Gynecologic Oncology Reports 50 (2023) 101292

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Impact of abnormal uterine bleeding care in premenopausal patients prior to endometrial malignancy diagnosis

Jessica Grubman [a,1,*], Vanessa Mora [b], May Nguyen [b,2], Nicholas Ladwig [c], Lee-may Chen [d], Vanessa Jacoby [a]

[a] Division of Obstetrics, Gynecology, and Gynecologic Subspecialties, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California San Francisco, San Francisco, CA, USA
[b] University of California San Francisco School of Medicine, San Francisco, CA, USA
[c] Division of Surgical Pathology, Department of Pathology and Laboratory Medicine, University of California San Francisco, San Francisco, CA, USA
[d] Division of Gynecologic Oncology, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California San Francisco, San Francisco, CA, USA

ARTICLE INFO

Keywords:
Abnormal uterine bleeding
Endometrial cancer
Endometrial hyperplasia
Access to care

ABSTRACT

Background: Literature evaluating the management of abnormal uterine bleeding in premenopausal patients prior to endometrial malignancy diagnosis is lacking.
Objective: To evaluate predictors and consequences of inadequate evaluation and management of abnormal uterine bleeding and time to endometrial sampling in premenopausal patients prior to endometrial malignancy diagnosis.
Study Design.
This was a retrospective cohort study of premenopausal individuals with endometrioid endometrial cancer or atypical hyperplasia at a single institution from 2015 to 2020.. Complete noninvasive management encompassed pelvic exam, ultrasound, and progestin treatment before or in conjunction with the endometrial sampling of diagnosis. Multivariable logistic and ordinal odds models were used to evaluate predictors and outcomes.
Results: 152 subjects were included, 80.3 % with cancer and 19.7 % with atypical hyperplasia. The majority of patients had anovulatory bleeding, obesityand recent health care. Only 20.4 % had complete nonvinvasive management, and only 12.5 % had complete noninvasive management or endometrial sampling within 2 months of presentation with abnormal bleeding. Class III obesity reduced the likelihood of complete assessment and increased time to sampling, while age 45 and up and parity reduced time to sampling. Most patients had partial workup but no progestin treatment and long intervals before endometrial sampling after presentation to a provider with abnormal bleeding. Incomplete workup correlated to worse cancer grade and stage.
Conclusion: Despite high clinical risk and health care contact, most patients had insufficient gynecologic management preceding a diagnosis of endometrial malignancy. Inadequate care correlated to worse oncologic outcomes and demonstrates missed opportunities for early detection and prevention of endometrial cancer.

1. Introduction

Endometrial cancer is increasing fastest among premenopausal patients (National Cancer Institure Surveillance, 2020). This is largely due to obesity and its risk of anovulatory abnormal uterine bleeding (AUB-O) and Type I (estrogen-driven) endometrial malignancy (Lortet-Tieulent et al., 2018; Wise et al., 2016), wherein excess estrogen and insufficient progesterone drive endometrial proliferation and dysplastic changes (Brinton et al., 1992; Onstad et al., 2016).

AUB can be a precursor and symptom of endometrial malignancy; (Clarke et al., 2020) its treatment may prevent or allow earlier diagnosis of malignant disease. (Moyer & Felix, 1998; ACOG, 2021; ACOG, 2013). The American College of Obstetricians and Gynecologists' (ACOG) recommended workup of AUB in reproductive-aged patients includes a pelvic exam, consideration for imaging via pelvic ultrasound, and endometrial sampling if high risk, as with obesity, age 45 or more, and

* Corresponding author at: UTSW Dept. of Obstetrics and Gynecology, 5235 Harry Hines Blvd, Dallas, TX 75390, USA.
E-mail address: jessica.grubman@utsouthwestern.edu (J. Grubman).
[1] Present affiliation: Division of Gynecology, Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, TX.
[2] Present affiliation: Department of Obstetrics and Gynecology, Harbor-UCLA Medical Center, Los Angeles, CA.

https://doi.org/10.1016/j.gore.2023.101292
Received 9 August 2023; Received in revised form 5 October 2023; Accepted 7 October 2023
Available online 10 October 2023

bleeding non-responsive to medication. (ACOG, 2021; ACOG, 2013) With their anti-proliferative effect on the endometrium, progestins are first-line treatment and are widely recommended for management of AUB. (Moyer & Felix, 1998; ACOG, 2013).

