



## Survey article



# Prevalence of endometrial cancer symptoms among overweight and obese women presenting to a multidisciplinary weight management center

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## ARTICLE INFO

## Keywords:

Obesity  
Uterine cancer  
Endometrial cancer  
Bariatric surgery  
Endometrial hyperplasia  
Endometrial intraepithelial neoplasia

## ABSTRACT

Endometrial cancer rates are rising in parallel with the obesity epidemic. We aimed to determine the prevalence of endometrial hyperplasia or cancer (EH/EC) bleeding symptoms among at-risk women. We conducted a retrospective cohort study of overweight and obese women at a multidisciplinary weight management center who had completed a gynecologic/menstrual history questionnaire from May 2018 to October 2019. The primary outcome of any EH/EC symptom was defined as follows: in premenopausal women, any recent abnormal uterine bleeding (AUB); in postmenopausal women: any bleeding/discharge. The prevalence of EH/EC symptoms was compared by menopausal status using Fisher's exact tests, and multivariable regression identified independent factors associated with having EH/EC symptoms. A total of 103 women were included, and 4 (4%) had a history of EH/EC. Of the 84 (n = 82%) of women with no prior hysterectomy, 57% (n = 33/58) of premenopausal women reported any EH/EC symptom compared to 15% (n = 15/26) of postmenopausal women (p < 0.001). Two-thirds of symptomatic premenopausal women had two or more symptoms, most commonly heavy menses (49% (n = 25/51)) and irregular periods (39% (n = 17/44)). Sixty percent (n = 20/33) had discussed these with a gynecologist, and one third had undergone an endometrial biopsy. A history of polycystic ovarian syndrome (RR:1.72, 95% CI 1.24–2.38) was associated with EH/EC symptoms, while being postmenopausal was not (RR:0.32, 95%CI: 0.12–0.87). We demonstrate that EH/EC bleeding symptoms are prevalent in this at-risk population, but frequently are not discussed with gynecologists. Providers who care for obese women should ask about EH/EC symptoms, and provide prompt referrals to facilitate prevention and early detection of this cancer.

## 1. Introduction

Endometrial cancer (EC) rates in the U.S. have risen dramatically due to the obesity epidemic and now exceed nearly every other country globally (Lortet-Tieulent et al., 2018). The conversion of peripheral androgens to estrogen by adipocytes drives endometrial hyperplasia (EH), the precursor to EC (Fader et al., 2009). As a result, 85% of women who present with EC are obese, and 50% of all EC cases are attributable to obesity (Beral et al., 2005). In premenopausal women, BMI may have a more potent effect on EC risk as a BMI  $\geq 40$  kg/m<sup>2</sup> incurs a 20-fold increase in risk (Wise et al., 2016). Additionally, BMI may also be

more predictive of EH/EC than age in premenopausal women, suggesting that current guidelines for endometrial sampling primarily based on age are not sufficient (Wise et al., 2016).

Many obese women do not perceive themselves to be at risk of EH/EC or recognize their menstrual symptoms as abnormal (MacKintosh et al., 2019; Henretta et al., 2014). Abnormal uterine bleeding (AUB) is common in obese women, but often not discussed with providers (Henretta et al., 2014; Fraser et al., 2015). While in postmenopausal women bleeding always warrants work-up, in premenopausal women the significance of AUB is less clear.

Further research is needed to better appreciate the rates at which at-

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<https://doi.org/10.1016/j.gore.2020.100643>

Received 10 June 2020; Received in revised form 22 July 2020; Accepted 4 September 2020

Available online 11 September 2020

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risk women experience menstrual symptoms that could be indicative of EH/EC. We aimed to determine the prevalence of abnormal bleeding symptoms associated with EH/EC in an at-risk population, and determine the proportion who had sought care.

