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To do or not to do? – Endometrial biopsy in younger women with abnormal uterine bleeding

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ABSTRACT

Objective: Abnormal uterine bleeding (AUB) can be associated with underlying endometrial pathology. The current existing guidelines discuss the role of endometrial biopsy in women 40 years old and above, however, there are no clear recommendations for younger women. This study aims to identify the factors that increase the risk of endometrial pathology in women below 40 years of age presenting with AUB for consideration of endometrial biopsy.

Methods: We conducted a retrospective observational study reviewing the records of 464 women aged under 40 years old who underwent endometrial biopsy for AUB. The data analysis included demographics, investigations undertaken, ultrasound findings, biopsy results, and treatment. Multivariable analysis was performed using modified Poisson regression models to compare women with endometrial hyperplasia (EH) (with or without atypia) and endometrial cancer (EC), to those with benign pathology, to identify risk factors for endometrial pathology.

Results: In our study, 71.3 % of women had a benign histology, 22.8 % had EH with and without atypia and 2.2 % of women had a diagnosis of EC. A BMI $\geq$ 30 (RR 1.76, $p = 0.002$), nulliparity (RR 1.84, $p = 0.001$), ultrasound findings of thickened endometrium $\geq$ 15 mm (RR 1.39, $p = 0.048$) and cystic spaces in the endometrium (RR 1.83, $p < 0.001$) were identified as significant risk factors after a multivariate analysis. A combination of at least 3 of these risk factors had a cumulative increased risk of EH/EC (RR 3.80, $p < 0.001$).

Conclusion: Endometrial biopsy in younger women with AUB should be carefully considered on a case-by-case basis and reserved for those with risk factors for a serious endometrial pathology.

Introduction

Abnormal uterine bleeding (AUB) is one of the most common gynecological conditions. It can affect up to 35 % of reproductive aged women and contributes to 70 % of gynecologic clinic visits in premenopausal women[1,2]. The International Federation of Gynaecology and Obstetrics (FIGO) described AUB in 2018[3] as the presence of amenorrhea, altered frequency (less than 24 days or more than 38 days cycles), prolonged duration (more than 8 days), irregularity (cycle variation of more than 8–10 days), presence of heavy flow, intermenstrual bleeding or presence of unscheduled bleeding while on gonadal steroid medication. AUB can be indicative of underlying endometrial pathologies.

Current guidelines discuss the role of endometrial biopsy in older women 40 years old and above[4] presenting with persistent AUB as they are at greater risk of endometrial hyperplasia or cancer. Other factors[5–8] that increase the risk of endometrial pathology include nulliparity, obesity, polycystic ovarian syndrome resulting in anovulation, drug-induced endometrial stimulation (such as tamoxifen or systemic estrogen replacement therapy), genetic factors (e.g., Lynch syndrome) and poor response to first-line treatment. However, in women younger than 40 years old, there are no clear recommendations regarding endometrial biopsy, and the diagnostic approach and patient selection criteria are still controversial. The associated risks that may

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affect fertility is a consideration in this reproductive age group. In addition, there are substantial costs associated with the diagnostic assessment required to evaluate for the presence of endometrial pathologies in women with AUB[9]. Lastly, despite being a minimally invasive procedure, endometrial biopsy in the outpatient setting is painful, with patients requiring effective preprocedure analgesia[10]. This study aims to identify factors that increase the prevalence of endometrial pathologies in young women below 40 years old, with a view to profile and prioritize those at higher risk who will irrefutably benefit from endometrial biopsy.

Materials and methods

This was a retrospective observational study in KK Women's and Children's hospital, a tertiary hospital and largest maternity hospital in Singapore, from 2020 to 2021. Inclusion criteria were women aged under 40 years old who underwent an endometrial biopsy for AUB (according to FIGO definition[3]). Exclusion criteria were women who had the procedure performed for reasons other than AUB (e.g. asymptomatic thickened endometrium, endometrial cells on routine pap smear, or subfertility), or those with known histologically-diagnosed EH and/or EC who were undergoing a repeat biopsy. Ethics approval was waived by the Institutional Review Board (IRB No. 2021/2611).