Unfortunately, patients and providers under-recognize AUB, contributing to endometrial malignancy's rise (Franceschi et al., 1983; Henry et al., 2020). Premenopausal versus postmenopausal individuals more frequently face delayed diagnosis, negatively affecting outcomes. (Gitsch et al., 1995; Dolly et al., 2016) While nonadherence to guidelines for postmenopausal bleeding management has been directly correlated to worse cancer outcomes, (Doll et al., 2018) there is a dearth of literature specifically evaluating patterns in premenopausal AUB diagnosis and treatment in the United States (US) health care system. Similarly, data on the management of AUB and interface with the health care system in premenopausal patients prior to a diagnosis of endometrial malignancy in the US is lacking.

This paper aims to overcome these gaps by evaluating predictors and consequences of type and timeframe of AUB evaluation and management in a cohort of premenopausal patients prior to a diagnosis of diagnosis of atypical endometrial hyperplasia, endometrial intraepithelial neoplasia (EIN), or endometrioid endometrial carcinoma, and to identify missed opportunities for endometrial cancer prevention in our population.

2. Materials and methods

This is a retrospective cohort study of premenopausal individuals with diagnoses of endometrioid endometrial cancer, atypical endometrial hyperplasia (also named endometrial hyperplasia with atypia) or EIN, which we refer to collectively as endometrial malignancy, treated at the University of California, San Francisco (UCSF), a tertiary academic medical center, between 2015 and 2020. Approval for the study was received from the UCSF Institutional Review Board and the UCSF Helen Diller Family Comprehensive Cancer Center. We followed the STROBE guidelines for observational study design and reporting (von Elm et al., 2014).

Our objectives were to define the proportion and characteristics of premenopausal patients who received noninvasive evaluation and management of AUB in the three years prior to malignancy diagnosis, and to evaluate timing of invasive evaluation of AUB via endometrial sampling after presentation to a health care provider with AUB. We analyzed the effects of time to endometrial sampling and complete versus incomplete non-invasive AUB workup and management on oncologic outcomes including final malignancy grade and stage.

The International Federation of Gynecology and Obstetrics PALM-COIEN terminology denoting structural and nonstructural causes of abnormal uterine bleeding (PALM- polyp, adenomyosis, leiomyoma, malignancy; COIEN – coagulopathy, ovulatory dysfunction, iatrogenic, endometrial, and not otherwise classified) was used to classify AUB (Munro et al., 2011). Noninvasive workup and management was considered complete if patients received a pelvic exam and pelvic ultrasound to evaluate AUB and progestin-containing therapy for management in the three years prior to their hyperplasia or cancer diagnosis. We defined this outcome based on the ACOG recommendations (ACOG, 2021; ACOG, 2013) and other published best practices for the evaluation and treatment of premenopausal AUB with regards to the PALM-COIEN classification (Marnach and Laughlin-Tommaso, 2019; Levy-Zauberman et al., 2017; Ely et al., 2006). We included ultrasound because the hallmark of the PALM-COIEN classification is distinction of structural versus non-structural causes of AUB, typically assessed via ultrasound. (ACOG, 2021; Munro et al., 2011) Acceptable progestin medications included any prescribed combination estrogen-progestins (contraceptive vaginal ring and oral contraceptive pills); oral progestins including medroxyprogesterone acetate, megestrol acetate, and norethindrone; depot medroxyprogesterone acetate; or levonorgestrel intrauterine device (IUD). Because some patients underwent endometrial sampling as a first step in evaluation of AUB, we also considered time from first health care presentation with AUB to sampling, categorized as within 2 months, between 2 and 6 months, or 6 or more months. Oncologic outcomes included final diagnosis of endometrial hyperplasia with atypia or EIN versus endometrial cancer, and, among those with cancer, final tumor grade and stage.

Comprehensive review of the electronic medical record (EMR) encompassed care before and after diagnosis of endometrial malignancy. We reviewed all health care visits and notes, both at our institution and records from outside facilities, for information including patient demographics, clinical history, and pertinent laboratory, imaging, and pathology studies in the three years prior to malignancy diagnosis.

Cases were obtained by pathology diagnosis. The UCSF pathology database was searched for the terms "endometrioid adenocarcinoma," "endometrioid carcinoma," "hyperplasia with atypia," "atypical endometrial hyperplasia," "abnormal glandular proliferation," and "atypical glandular proliferation" on specimens obtained from 2015 to 2020. Specimens from patients with male biologic sex, non-endometrial disease, and non-endometroid endometrial cancer were excluded. Additionally, individuals who had pathology specimen review but no clinical care at our institution were excluded. To target premenopausal endometrial malignancy, patients with specimens obtained at age 50 or younger were further investigated; those documented as postmenopausal at time of sampling were excluded. We then excluded those without records of care prior to malignancy diagnosis. For patients with more than one pathology study at UCSF (eg, endometrial biopsy of EIN followed by hysterectomy showing endometrial cancer), the first specimen with a diagnosis of atypical hyperplasia, EIN, or carcinoma was used to mark the time of diagnosis. Time of first presentation for AUB was determined by description in clinician history and physical (H&P) notes and/or mention of AUB as a patient complaint or provider diagnosis in prior visits. Three authors (JG, MN and VM) reviewed records and abstracted data. Any disagreements about inclusion versus exclusion were discussed and consensus reached.

