Body Mass Index as an Indicator for Endometrial Biopsy in Premenopausal Women with Heavy Menstrual Bleeding

Wafaa Salah Abd-Al Amieer[1], Lamees Adnan Shubber[1], Shaymaa Mareai Qaddoori[2]

[1]C.A.B.O.G, Consultant Obstetrics and Gynecology, Al-Emamein Al-Kadhemein Medical City, Baghdad, Iraq,
[2]M.B.Ch.B, Doctor, Al-Emamein Al-Kadhemein Medical City, Baghdad, Iraq

Abstract

Background: Although Obesity is a risk factor of endometrial hyperplasia/ carcinoma, there is no consensus on using the BMI as a predictor for endometrial biopsy screening in patients with heavy menstrual bleeding in pre-menopausal women. Therefore, it's clinically important to identify BMI cutoff values as a predictor for endometrial hyperplasia/ carcinoma in premenopausal women with heavy menstrual bleeding.

Aim of the Study: To determine the feasibility of using Body Mass Index (BMI) as an indicator to perform endometrial biopsy in premenopausal women presented with heavy menstrual bleeding.

Patients & Methods: This is a cross-sectional study that was conducted in Obstetrics and Gynecology Clinic /Al-Emamain Al-Kadhemein teaching medical city in Baghdad where women 150 women who are 40-50 years old with heavy menstrual bleeding where sent for endometrial biopsy. 100 women had abnormal endometrial biopsy results, histopathological results of the abnormal endometrial samples were classified into following groups: hyperplasia without atypia, hyperplasia with atypia, and hyperplasia with atypia and cancer. Statistical analysis conducted to correlate The Body Mass Index (BMI) with the status of endometrial biopsy.

Results: 42% of the women with BMI≥30 kg/m^2 have hyperplasia with atypia or carcinoma compared to 10% of women who BMI<30 kg/m^2 ($p<0.001$). from 54 women who had hyperplasia with atypia in endometrial sample results; 77.7% of such patients were BMI≥30 kg/m^2. Receiver operating characteristic analysis shows that using BMI ≥30 kg/m^2 as a predictor of hyperplasia with atypia or carcinoma carries a sensitivity of 80.77 % and specify of 86.00% with area under the curve (AUC) value of 0.83 (CI. 0.75-0.92) and ($p<0.001$). women with BMI≥30 kg/m^2 has a relative risk (RR) of 3.98 of developing endometrial hyperplasia (without atypia or with atypia+carcinoma) and a relative risk (RR) of 4.11 of developing hyperplasia with atypia or carcinoma ($p<0.001$).

Conclusion: Our results indicate that BMI regardless of the age is the highest risk factor for abnormal endometrial hyperplasia premenopausal women. Also, BMI≥30 kg/m^2 has highest risk for developing endometrial hyperplasia with atypia or carcinoma. BMI≥30 kg/m^2 can be used as predictor of endometrial hyperplasia in premenopausal women with heavy uterine bleeding.

Keywords: *Body mass index, endometrial biopsy, menstrual bleeding,*

Background

Obesity and overweight estimated to account for up to 45% of endometrial cancer incidence in Europe[1] and 57% in the United States[2]. Endometrial cancer (EC) is the second most common gynecological malignancy worldwide. The incidence of EC is steadily increasing, primarily due to an aging population and escalating rates of obesity[3]. The unopposed exposure of endometrium to the effect of estrogen is a risk factor in endometrial hyperplasia & carcinoma. Other factors that are influencing estrogen exposure like obesity, polycystic ovarian syndrome, anovulation, nulliparity, and type II diabetes mellitus also increase the risk of endometrial cancer[4].

Although, different parts of the world started to research the use of Body Mass Index (BMI) as an indicator for endometrial biopsy, the data obtained are inconstant from country to another, this might be attributed to the racial and demographic variabilities associated with women in different part of the world[5]. It may also be that most of the researchers examined the role of BMI in undedicated studies but in retrospective manner using the non-objective reported BMI for the patients[2,5] The mechanism underlying BMI measurement is done by dividing the individual's weight (in kilograms) by height (in meters squared). The resulting unit is kg/m^2 [6].