Endometrial biopsies in our institution were performed either blind with Pipelle or Explora endometrial curette (i.e. sampling performed in the outpatient clinic or in the inpatient ward) or under hysteroscopic guidance. The hysteroscopies were performed either in the clinic with pre-procedure cervical priming and analgesia or in the operation theater under anesthesia. Medical records were reviewed, and data were collected and analyzed.

From each medical record, data was collected for: (1) demographics including age, ethnicity, parity, mode of delivery (if parous), Body Mass Index (BMI), past medical history and medication use, (2) relevant investigations including ultrasound findings, (3) method of endometrial biopsy (4) histology result (5) treatment methods for EH/EC.

We identified possible risk factors based on clinical knowledge, directed acyclic graph and literature review. Age was treated as continuous variable; BMI was treated as continuous and later categorized into lower than 30 and more than or above 30 using WHO guideline on defining obesity[11,12] in multivariable analysis. Endometrial thickness was treated as continuous variable and later classified into < 15 mm and ≥ 15 mm in multivariable analysis. The cut-off of 15 mm was used as it is the upper limit of normal endometrium during the secretory phase of the menstrual cycle[12]. Ethnicity included Chinese, Malay, Indian and Others (e.g., Caucasian, Eurasian). Polycystic ovaries, diabetes mellitus, cystic spaces and nulliparous were treated as dichotomous variables.

Sample size calculation was performed in order to develop a predictive model. Eight risk factors for EH/EC were identified. Using the guideline proposed by Machin and Campbell[13], 10 events were required per category per risk factor to obtain reasonably stable estimates of the regression coefficients. Thus, 170 individuals with EH/EC in the study were required.

Continuous variables were described as median with interquartile range (IQR; 25th – 75th percentile) and were assessed for normality assessing the skewness, kurtosis and quantile-quantile plot. Student's *t*-test or Mann-Whitney *U* test were applied on continuous variables where appropriate. Nominal variables were assessed using the Chi-square test or Fisher's exact test where appropriate. Multivariable analysis was performed using modified Poisson regression model to assess the association between participant characteristic and the presence of EH/EC on complete data set (n = 415). Variables were selected in the multivariable analysis based on univariate analysis with p value < 0.05. A risk predictive model was developed with inclusion of risk factors in multivariable analysis with p value < 0.05. Results were presented in risk ratio and their respective 95 % confidence interval (CI). For all tests, a p-value of < 0.05 was considered to be statistically significant. All analysis was performed using Institutional access to Windows IBM (SPSS, Chicago, IL, USA, version 20.0) and Stata, release 18 (StataCorp LLC).

Results

Between 2020 and 2021, 464 women less than 40 years old underwent endometrial sampling in our hospital. The median age of the study population was 34 years old, 53 % (246/464) of the women were nulliparous and 48.1 % (210 /437) had a BMI ≥ 30. Of note, 22.8 % (106/464) of the women had polycystic ovaries while 7.5 % (35/464) had diabetes mellitus (Table 1). The median endometrial thickness (ET) was 11 mm and 18.6 % (84/451) of the women had ultrasound finding of cystic spaces in the endometrium. Majority of women (92 %, 426/464) had blind endometrial sampling, 5 % (25/464) had outpatient hysteroscopy with endometrial biopsy and 3 % (13/464) underwent a dilatation, curettage, and hysteroscopy (DCH) under anesthesia. None of the women who underwent a blind endometrial biopsy had ultrasound findings suggestive of a polyp. Those who underwent DCH under anesthesia did so in view of abnormal ultrasound findings of a focal lesion on ultrasound (such as a polyp, submucosal fibroid or endometrial mass) requiring targeted biopsy, virgo intact status, or were undergoing another surgery in the same setting (e.g., myomectomy). There were no reported procedural complications such as uterine perforation, infection, or intrauterine scarring. While histology was benign in majority of women (75 % (348/464)), 19.8 % (92/464) of women had EH without atypia, 3.0 % (14/464) had EH with atypia, and 2.2 % (10/464) had EC. One woman's histology was reported as a placental site nodule.