## 2. Materials and methods

A retrospective cohort study of overweight or obese (BMI > 25 kg/m<sup>2</sup>) women presenting to the Johns Hopkins Weight Management Center (JHWMC) in Baltimore, MD from May 2018–October 2019 was conducted. This study was approved by the Johns Hopkins Medicine Institutional Review Board (IRB). The JHWMC provides multidisciplinary weight loss treatment and care coordination by an internist, registered dietician, exercise physiologist, and behavioral therapist. It is separately located from Johns Hopkins Hospital, and has a separate paper medical record system. In May 2018, the Johns Hopkins Kelly Gynecologic Oncology Service collaborated with the JHWMC to add a gynecologic and menstrual symptomatology questionnaire to the standard JHWMC intake form (see [supplementary material](#)). Questions were adapted from the Aberdeen Menorrhagia Severity Scale, a validated tool use to assess recent AUB in menstruating women (Ruta et al., 1995). Postmenopausal women were asked to report any history of vaginal bleeding or discharge after menopause. Additional questions asked about gynecologic history (e.g. infertility, polycystic ovarian syndrome (PCOS), pregnancy history, contraceptive use) and prior gynecologic work-up. The JHWMC staff were educated on the increased risk of EH/EC due to obesity. The intake form included a written recommendation for women to seek gynecologic care for any premenopausal AUB or postmenopausal bleeding/discharge. JHWMC health records are not linked to the hospital health records, and many patients receive gynecologic care outside of the Johns Hopkins system; we were therefore unable to track referrals or future gynecologic workup.

Demographics, menstrual and menopausal history, and gynecologic history were abstracted from the JHWMC medical record, including the prevalence of previously diagnosed EH/EC in all women. The primary outcome of interest was any EH/EC bleeding symptom, assessed in women who had not undergone hysterectomy who were both pre- and post-menopausal. In premenopausal women, the following were considered potential EH/EC symptoms: irregular periods, abnormal cycle length, passing clots during menses, “heavy” or “very heavy” menses, or bleeding between periods. In postmenopausal women, vaginal bleeding or discharge were considered EH/EC symptoms. Secondary outcomes addressing work-up for symptoms were examined in women with EH/EC symptoms, including 1) reporting prior discussion of symptoms with a gynecologist, and 2) having undergone an endometrial biopsy (EMB) in the past.

### 2.1. Statistics

Descriptive statistics were used to report the demographic and clinical characteristics of the entire cohort, including prevalence of clinical factors associated with EH/EC (e.g. diabetes, hypertension, PCOS), and the prevalence of prior EH/EC. In women with no prior history of hysterectomy, the prevalence of each abnormal menstrual symptoms was reported. The prevalence of the primary combined outcome of any EH/EC symptom was calculated and compared between pre- and postmenopausal women using Fisher’s exact tests. The prevalence of prior gynecologic workup was calculated for those women who reported any EH/EC symptom.

Univariable Poisson regression was used to identify associations between clinical factors previously associated with EC, including age, race, BMI (categorized as overweight BMI 25.0–29.9, and obese (BMI 30–34.9 kg/m<sup>2</sup>, 35–39.9 kg/m<sup>2</sup>, ≥40 kg/m<sup>2</sup>)), history of diabetes, hypertension, hyperlipidemia, OSA, PCOS, gravida, infertility, and menopausal status (categorized as premenopausal not using hormonal contraceptives, premenopausal using hormonal contraceptives, and

postmenopausal), and the presence of any EH/EC bleeding symptom. Any factor associated at  $p \leq 0.1$  on univariate analysis was included in the multivariate analysis. All statistical calculations were conducted using Stata version 15.0. An alpha level of 0.05 was considered significant.

## 3. Results

A total of 103 women completed the intake form during the time period, representing 100% of new female patients seen during the study period. Their median age was 47 years old (range 24–72), median BMI was 35.3 kg/m<sup>2</sup> (range 26.3–60.2) and 56% (n = 58) were premenopausal (Table 1). Most women (70%, n = 65) were of white race, with 23% (n = 21) of African American/black race. Almost a third reported a history of hypertension or high cholesterol, 15% (n = 14) had sleep apnea, 10% (n = 10) had diabetes, 10% (n = 9) had a history of PCOS, and 10% (n = 10) reported a history of infertility. Approximately one third (n = 21, 36.8%) of premenopausal women were using hormonal contraceptives. Four women (4%) reported a history of EH/EC: 1 with EC, and 3 with EH.