Epidemiologically speaking; endometrial hyperplasia is common in women aged 50-54 years with body mass index (BMI) over 30, the average age for EH is 52 years, which is nine years lower than the average age for EC[7]. The increased risk of endometrial cancer among overweight (BMI > 25) and obese persons have been observed recently. Endometrial hyperplasia is one of the most common causes of abnormal uterine bleeding, which leads to endometrial carcinoma if left untreated. ***Therefore; in our study, we will examine the role of BMI in premenopausal women***. ***We hypothesize*** that Body Mass Index (BMI) correlates positively with histopathological features of endometrial biopsy in premenopausal women with abnormal uterine bleeding, thus BMI can be used an indicator for endometrial biopsy.

Patients and Methods

This is a cross-sectional study that was conducted from 1st of August 2018 to the end of May 2019 in Obstetrics and Gynecology Clinic /Al-Emamain Al-Kadhemein teaching medical city in Baghdad where women 150 women who are 40-50 years old with heavy menstrual bleeding where sent for endometrial biopsy. 100 women had abnormal endometrial biopsy results, histopathological results of the abnormal endometrial samples were grouped into following groups: hyperplasia without atypia, hyperplasia with atypia, and hyperplasia with atypia and cancer. Statistical analysis conducted to correlate The Body Mass Index (BMI) with the status of endometrial biopsy.

Results

Our results showed that 42% of the women with BMI≥30 kg/m^2 have hyperplasia with atypia or carcinoma compared to 10% of women who BMI<30 kg/m^2 ($p<0.001$). Out of 54 women who had hyperplasia with atypia in endometrial sample results; 77.7% of such patients were BMI≥30 kg/m^2. Receiver operating characteristic analysis shows that using BMI ≥30 kg/m^2 as a predictor of hyperplasia with atypia or carcinoma carries a sensitivity of 80.77 % and specify of 86.00% with area under the curve (AUC) value of 0.83 (CI. 0.75-0.92) and ($p<0.001$). It was observed that women with BMI≥30 kg/m^2 has a relative risk (RR) of 3.98 of developing endometrial hyperplasia (without atypia or with atypia+carcinoma) and a relative risk (RR) of 4.11 of developing hyperplasia with atypia or carcinoma ($p<0.001$).

Table 1 shows the patients with abnormal endometrial biopsy characteristics.

Table 1: Patients Characteristics

Variable	No.	%
Age (years) Mean ± SD (Range)	46.1±3.67	(40-50)
BMI Mean ± SD (Range)	29.88±2.71	(20.81-37.64)
Parity Mean ± SD (Range)	4.62±2.09	(0-8)
Nulliparity	13	(8.6%)
Diabetes	56	(37.22%)
Hypertension	60	(40%)
Family History	23	(15.33%)

Table 2: Distribution of the cases based on Age and BMI cutoff values

Variable		Benign	Hyperplasia without atypia	Hyperplasia with atypia	Carcinoma	Total
Age (years)	**40-44**	19	16 (55.17%)	11 (37.93%)	2 (6.90%)	29 (29%)
	≥45	31	32 (45.07%)	34 (47.89%)	5 (7.04)	71 (71%)
BMI	**<25**	1	7 (87.5%)	1 (12.5%)	0	8 (8%)
	25-29.9	42	29 (76.32%)	9 (23.68%)	0 (0%)	38 (38%)

Cont... **Table 2: Distribution of the cases based on Age and BMI cutoff values**

(kg/ m^2)	30-34.9	7	12 (22.64 %)	35 (66.04%)	6 (11.3 2%)	53 (53%)
	≥35	0	0 (0%)	0 (0%)	1 (100 %)	1 (1%)

Table 2 shows the distribution of the cases stratified according to age and BMI cutoff values.

Table 3 shows the prevalence analysis of hyperplasia with atypia or carcinoma with different age and BMI

Table 4: Prevalence of hyperplasia and carcinoma according to different age and BMI groups.

Variable		Hyperplasia with Atypia + Carcinoma prevalence (%)
All patients		52/100 (52%)
Age ≥45 years		39/71 (55%)
BMI ≥30		42/54 (77.7%)
Age <45	BMI ≥30	12/15 (80%)
	BMI <30	1/14 (7.14%)
Age ≥45	BMI ≥30	30/39 (76.9%)
	BMI <30	9/32 (28.13%)

groups.