Among women diagnosed with EH with or without atypia, 64.5 % (68/106) were treated with oral progestogen and 26.4 % (28/106) had a Mirena intrauterine device inserted. All of the women diagnosed with EC had FIGO Grade 1 endometrioid carcinoma. Of this group, 60 % were treated with oral progestogens, 20 % had Mirena inserted and 20 % opted to undergo treatment in another hospital and were lost to follow-

Table 1
Participants characteristics and endometrial hyperplasia or endometrial cancer (EH/EC) (n = 464).

	Women with EH/EC (n = 116)	Women without EH/EC (n = 348)	p value
Age, median (IQR)	33.0 (29.5–35.0)	35.0 (31.0–37.0)	< 0.001
BMI, median (IQR)	33.4 (26.9–39.7)	28.0 (23.3–35.3)	< 0.001
Ethnicity, no. (%)			0.047
Chinese	52 (24.3 %)	162 (75.7 %)	
Malay	38 (31.9 %)	81 (68.1 %)	
Indian	9 (13.4 %)	58 (86.6 %)	
Others	17 (26.6 %)	47 (73.4 %)	
Nulliparous, no. (%)			< 0.001
No	32 (14.7 %)	186 (85.3 %)	
Yes	84 (34.1 %)	162 (65.9 %)	
Polycystic ovaries, no. (%)			< 0.001
No	75 (20.9 %)	283 (79.1 %)	
Yes	41 (38.7 %)	65 (61.3 %)	
Diabetes Mellitus, no. (%)			0.361
No	105 (24.5 %)	324 (75.5 %)	
Yes	11 (31.4 %)	24 (68.6 %)	
Endometrial Thickness, median (IQR) (mm)	11.0 (8.0–15.4)	9.0 (6.0–13.0)	< 0.001
Cystic spaces, no. (%)			
No	72 (19.8 %)	292 (80.2 %)	< 0.001
Yes	41 (50.0 %)	41 (50.0 %)	

BMI: body mass index; IQR: interquartile range.
P value was calculated from Pearson's chi-squared test or Fisher's exact test where appropriate for categorical variables and Mann-Whitney test for continuous variables.
Missing data: BMI (n = 27); Cystic spaces (n = 18); Endometrial thickness (n = 22)

up. A repeat endometrial sampling done for all women on follow-up showed regression to either EH or benign histology.

A comparison between women with EH/EC versus a benign histology showed a significant association with endometrial pathologies in women who were nulliparous, had BMI ≥ 30 (adjusted risk ratio: 1.76, 95 % CI 1.23–2.52), and had ultrasound findings of thickened endometrium ≥ 15 mm (1.39, 1.00–1.94)) and cystic spaces (1.83, 1.31–2.57) (Table 2). A further analysis done showed that women who had multiple simultaneous risk factors had a cumulative increased risk of EH/EC (Table 3), and those with 3–4 risk factors had a risk ratio (RR) of 3.80 (95 % CI 2.41–6.00)

Discussion

Despite the low incidence of EC in this group, the risk of progression to cancer for EH without atypia can be as high as 5 % and up to 30 % for those diagnosed with an EH with atypia[14]. Endometrial biopsy is a relatively simple procedure to obtain histology to confirm or exclude EH/EC. However, it should not be routinely offered in all women with AUB as it is invasive, associated with pain (when done in the outpatient setting), may result in complications such as infection, increase women's anxiety for malignancy, and add to the healthcare and economic burden in low-risk women.