Predictors of complete noninvasive pre-malignant AUB management encompassed demographic, clinical, and hospital system factors. Clinical factors included type of AUB (specifically, irregular bleeding/anovulatory AUB versus AUB with regular cycles), obstetric history, family history of endometrial cancer, body mass index (BMI) at time of diagnosis and receipt of blood transfusion for AUB-related anemia. Hospital system variables included any health care visits within 3 years prior to malignancy diagnosis, as viewed in Care Everywhere or as documented in provider care notes, and provider specialty and location of care. We included visits to any health care facility for non-AUB complaints as a surrogate for general access to care, as well as AUB-specific visits, analyzed separately. Descriptive information was cross-referenced with objective information, including dates of contact with the health care system and studies ordered for evaluation of AUB.

Statistical analysis was performed with Stata, version 17 (StataCorp, 2021). Chi-square test and Fisher exact tests were used to compare the proportion of patients with each predictor of interest and complete versus incomplete noninvasive workup; with complete versus incomplete noninvasive workup and each oncologic outcome (cancer versus hyperplasia and grade and stage of cancer); and with longer versus shorter time from AUB presentation to initial invasive workup via endometrial sampling and oncologic outcomes. Multivariable logistic regression models were used to obtain adjusted odds ratios of complete versus incomplete noninvasive workup, of time to endometrial sampling, and of highest disease diagnosis as cancer versus hyperplasia, controlling for potential confounding effects of included predictor variables. Ordinal logistic regression was performed to obtain adjusted proportional odds ratios for the multilevel outcomes of cancer grade and cancer stage. Alpha was set at 0.05, with $p < 0.05$ considered statistically significant.

Model fit was assessed with the corresponding Hosmer-Lemeshow

goodness of fit tests for both the binary and ordinal regression models, and model fit confirmed. Complete case analysis was used to address missing data in multivariable models.

3. Results

The pathology database search returned 2162 unique specimens belonging to 1535 patients. Of 328 individuals aged 50 or younger, 154 were excluded due to non-endometrioid endometrial cancer or lack of cancer care at UCSF. Chart review was performed for the remaining 174 patients, of which 22 were excluded due to insufficient records. Of the included 152 patients, 30 (19.7 %) had a final diagnosis of atypical hyperplasia or EIN and 122 (80.3 %) endometrioid endometrial cancer, 55.9 % grade 1 and 25 % grade 2 or higher. As detailed in Table 3, 24.3 % of patients were treated conservatively for EIN/atypical endometrial hyperplasia or clinical stage I endometrial cancer. Of the patients who underwent surgical management with staging, 53.3 % had stage I disease and 19.7 % stage II or higher.

Table 1 details subject characteristics. Mean age was 41.9 years (median 43, range 24–50); 63.8 % of patients were under 45 years. Subjects were demographically diverse in terms of race/ethnicity, marital status, geographical provenance, and insurance status. Most

Table 1
Patient Characteristics and Completeness of Noninvasive AUB Evaluation and Management.