Table 4: Risk factors for endometrial hyperplasia and carcinoma in premenopausal women with Abnormal menstrual bleeding

Risk Factor	All Abnormal Findings			Hyperplasia with atypia + Carcinoma		
	RR (95% CI)	*p*	*Odds Ratio*	*RR (95% CI)*	*p*	*Odds Ratio*
Age≥45 (years)	1.13 (0.60-2.32)	0.73	1.17	1.27 (0.85-1.92)	0.316	1.61
BMI ≥30(kg/m^2)	3.98 (1.92-8.25)	<0.001	6.65	4.11 (2.32-7.32)	<0.001	15.96

Table 4 shows multivariate analysis of the risk factors Age (≥45 years old) and BMI (BMI≥30 kg/m^2)

Table 5: show ROC analysis which demonstrated a significant relationship between all abnormal endometrial histological findings and BMI.

Cut-off BMI (Kg/m2)	SENSITIVITY	SPECIFICTY	ROC (95% CI)	P
	(%)	(%)		
All Abnormal findings				
≥25	91	2		
≥30	52	86	0.68 (0.60-0.77)	0.00026
≥35	3	100		
Hyperplasia with atypia + carcinoma				
≥25	98.08	2		
≥30	80.77	86	0.83 (0.75-0.92)	< 0.0001
≥35	5.769	100		

Discussion

The findings of this study revealed abnormal endometrial histology in 66.6% of cases (100 out of 150) of premenopausal women with abnormal uterine bleeding. The major risk factors for endometrial hyperplasia and carcinoma in this study were BMI ≥ 30 kg/m^2 and diabetes mellitus. Even that the hyperplasia without atypia was reported with age of 40-44 years and the hyperplasia with and without atypia were reported with BMI index of 25.9-29.9 kg/m^2 but the association did not reach the significant level.

The mean age and BMI of the patients in this study was higher than that those who has been reported by Sun et al were they found that the mean age of included women was 35.9±9.3 years and the mean BMI was 23.5±3.9 kg/m2[8]. The difference in age average is because Sun Y et al inclusion criteria for age was 15-55 years old while our study design used age selection of 40-50 years old. Our data shows higher BMI average for our samples in comparison

to Sun et al, which might be attributed to the older women in our study (40-50 years old) as BMI tends to increase with age.[9]

The authors Wise et al found that the mean age of included women with abnormal uterine bleeding was 43.7 ± 6.4 in the non-obese group and 42.0 ± 7.2 in the obese group.[10] The diabetes mellitus and hypertension were reported in 37.22% and 40% respectively and nulliparity in 8.6%. The significant association of abnormal uterine histological findings was confirmed with diabetes mellitus only. Nearly similar proportion of patient with such comorbid illness and nulliparity were reported by Epplein et al who were found an increased risk of endometrial hyperplasia with increasing body mass index and nulliparity but no association with diabetes or hypertension was found.[11].

With cases of age> 45 years old, our results revealed that the hyperplasia without atypia also represent the commonest abnormal finding (45.07%) followed by hyperplasia with atypia (47.8%) but the prevalence of carcinoma was higher than younger patients (7.04% vs.6.9%) as well 39 out of 71 cases of age ≥45 years were showed hyperplasia with Atypia & Carcinoma. These finding in accordance with the results of Guraslan et al that found the commonest pathology was hyperplasia without atypia followed by hyperplasia with atypia and carcinoma with both age groups and higher prevalence of carcinoma also reported with a women of ≥ 45 years old.[12]

Our findings were partially in discordant with authors Nicholls-Dempsey et al who has been found 13% of cases had endometrial hyperplasia or neoplasia but 42% of patients with Abnormal uterine bleeding between 41 and 45 years old did not showed hyperplasia or neoplasia.[15] Our results showed the hyperplasia without atypia, hyperplasia with atypia or endometrial carcinoma represented were reported with BMI >25-29 and >35 kg/m^2. These findings agreed with Guraslan et al as they also found that all the abnormal findings including hyperplasia without atypia, hyperplasia with atypia, and carcinoma were observed among patients with BMI ≥30 and the difference was statistically significant[12].