A total of 84 women had no prior history of hysterectomy and were included in the analysis of prevalence of any EH/EC symptom. In the premenopausal group, 57% (n = 33/58) reported any EH/EC bleeding symptom (Fig. 1). The most common symptom was heavy menstrual bleeding, reported by 49% (n = 25/51) of women. Thirty-nine percent (n = 17/44) reported irregular periods, 16% (n = 8/51) had spotting between periods, and 22% (n = 13/42) had abnormal cycle length. Of women with symptoms, 37% (n = 12/33) had one, 39% (n = 13/33) had two, and 24% (n = 8/33) reported three or more symptoms. Of symptomatic premenopausal women, 60% (n = 20/33) had discussed their symptoms with a gynecologist, 15% (n = 5/33) reported that they had

**Table 1**  
Demographic characteristics of women included in the study.

N = 103	N	(%)
Age, median (IQR)	47.0	(38.0, 57.0)
Race		
White	65	(70%)
Black	21	(23%)
Other	7	(8%)
Smoking status		
Never	98	(95.1%)
Current smoker	2	(1.9%)
Former smoker	3	(2.9%)
BMI (kg/m <sup>2</sup> )		
25–29.9 (overweight)	15	(14.9%)
30–34.9 (class I obesity)	35	(34.7%)
35–39.9 (class II obesity)	23	(22.8%)
40+ (class III obesity)	28	(27.7%)
<b>Medical history</b>		
Hypertension	35	(34.3%)
Diabetes	10	(9.7%)
Obstructive sleep apnea	14	(15%)
High cholesterol	33	(32.0%)
<b>Gynecologic history</b>		
Gravida, median (IQR)	1	(0, 2)
PCOS	9	(10%)
History of infertility	10	(9.7%)
Postmenopausal	45	(43.7%)
Premenopausal	58	(56.3%)
History of hysterectomy	19	(18.4%)
Personal history of endometrial cancer	1	(1%)
Personal history of endometrial hyperplasia	3	(3%)
Number of abnormal menstrual symptoms (premenopausal women only, n = 58)		
0	25	(43.1%)
1	12	(20.7%)
2	13	(22.4%)
≥3	8	(13.8%)

IQR = interquartile range; BMI = body mass index.

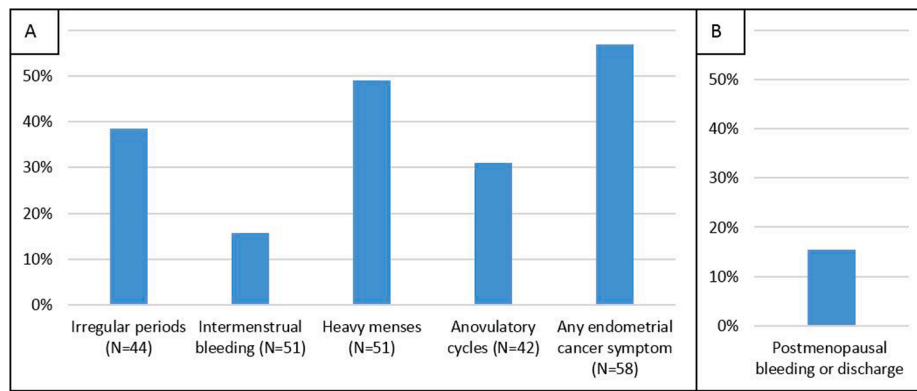


Fig. 1. Prevalence of symptoms of endometrial cancer symptoms in A) premenopausal women (n = 58) and B) postmenopausal women (n = 26).

not, and 24% (n = 8/33) did not report if they had discussed them not. A third of premenopausal women with symptoms (n = 10/33) had undergone an EMB in the past.

Fifteen percent (n = 4/26) of postmenopausal women reported any EH/EC bleeding symptom, significantly fewer than in premenopausal women (15% vs. 57%; p < 0.001). None answered the question regarding whether they had discussed their symptoms with a gynecologist, but 50% (n = 2) reported having an EMB in the past.