Characteristic	Pelvic Exam N (percent)	Ultrasound N (percent)	Progestin Therapy within 3y N (percent)	Complete N (percent)	Complete OR (95 % CI, p-value)
Total	74 (48.7)	129 (84.9)	60 (39.5)	31 (20.4)	n/a
Demographic Factors					
Ageat Diagnosis					
<45 y*	47 (48.5)	84 (86.6)	45 (46.4)	25 (25.8)	Ref
45 y or older	22 (40)	45 (81.8)	14 (25.5)	6 (10.9)	**0.11 (0.03–0.34, <0.01)**
Race					
White*	24 (39.3)	51 (83.6)	27 (44.3)	13 (21.3)	Ref
Asian/Pacific Islander	24 (58.5)	36 (87.8)	15 (36.6)	11 (26.8)	0.55 (0.19–1.61, 0.27)
Other	23 (52.3)	36 (81.8)	15 (34.1)	5 (11.4)	0.32 (0.1–1.02, 0.055)
Ethnicity					
Hispanic/Latino	24 (46.2)	41 (78.9)	22 (42.3)	8 (15.4)	1.23 (0.35–4.31, 0.74)
Not Hispanic/Latino*	49 (49.5)	87 (87.9)	37 (37.4)	22 (22)	Ref
Primary Language					
English*	65 (49.2)	114 (86.4)	50 (37.9)	26 (19.7)	Ref
Spanish	3 (23.1)	8 (61.5)	6 (46.2)	1 (7.7)	1.52 (0.21–10.8, 0.68)
Other	6 (85.7)	7 (100)	4 (57.1)	4 (57.1)	4.47 (0.59–33.9, 0.15)
County of Residence					
San Francisco*	14 (63.6)	22 (100)	9 (40.9)	8 (36.4)	Ref
Bay Area, not SF	28 (46.7)	49 (81.7)	22 (36.7)	9 (15)	0.42 (0.12–1.51, 0.18)
Outside of Bay Area	32 (45.7)	58 (82.9)	29 (41.4)	14 (20)	0.52 (0.14–1.99, 0.34)
Insurance type					
Private Insurance*	31 (58.5)	48 (90.6)	18 (34)	14 (26.4)	Ref
Medicaid or Medicare	41 (43.6)	78 (83)	40 (42.6)	16 (17)	1.12 (0.42–3, 0.83)
Self-Pay	2 (40)	3 (60)	2 (40)	1 (20)	3.52 (0.37–34, 0.28)
Marital status					
Partnered*	42 (50.6)	73 (88)	34 (41)	16 (19.3)	Ref
Single	22 (42.3)	42 (80.8)	19 (36.5)	10 (19.2)	0.78 (0.31–1.98, 0.6)
Previous partnered	6 (50)	10 (83.3)	4 (33.3)	2 (16.7)	1.22 (0.25–5.87, 0.81)
Clinical Factors					
Obstetric History					
Nulliparous	40 (44.4)	78 (86.7)	34 (37.8)	17 (18.9)	Ref
Parous	34 (54.8)	51 (82.3)	26 (41.9)	14 (22.2)	1.75 (0.77–3.97, 0.77)
Years of AUB					
<1y	19 (42.2)	36 (80)	11 (24.4)	7 (15.6)	**Ref**
1-2y	12 (46.2)	24 (92.3)	11 (42.3)	4 (15.4)	2.18 (0.59–8.07, 0.24)
>=3y	39 (52)	65 (86.7)	38 (50.7)	20 (26.7)	**4.3 (1.53–12.03, <0.01)**
Anovulatory bleeding	64 (66.7)	107 (84.9)	55 (43.7)	29 (23)	1.59 (0.42–6.02, 0.5)
Transfusion	11 (44)	22 (88)	14 (56)	7 (28)	0.94 (0.31–2.81, 0.91)
Body Mass Index					
Non-obese	26 (59.1)	37 (84.1)	17 (38.6)	13 (29.6)	Ref
Class I Obesity	10 (47.6)	16 (76.2)	6 (28.6)	2 (9.5)	0.38 (0.1–1.48, 0.16)
Class II Obesity	13 (61.9)	19 (90.5)	11 (52.4)	8 (38.1)	0.79 (0.23–2.73, 0.72)
Class III Obesity	24 (37.5)	55 (85.9)	25 (39.1)	7 (10.9)	**0.36 (0.13–0.97, 0.04)**
Family Hx Endometrial Cancer	13 (68.4)	13 (68.4)	8 (42.1)	5 (26.3)	0.93 (0.28–3.1, 0.9)
Health Systems Factors					
Any care ≤ 3y prediagnosis**	64 (46.4)	118 (85.5)	55 (40.2)	31 (23.9)	n/a**
Emergency Department	23 (45.1)	47 (92.2)	16 (31.4)	8 (15.7)	0.64 (0.25–1.67, 0.36)
Primary Care Provider	55 (52.9)	88 (84.6)	37 (35.6)	22 (21.2)	0.59 (0.23–1.53, 0.28)
Subspecialty Care	54 (54.6)	87 (87.9)	40 (40.4)	25 (25.3)	1.27 (0.46–3.5, 0.64)
Gynecology within 3y	50(79.4)	56 (88.9)	33 (52.4)	25 (39.7)	**10.9 (3.92–30.4, <0.01)**
Location, First AUB Presentation					
Gyn	43 (66.2)	50 (76.9)	32 (49.2)	20 (30.8)	Ref
PCP	17 (38.6)	42 (95.5)	11 (25)	6 (13.6)	0.52 (0.16–1.65, 0.27)
ED	7(22.6)	28 (90.3)	10 (32.3)	3 (9.7)	0.95 (0.26–3.5, 0.94)
Other/missing	7 (58.3)	9 (75)	7 (58.3)	2 (16.7)	0.53 (0.11–2.49, 0.43)