Patients with BMI>24 kg/m^2 are obese, since in patients with higher BMI, the fat constituent of the body is higher, this will lead to overproduction of estrogen, as excessive adipose tissue increases the peripheral aromatization of Androstenedione to estrone in premenopausal women. This abnormal feedback loop associated with premenopausal women will cause anovulation, which cause unopposed effect of estrogen on the endometrium leading to thicker endometrium and higher risk for abnormal uterine bleeding[14].

These results were in consistent with findings of retrospective cohort study that carried out to evaluate the effect of BMI on endometrial hyperplasia and cancer done in Auckland from 2008 to 2014 (916 women met the inclusion and exclusion criteria) were they found that the obese women had higher odds of having complex hyperplasia or cancer compared to non-obese women[14], also in line with Giannella et al that found the odd ratio for association with endometrial hyperplasia(EH)/endometrial carcinoma(EC)by univariate analysis for different factors as following; for BMI ≥ 30 was 8.13(95% CI 2.34 - 28.21)[15].

Our findings also revealed that BMI is risk factor for hyperplasia with atypia and carcinoma ($p<0.001$) were in disagreement with Parslov M et al who found that the BMI was not demonstrated to be an independent risk factor in their study for endometrial cancer but the family history (OR; 2.1), completion of 1 term pregnancy (OR; 0.6), receiving hormone replacement therapy for 1-5 years (OR; 1.4-7) are the indicator of predicting endometrial carcinoma.[16]

Our results also showed that diabetes mellitus and BMI≥30 kg/m^2 are the factors that significantly associated with increasing the incidence of hyperplasia with atypia and carcinoma (P=0.001 for both) and this findings are in agreement with

Guraslan et al concerning the association of diabetes mellitus disease with increasing the incidence of these pathologies but in discordance with regard to the nulliparity status, however they identified the PCOS as a risk factor associated with these disorders but they found when hyperplasia without atypia was excluded, age of 45 years and older determined as a risk factor but PCOS was not a risk factor (p = 0.02 and 0.12, respectively)[12]. The findings were in disagreement with Wise MR et al concerning the associated risk factors for abnormal uterine histological findings as they found nulliparity (OR, 2.51; 95% CI, 1.25-5.05), anemia (OR, 2.38; 95% CI, 1.25-4.56), and thickened endometrium on ultrasound (OR, 4.04; 95% CI, 1.69-9.65) as other variables associated with the outcome[10]. It was also against the findings of Soliman et al who found the nulliparity is a risk factor for abnormal uterine finding[17].

Our study revealed that abnormal findings were higher with BMI >30 kg/m2 regardless the age group of the patients. These results were in agreement with Xu et al were also concluded that high BMI at all adult ages significantly predicted complex endometrial findings.[18] But our results were in discordance with findings of Thomas CC et al that found the increased risk of abnormal uterine findings with women who had BMIs of at least 35 who are younger than 45 years at the time of last menstrual period[19].

At the best cut-off value, sensitivity and specificity were 75.0% and 90.79%, respectively; the PPV and NPV were 30.0% and 98.6%, respectively.[10] Our findings showed that the BMI not the age of the patient is risk factor for endometrial hyperplasia and carcinoma as the results revealed significant high odd ratio with BMI ≥30 (kg/m2), OR; 4.11,P<0.001. These findings in agreement with Yamazawa et al who were found the odd ratio (OR) of obesity (BMI≥30) was 6.66 (p = 0.001; CI 2.40–18.48) for endometrial cancer and this ratio significantly considered as good indicator or predictor of endometrial carcinoma.[20] It has been concluded in their study that the body mass index showed a positive trend for risk of endometrial carcinoma as the BMI of the woman increases the risk of endometrial carcinoma was also increases.

Conclusions

The results of the current study confirm that obesity is the most regardless the age of the women is a significant risk factor for endometrial hyperplasia with atypia and carcinoma in premenopausal patients with abnormal uterine bleeding as we found the patients with BMI 30 whether their age is 45-years old or <45-year-old showed the highest risk for endometrial hyperplasia with atypia or carcinoma while the patients with BMI <30 whether aged <45-years old or 45-years old had the lowest risk for endometrial hyperplasia with atypia or carcinoma. Diabetes mellitus also identified as a risk factor associated with increasing the incidence of endometrial hyperplasia with atypia and carcinoma. BMI is independent indicator for prediction of serious medical condition such as endometrial carcinoma in patient with abnormal uterine bleeding