On univariable Poisson regression, age, menopausal status (categorized as premenopausal +/- hormonal contraceptives, and postmenopausal), and a history of PCOS were associated with any EH/EC bleeding symptom (Table 2). On multivariable analysis, PCOS remained independently positively associated with having any EH/EC symptom (RR 1.72, 95% confidence interval [CI]: 1.24–2.38; Table 2). Postmenopausal women were less likely to report any EH/EC symptom (RR = 0.32; 95%CI: 0.11–0.87); premenopausal women using hormonal contraceptives were 42% less likely (RR 0.58, 95%CI: 0.32–1.05) to report any EH/EC symptom, though this did not reach statistical significance p = 0.07.

4. Discussion

This study demonstrates a high prevalence of bleeding symptoms

that can be seen with EH/EC among overweight and obese at-risk women seeking care at a multidisciplinary weight management clinic. Almost half of all women without a history of hysterectomy reported a bleeding symptom of EH/EC. These symptoms were more common in premenopausal women and often women had not discussed these symptoms with a gynecologist. This may represent a lack of recognition of the significance of abnormal bleeding in the overweight and obese population. Heavy menstrual bleeding and irregular bleeding were the most common symptoms, and both raise concern for underlying EH/EC. We identified only one risk factor – PCOS – to be positively associated with EH/EC symptoms, which may be due to the common symptom of AUB in both PCOS and EH/EC. Postmenopausal women were less likely to have symptoms, demonstrating the high prevalence of AUB in premenopausal at-risk women and highlighting the need for more nuanced guidelines for endometrial sampling in this population.

The prevalence of abnormal menstrual symptoms in this study is consistent with data from the bariatric surgery literature where as many as 51% of morbidly obese women have menstrual dysfunction (Henretta et al., 2014). In contrast, 25% of women in the general population report heavy menstrual bleeding (Fraser et al., 2015). Similar to other studies, we found that few women have consulted a physician about their symptoms (Fraser et al., 2015).

Low levels of awareness of EH/EC symptoms and low perceived risk

Table 2

Univariate and multivariate regression analyses of patient factors on the composite outcome: any endometrial hyperplasia/cancer symptom. Variables with an association with p-value ≤ 0.1 on univariate analysis were included in the multivariable regression analysis (indicated with \*).

	Univariate analysis				Multivariate analysis			
	IRR	Upper 95% CI	Lower 95% CI	p-value	IRR	Upper 95% CI	Lower 95% CI	p-value
Age*	<b>0.97</b>	<b>0.95</b>	<b>0.99</b>	<b>0.006</b>	0.99	0.97	1.02	0.56
BMI								
Overweight (25–29.9 kg/m <sup>2</sup> )	Ref	Ref	Ref					
Class I obesity (30–34.9 kg/m <sup>2</sup> )	0.79	0.41	1.50	0.47				
Class II obesity (35–39.9 kg/m <sup>2</sup> )	0.62	0.27	1.42	0.26				
Class III obesity (≥40 kg/m <sup>2</sup> )	0.93	0.48	1.82	0.83				
Race								
White	Ref	Ref	Ref					
Black	1.10	0.59	2.05	0.78				
Other	1.00	0.40	2.51	0.99				
Menopausal status*								
Premenopausal not using HCT	Ref	Ref	Ref		Ref	Ref	Ref	
Premenopausal using HCT	0.55	0.30	1.00	0.05	0.58	0.32	1.05	0.07
Postmenopausal	0.22	0.09	0.56	<b>0.002</b>	<b>0.32</b>	<b>0.11</b>	<b>0.87</b>	<b>0.03</b>
History of diabetes	0.74	0.23	2.38	0.62				
History of hypertension	1.10	0.65	1.84	0.73				
History of infertility	0.90	0.40	2.00	0.79				
History of OSA	1.24	0.65	2.34	0.52				
History of hyperlipidemia	1.07	0.64	1.79	0.79				
History of PCOS*	<b>2.05</b>	<b>1.30</b>	<b>3.26</b>	<b>0.002</b>	<b>1.72</b>	<b>1.24</b>	<b>2.38</b>	<b>0.001</b>

Bold text indicates statistically significant association on multivariate analysis (p < 0.05).

