologic examination in this study is conducted by dilatation and curettage for diagnosis as well as therapy in patients with abnormal uterine bleeding.[17,18]

In Manado, there are no studies showing the incidence of AUB that leads to endometrial hyperplasia and endometrial hyperplasia predisposing factors. Therefore, we aim to examine endometrial histology in patients with AUB aged >35 years old (reproductive age, premenopausal and menopause), with suspected risk factors affecting the possibility of malignancy.

METHODS

This research is a cross sectional study with analytic approach. The population is AUB patients aged over 35 years who came for treatment at the outpatient clinic of Prof. Dr. R. D. Kandou General Hospital, Manado during the period of July 2013 to October 2013. This is also associated with risk factors of age, parity, obesity and fasting blood glucose. Patients who have agreed to participate in this study underwent D&C to determine the histologic picture of endometrium, and are grouped into the hyperplasia and non-hyperplasia group. The data obtained is analyzed statistically by performing Fischer's exact test to assess the significance of a relationship of the specified risk factors in influencing AUB.

RESULTS

On the characteristics of the patient sample by age, we obtained that in our patients AUB most commonly occurred in the 41-50 years age group, consisting of 23 samples (76.7%), and in the 35-40 years age group consisted of 7 samples (23.3%). Based on parity, we obtained that the multiparous group consisted of a total of 19 samples (63.3%) and the nulliparous group consisted of 11 samples (36.7%). Based on the BMI classification, AUB patients were more likely to be obese with 16 samples (53.3%) in the obese group, while in the non-obese group consisted of 14 samples (46.7%). From the fasting blood glucose, either group of normal and abnormal glucose profile each obtained 15 samples (50%). After performing D&C on the 30 samples, it was found that 21 samples (70%) had hyperplasia, and 9 samples (30%) had non-hyperplasia.

Table 1.   Sample Characteristics Based on Age

Age	D & C Result	
	Hyperplasia	Non-Hyperplasia
35-40	5	2
41-50	16	7

In regards to age, we obtained that among patients who were 35-40 years of age, 5 were found to have hyperplasia and 2 were observed as non-hyperplasia. Among patients over 40 years old, the result was 16 with hyperplasia and non-hyperplasia was as many as 7. Analysis using Fischer exact test found that p=1.00, indicating that there is no significant relationship between age and the status of endometrial hyperplasia.

Table 2.   Sample Characteristics Based on Parity

Parity	D & C Result	
	Hyperplasia	Non-Hyperplasia
Nulliparous	8	3
Multiparous	14	5

In regards to parity, we found that in the nulliparous group, 8 patients had endometrial hyperplasia and 3 did not have hyperplasia. In the multiparous group, as many as 14 showed hyperplasia and 5 did not have hyperplasia. The p-value based on Fischer exact test was 1.00, implicating that there is

no relationship between parity with endometrial hyperplasia as determined by D & C.

Table 3. Sample Characteristics Based on BMI

BMI	D & C Result	
	Hyperplasia	Non-Hyperplasia
> 25	16	0
< 25	5	9

In our sample, all the patients in the obese group had endometrial hyperplasia. Meanwhile, among patients whose BMI was lower than 25 kg/m², five had hyperplasia and nine did not have hyperplasia. The results of Fischer exact test showed that there is a significant association between BMI status endometrial hyperplasia (p=0.00).

Table 4. Sample Characteristics based on Fasting Blood Glucose

Fasting Blood Glucose	D & C Result	
	Hyperplasia	Non-Hyperplasia
Normal	8	7
Abnormal	14	1

From the patient characteristics based on fasting blood glucose, we found that in the group with normal fasting blood glucose, eight had endometrial hyperplasia and seven did not. However, in patients with abnormal fasting blood glucose, as much as 14 patients had hyperplasia and only one was found without hyperplasia. The result of Fischer exact test indicates that there is a significant relationship between fasting blood glucose and endometrial hyperplasia (p=0.035).