Table 2
Associations between characteristics and endometrial hyperplasia or endometrial cancer (EH/EC) with complete data (n = 415).

			Univariate	Multivariable
	Women with EH/EC (n = 110)	Women without EH/EC (n = 305)	Risk ratio (95 % CI), p-value	Risk ratio (95 % CI), p-value
Age, median (IQR)	33.0 (30.0–35.0)	35.0 (31.0–37.0)	0.95 (0.92–0.98), p = 0.001	1.00 (0.97–1.04), p = 0.831
BMI, no. (%)				
< 30	38 (34.6)	175 (57.4)	Reference	Reference
≥ 30	72 (65.5)	130 (42.6)	2.05 (1.46–2.88), p < 0.001	1.76 (1.23–2.52), p = 0.002
Ethnicity, no. (%)				
Chinese	49 (44.6)	137 (44.9)	Reference	Reference
Malay	36 (32.7)	74 (24.3)	1.31 (0.92–1.87), p = 0.130	0.97 (0.68–1.39), p = 0.875
Indian	9 (8.2)	50 (16.4)	0.55 (0.29–1.06), p = 0.075	0.56 (0.30–1.03), p = 0.064
Others	16 (14.6)	44 (14.4)	1.09 (0.68–1.75), p = 0.711	1.16 (0.74–1.81), p = 0.511
Nulliparous, no. (%)				
No	31 (28.2)	161 (52.8)	Reference	Reference
Yes	79 (71.8)	144 (47.2)	2.33 (1.62–3.35), p < 0.001	1.84 (1.26–2.68), p = 0.001
Polycystic ovaries, no. (%)				
No	71 (64.6)	246 (80.7)	Reference	Reference
Yes	39 (35.5)	59 (19.3)	1.85 (1.35–2.53), p < 0.001	1.32 (0.96–1.83), p = 0.092
Diabetes Mellitus, no. (%)				
No	100 (90.9)	285 (93.4)	Reference	
Yes	10 (9.1)	20 (6.6)	1.28 (0.77–2.15), p = 0.344	
Endometrial thickness, no. (%)				
< 15 mm	75 (68.2)	245 (80.3)	Reference	Reference
≥ 15 mm	35 (31.8)	60 (19.7)	1.71 (1.24–2.36), p = 0.001	1.39 (1.00–1.94), p = 0.048
Cystic spaces, no. (%)				
No	71 (64.6)	266 (87.2)	Reference	Reference
Yes	39 (35.5)	39 (12.8)	2.53 (1.87–3.40), p < 0.001	1.83 (1.31–2.57), p < 0.001

IQR: Interquartile range

Table 3
Associations between risk factors and endometrial hyperplasia or endometrial cancer (EH/EC).

Number of risk factors present (Nulliparous, BMI≥30, ET≥15 mm, Cystic spaces) no. (%)	Women with EH/EC (n = 110)	Women without EH/EC (n = 305)	Univariate (Risk ratio, 95 % CI, p value)	Multivariable (Risk ratio, 95 % CI, p value)
0–1	29 (26.4)	189 (62.0)	Reference	Reference
2	51 (46.4)	88 (28.9)	2.76 (1.84–4.13), p < 0.001	2.70 (1.77–4.13), p < 0.001
3–4	30 (27.3)	28 (9.2)	3.89 (2.55–5.92), p < 0.001	3.80 (2.41–6.00), p < 0.001

BMI: Body mass index, CI: confidence interval, ET: Endometrial thickness.