Ethical Clearance- Taken from Al-Emamein Al-Kadhemein Medical City, Baghdad, Iraq

Source of Funding- Self

Conflict of Interest - None

References

1. Bergstrm, A., Pisani, P., Tenet, V., Wolk, A. & Adami, H. O. Overweight as an avoidable cause of cancer in Europe. *International Journal of Cancer,* 2001 (91):421–430.
2. Calle, E. E. & Kaaks, R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. *Nature Reviews Cancer,* 2004 (4):579–591.
3. Cramer, D. W. The Epidemiology of Endometrial and Ovarian Cancer. *Hematology/Oncology Clinics of North America,* 2012 (26):1–12.
4. Raglan, O. *et al.* Risk Factors for Endometrial Cancer: An umbrella review of the literature. *International Journal of Cancer* (2018).

doi:10.1002/ijc.31961

5. Anderson, S. E., Dallal, G. E. & Must, A. Relative Weight and Race Influence Average Age at Menarche: Results From Two Nationally Representative Surveys of US Girls Studied 25 Years Apart. *P*ediatrics*,* 2003 (111):844–850.
6. Ferrera, L. A. *Body mass index : new research*. (Nova Publishers, 2005).
7. Lacey, J. V & Chia, V. M. Endometrial hyperplasia and the risk of progression to carcinoma. *Maturitas,* 2009 (63):39–44.
8. Sun, Y., Wang, Y., Mao, L., Wen, J. & Bai, W. Prevalence of abnormal uterine bleeding according to new International Federation of Gynecology and Obstetrics classification in Chinese women of reproductive age: A cross-sectional study. *Medicine (United States),* 2018 (97):e11457.
9. Stevens, J. *et al.* The Effect of Age on the Association between Body-Mass Index and Mortality. *New England Journal of Medicine,* 2002 (338):1–7.
10. Wise, M. R., Gill, P., Lensen, S., Thompson, J. M. D. & Farquhar, C. M. Body mass index trumps age in decision for endometrial biopsy: cohort study of symptomatic premenopausal women. *American Journal of Obstetrics and Gynecology,* 2016 (215): 598.e1-598.e8.
11. Epplein, M. *et al.* Risk of complex and atypical endometrial hyperplasia in relation to anthropometric measures and reproductive history. *American Journal of Epidemiology* (2008).
12. Guraslan, H. *et al.* Could body mass index be an indicator for endometrial biopsy in premenopausal women with heavy menstrual bleeding? *Archives of Gynecology and Obstetrics,* 2016 (294):395–402.
13. Nicholls-Dempsey, L. *et al.* Endometrial Biopsy in an Outpatient Gynaecological Setting: Overinvestigation. *Journal of Obstetrics and Gynaecology Canada,* 2018(40): 1309–1314.
14. Hoffman, L. B. *et al. Williams Gynecology*. *Williams Gynecology* (McGraw Hill Professional, 2012).
15. Giannella, L., Cerami, L. B., Setti, T., Bergamini, E. & Boselli, F. Prediction of Endometrial Hyperplasia and Cancer among Premenopausal Women with Abnormal Uterine Bleeding. *BioMed Research International,* **2019**(2019):1–6.
16. Parslov, M. *et al.* Risk factors among young women with endometrial cancer: A danish case-control study. *American Journal of Obstetrics and Gynecology* (2000). doi:10.1016/S0002-9378(00)70486-8
17. Soliman, P. T. *et al.* Risk factors for young premenopausal women with endometrial cancer. *Obstetrics and Gynecology* (2005). doi:10.1097/01.AOG.0000154151.14516.f7
18. Xu, W. H. *et al.* Weight history and risk of endometrial cancer among Chinese women. *International Journal of Epidemiology* (2006). doi:10.1093/ije/dyi223
19. Thomas, C. C., Wingo, P. A., Dolan, M. S., Lee, N. C. & Richardson, L. C. Endometrial cancer risk among younger, overweight women. *Obstetrics and Gynecology* (2009). doi:10.1097/AOG.0b013e3181ab6784
20. Yamazawa, K., Matsui, H., Seki, K. & Sekiya, S. A case-control study of endometrial cancer after antipsychotics exposure in premenopausal women. *Oncology* (2003). doi:10.1159/000067769