DISCUSSION

Based on our results, most of our patients were aged 41-50 years old (76.7%). Two-thirds of women who were treated for AUB in our hospital were aged over 40. In the study by Dinic et al in Serbia, it was concluded that the incidence of AUB increases with the age of patients. In their study, 2.13% was <30 years old, as much as 35.8% were aged 30-45 years old, and the majority was older than 45 years old (61.9%). The data characteristic above is similar to our study, in which patients with AUB mostly belonged to the 41-50 years age group.

After further analysis, we found that of the 23 samples aged 41-50 year old, 16 samples (69.5%) had endometrial hyperplasia and 7 samples did not have hyperplasia. Subhankar et al in India obtained as much as 34.5% endometrial hyperplasia with a sample of 252 patients and the highest incidence being in the perimenopausal age group (aged 46-50 years).[19]

In this study we found no association between age and status of endometrial hyperplasia, although there seems to be clinically significant endometrial hyperplasia occurring in above 40 years of age, with a total 16 of 23 samples. Statistically, this could be caused by a random error factor. In general, of all the subjects aged over 35 years old in this study, histology of hyperplasia was obtained in 21 patients.

Based on the characteristics of parity, we obtained that the patients with AUB in this study is mostly comprised of multiparous women (63.3%) and 36.7% consist of nulliparous women. These results is same with the results of Subhankar et al, that found 88.5% of 252 patients with AUB were multiparous.[19]

Out of the 11 patients who were nulliparous, 72.7% had a picture of endometrial hyperplasia, while out of the 19 multiparous patients as many as 14 patients (73.7%) had a picture of hyperplasia. Clinically, the incidence of endometrial hyperplasia is similar between nullipara and multipara, but statistically there was no significant association between parity and the status of endometrial hyperplasia. Theoretically, hyperplasia occurs more frequently in the nulliparous group, where there is an increase in cumulative exposure to estrogen because of the higher total number of menstrual cycles throughout life. Our results could be explained by the possibility of random error, and further research of AUB on nullipara population should be carried out.

Based on the characteristics of BMI we discovered that AUB incidence was slightly higher in the obese group (53.3%), compared to the non-obese group (46.7%). Parazzini et al in Italy observed that 60.4% of endometrial hyperplasia patients had BMI >25. Of the 16 samples with obesity, all of them had the histologic picture of endometrial hyperplasia, so that clinical data shows the influence of obesity on endometrial hyperplasia. Whereas the sample with a lower BMI, showed that the majority did not have endometrial hyperplasia. Statistical tests showed that there was a significant relationship

between BMI with endometrial hyperplasia. So both clinically and statistically, our result was in accordance with the theory in which hyperplasia is a disease that is estrogen-dependent, with endogenous and exogenous estrogen stimulating endometrial proliferation excessively.[12]

Based on the fasting blood glucose, the normal and abnormal groups both had equal samples. In statistical tests, we obtained that in the group with abnormal fasting blood glucose the results is not normal, with 14 samples showing histologic picture of endometrial hyperplasia. Meanwhile, the occurrence of endometrial hyperplasia is approximately equal in populations with normal blood sugar. Clinically, we obtained that 93.3% of samples with high fasting blood glucose had symptoms of AUB showing histology of endometrial hyperplasia. Statistically, we found a significant relationship between fasting blood glucose and endometrial hyperplasia. This is consistent with the theory stating that women with diabetes have a two-fold risk of developing endometrial hyperplasia.[20] Lindemann et al (2010) mentioned that the risk of developing endometrial cancer is three times higher in diabetes patients.[11]

CONCLUSION

There is a significant relationship between BMI and high fasting blood glucose with endometrial hyperplasia, but this significant relationship was not identified between age and parity towards endometrial hyperplasia. This research is a beginning to reveal the endometrial histology in AUB, in relation with numerous risk factors. In this study, we hypothesized that examination of BMI and fasting blood glucose can be used to predict the likelihood of malignancy in patients with AUB. However, further research is needed with a larger sample size and evaluating other risk factors to improve the accuracy of the study.

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