Literature review shows that different guidelines have various age cut-offs for recommending an endometrial biopsy in women with AUB. The American College of Obstetricians and Gynecologists (ACOG) recommends endometrial biopsy in women above 45 years old with AUB as a first-line test[15]. The Society of Obstetricians and Gynecologists of Canada (SOGC) suggests performing endometrial biopsy in women aged over 40 years[16]. The Royal College of Obstetricians and Gynecologists (RCOG) does not recommend a specific age cut-off for endometrial biopsy but advise that women presenting with AUB above 40 years old or failed first-line medical treatment be referred to secondary care for further management[17]. Other studies have reported no correlation between age and EC[18,19]. In this study, the age cut-off of less than 40 years old was chosen, as although approximately 50 % of women affected with AUB are in the 40–50 years age group[18], the risk of EH/EC in younger women with AUB has not been studied as extensively. Fertility may also be a unique consideration in this age group. While the histology was benign in majority of women, with no complications from the endometrial biopsy, the decision to perform this procedure should be made after a thorough assessment and risk stratification to achieve a cost-effective approach and to minimize complications.

Although the overall incidence of EH with atypia and EC in our study group was low (5.2 %), interestingly the incidence of EH without atypia was 19.8 %. This is significantly higher than that noted in other studies which reported an incidence of EH without atypia of 5.2–6.4 %[20,21]. This difference could be attributed to a more appropriate selection of women with AUB who underwent endometrial biopsy in our study population. Even though spontaneous regression often occurs in women with EH without atypia and not requiring treatment, there is still a risk of progression to eventual cancer. These women should still be followed up to address reversible risk factors and ensure regression to normal endometrium.

While obesity is a risk factor for EH/EC[22], few studies have evaluated the effect of obesity on the decision to perform endometrial biopsy in younger women with AUB. In this study, a higher BMI is associated with an increased risk of EH/EC. This is in keeping with other studies, who reported that obese women (BMI > 30 kg/m^2) are four[18] to eight [23] times more likely to have a diagnosis of an EH/EC compared to women in the normal weight range. The Asian population in general has a lower mean BMI, but they have a greater tendency toward abdominal adiposity than the non-Asian population. Furthermore, Asian women have a higher percentage of body fat at a lower BMI compared to age-specific non-Asian women, which also reflects the increased risk of chronic diseases (e.g., diabetes mellitus, cardiovascular, hypertension) [24].

In postmenopausal women, the ET is a useful marker to triage

women at higher risk of EC. However, due to periodic changes in the thickness in various phases of the menstrual cycle in premenopausal women, its predictability is poor; hence, the best cut-off value for performing endometrial biopsy is debatable[25]. While some studies have shown that the ET was of little predictive value for EH/EC[20,26], other studies have recommended endometrial biopsy at ET > 8–13 mm[18,25,27]. In our study, ET > 15 mm was associated with a statistically significant increased risk of EH/EC and can be considered as a tool to triage AUB patients at high risk. Ideally, the ET should be interpreted in relation to the phase of the menstrual cycle to determine if it is abnormal, but this may be challenging in premenopausal women with irregular menstruation (e.g., women with polycystic ovarian syndrome). Future studies could investigate specific ET cut-off ranges for secretory versus proliferative phases for women with AUB that are associated with a higher risk of EH/EC.

The presence of cystic spaces in our study population was also significantly associated with EH/EC, in keeping with findings from other studies[28]. Unlike ET, the presence of cystic spaces may be less influenced by the menstrual cycle. While ultrasound findings should be interpreted in context, this study has shown that it is a useful tool in investigating AUB, with concordant findings of thickened ET and cystic spaces raising the clinical index of suspicion for EH/EC.

Majority of women in our study underwent an endometrial sampling. This allows a faster diagnosis and the avoidance of anesthesia and its associated risks. It is also more cost-effective compared to a DCH[29]. For those with a specific lesion on ultrasound and considered as a suitable candidate, outpatient hysteroscopy can be considered to further reduce anesthesia risk. Nonetheless, DCH under general anesthesia still remains a feasible option for women who are not as suitable for outpatient endometrial sampling or hysteroscopy (such as virgo-intacta or severe vaginismus), as majority of the women in this younger group are otherwise healthy with no significant comorbidities. For women requiring DCH under anesthesia who are high-risk (e.g., morbid obesity or severe asthma), working closely together with the anesthetist is crucial to minimize potential complications.