IRR = incidence rate ratio; CI = confidence interval. PCOS = polycystic ovarian syndrome. OSA = obstructive sleep apnea; HCT = hormonal contraceptive therapy

may contribute to the low reporting of symptoms. In a study of women presenting for bariatric surgery, half perceived their personal risk of developing uterine cancer as “not likely” or “not possible” (Henretta et al., 2014). However, up to 14% of asymptomatic morbidly obese women have undiagnosed EH/EC (MacKintosh et al., 2019). It is unclear if these women truly have no symptoms, or if they do not recognize their bleeding pattern as abnormal. The issue may lie in provider counseling: only a third of EC survivors reported that their provider has told them about the link between obesity and EC (Clark et al., 2016), and while gynecologists generally recognize the importance of obesity counseling, many do not feel comfortable providing it (Huepenbecker et al., 2019).

Given the low rates of women reporting symptoms to a gynecologist both in the present study and the published literature, it is key for providers to prompt discussion of EH/EC risk and symptoms with at-risk women. In a survey of 274 bariatric surgeons, 80% obtained routine gynecologic histories from female patients. However, few had ever referred a patient for endometrial evaluation or counseled them on their cancer risk (Winfree et al., 2010). The incorporation of questionnaires addressing EC symptoms at bariatric surgery or weight management clinics can be coupled with collaborative referral mechanisms to gynecologists.

This study additionally highlights the critical need for guidelines regarding when to evaluate premenopausal women for EH/EC, i.e. through endometrial sampling. Currently, guidelines are primarily driven by age, and specifically how to incorporate BMI as a risk factor, particularly in morbidly obese women, in the decision-making is not clear (American College of Obstetricians and Gynecologists, 2013). Targeting the highest risk populations such as women with BMI  $\geq 40$  kg/m<sup>2</sup> for symptomatology screening questionnaires may have greatest sensitivity to detect EH/EC and allow for initiation of preventive measures such as hormonal contraceptives to prevent the development of EH/EC. Risk prediction models which take account for key risk factors and symptomatology are needed to estimate EH/EC risk and guide individualized decision-making.

This study is limited by its retrospective nature and small sample size, as well as potential recall bias. Additionally, other symptoms of EC such as pelvic pain or pressure were not evaluated, and non-obese women were not included as a comparison group. Moreover, the potential for generalization of these results is limited due to this unique population. However, our analysis detailed menstrual symptomatology in a unique and high-risk patient population for which there is limited data. We demonstrated the feasibility of incorporating gynecologic symptom questions in the routine care of women seeking weight loss, though we were not able to track referrals based on the questionnaire.

Future studies are needed to better elucidate the predictive value of abnormal menstrual symptoms and risk for EH/EC, particularly in premenopausal women in order to determine the clinical utility of symptomatology questionnaires such as the one presented here. Over the next several decades, EH/EC incidence will continue to rise and it is important for both patients and providers to recognize the symptoms of EH/EC, and pursue workup when warranted. To ensure early detection and prevention of EC, gynecologists must work collaboratively with providers who care for obese women to ensure they and their patients are educated on the symptoms of EH/EC and facilitate prompt referrals for symptomatic women.

#### Author contribution

Beavis, Cheskin, and Fader were involved in study design. Beavis, Najjar, Langham, and Mangal contributed to data collection and management. Beavis and Rositch performed statistical analyses. Beavis, Mangal, and Najjar were responsible for initial manuscript drafting. All authors critically reviewed the manuscript and contributed to manuscript editing; all authors approve the manuscript in its final form.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Acknowledgements

This research was funded by the Building Interdisciplinary Careers in Women's Health (BIRCWH) grant 5K12HD085845-04 from the National Institutes of Health (NIH). Additional statistical support was provided by Johns Hopkins Institute for Clinical and Translational Research (ICTR) which is funded in part by Grant Number UL1 TR003098 from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the Johns Hopkins ICTR, NCATS or NIH.

#### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gore.2020.100643>.

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