The major strengths of the study are the strict inclusion and exclusion criteria, and that all clinical variables included in the study were measurable. All women had definitive histology as a reference value and pathology examinations were conducted by a team of pathologists specializing in gynecology, thus limiting diagnostic errors. However, a prospective study is recommended to estimate the true incidence of significant endometrial pathology in premenopausal women with AUB.

A limitation of this study is its retrospective nature. There may be unmeasured confounders not included in the analysis, which could influence the study results. This study was a retrospective observation study which highlighted a relatively high incidence of EH, which can be significant given a young population with a longer life expectancy (and consequent risk of progression and/or recurrence) and specific concerns such as fertility. Future case-control studies could be conducted to review association of the disease with specific individual risk factors. In addition, the observed number of women with EH/EC within the specified time frame of our study was less than the calculated sample size for the predictive model. Although we identified several statistically significant risk factors, their utility as predictive markers should be taken with caution. FIGO's definition of AUB was used in our study, therefore some women who were on follow-up for a change in their menstrual pattern but did not strictly meet the inclusion criteria were excluded. This study did not compare the different types of AUB (e.g., heavy menstrual bleeding versus intermenstrual bleeding (IMB)) as many of our women reported an overlap in symptoms, making this differentiation challenging. Other studies have interestingly shown an increased risk of EH/EC in women with IMB specifically[25,30]. A quality improvement study could be undertaken to improve documentation of AUB types for future audit and analysis. The study could also have been limited by institutional practices regarding biopsy methods. The two main biopsy methods used were that of sampling performed in the outpatient clinic or in the inpatient ward and hysteroscopic-guided biopsies under general anesthesia. The study team is aware regarding publications[31] which have shown increased accuracy of diagnosis via hysteroscopic-guided resection. This method could be considered in future prospective studies.

The risk factors identified in this study are important given the increasing prevalence of obesity in younger adults[32] and growing trend of delayed childbearing in developed countries, contributed by lifestyle choices or underlying subfertility[33]. In women with AUB and multiple simultaneous risk factors (Table 3), the cumulative risk of EH/EC significantly increases and endometrial biopsy is warranted. For those who decline endometrial biopsy or have less risk factors, they should be monitored closely and reversible factors such as obesity and diabetes should be identified and addressed. Future studies could validate the ultrasound parameters of thickened ET and cystic spaces and this could potentially be used in the surveillance of premenopausal women with AUB who do not undergo endometrial sampling.

Conclusion

This is the first study in a multi-ethnic population analyzing the factors and outcomes of women under 40 years old presenting with AUB undergoing endometrial biopsy. Our results show that the overall risk of EH/EC in this group of patients is low. An endometrial biopsy should be carefully considered in given its potential risks. It should be reserved for those who present with AUB and fulfill specific risk factors such as nulliparous status, BMI ≥ 30, ET ≥ 15 mm and ultrasound findings of cystic spaces in the endometrium.

Ethical approval

Ethics approval was waived by the Institutional Review Board (IRB No. 2021/2611).

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Patient consent

The requirement for obtaining informed consent was waived by the ethics review board owing to the retrospective nature of the study.

CRediT authorship contribution statement

Mathur Manisha: Writing – review & editing, Supervision, Conceptualization. **Merchant Khurshid:** Writing – review & editing, Resources, Conceptualization. **Chonkar Sonali Prashant:** Writing – review & editing, Supervision, Conceptualization. **Chan Madeline Hiu Gwan:** Formal analysis, Data curation. **Jaya-Bodestyne Sandra Lynn:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Goh Marlene Samantha Sze Minn:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization.

Declaration of Competing Interest

No potential conflict of interest relevant to this article was reported.

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