Notes: n/a, not applicable; Hx, history; PCP, primary care provider; ED, emergency department; OR, odds ratio. The collapsed "Other" race category includes groups with < 10 patients per category (Black or African American, n = 4; Native American or Alaskan Native, n = 6) and more than one race without specification or and self-identification as "other" race (n = 34). Body mass index < 30 is non-obese, class I 30–34.9, class II 35–39.9, class III 40 and greater. **Any care within 3y prior to diagnosis excluded from multivariable model due to collinearity.

patients had initial care for AUB at facilities near their homes and were then referred to our tertiary academic center for oncologic care.

The cohort had a high prevalence of clinical risk factors for endometrial malignancy, including obesity, nulliparity, and longterm irregular menses consistent with AUB-O. Mean BMI at diagnosis was 37.8 kg/m (Lortet-Tieulent et al., 2018) (median 37.3 range 18.3–78.9). Seventy one percent of patients had any obesity: 14 % class I (BMI 30–34.9 kg/m (Lortet-Tieulent et al., 2018)), 14 % class II (BMI 35–39.9 kg/m^2), 42.7 % class III obesity (BMI $\geq$ 40 kg/m^2).

Body mass index < 30 is non-obese, class I 30–34.9, class II 35–39.9, class III 40 and greater. Approximately half of patients had three or more years of AUB prior to diagnosis of hyperplasia or cancer, and 16.5 % had received a blood transfusion for AUB-related anemia. A minority of individuals in the cohort had familial endometrial cancer risk, with 4 % of all patients and 5 % with cancer having Lynch syndrome and12.5 % having na family history of endometrial cancer.

The vast majority of patients were established in the health care system prior to malignancy diagnosis. Many had regular follow-up for chronic conditions but no identification or evaluation of AUB by their providers for years, despite having contemporaneous AUB as reported in

Table 2
Time from First AUB Presentation to Endometrial Sampling.

	<2 months	2-6mos	>6mos	Time to sample	Complete or < 2mos	
	N (percent)	N (percent)	N (percent)	pOR (95 % CI, p-value)	N (percent)	OR (95 % CI, p-value)
Total	66 (44.9)	31 (21.1)	50 (34)	n/a	86 (56.6)	n/a
Demographic Factors						
Age at Dx						1
<45	34 (36.2)	17 (18.1)	43 (45.7)	Ref	54 (55.7)	Ref
45 or older	28 (51.9)	16 (29.6)	10 (18.5)	**0.4 (0.2–0.8, 0.01)**	33 (60)	0.98 (0.46–2.1, 0.95)
Race						
White*	29 (48.3)	7 (11.7)	24 (40)	Ref	36 (59)	Ref
Asian/Pacific Islander	18 (43.9)	11 (26.8)	12 (29.3)	0.9 (0.38–2.1), 0.8	26 (63.4)	1.1.22 (0.49–3.01, 0.67)
Other	18 (43.9)	11 (26.8)	12 (29.3)	0.45 (0.27–1.55), 0.32	21 (47.7)	0 0.82 (0.32–2.1, 0.67)
Ethnicity						
Hispanic/Latino	21 (42)	9 (18)	20 (40)	2.08 (0.81–5.39), 0.13	27 (51.9)	00.7 (0.26–1.92, 0.26)
Not Hispanic/Latino*	45 (46.4)	22 (22.7)	30 (30.9)	Ref	58 (58.6)	Ref
Primary Language						
English*	54 (41.9)	29 (22.5)	46 (35.7)	Ref	70 (53)	Ref
Spanish	9 (69.2)	1 (7.7)	3 (23.1)	0.31 (0.07–1.37), 0.12	10 (76.9)	4.52 (0.92–22.1, 0.06)
Other	3 (50)	2 (33.3)	1 (16.7)	0.95 (0.18–5.07), 0.96	6 (85.7)	4.49 (0.45–44.3, 0.2)
County of Residence						
San Francisco*	9 (45)	5 (25)	6 (30)	Ref	14 (63.6)	Ref
Bay Area, not SF	26 (44.1)	15 (25.4)	18 (30.5)	1.29 (0.47–3.53), 0.62	33 (55)	0.95 (0.31–2.84, 0.92)
Outside of Bay Area	31 (44.9)	12 (17.2)	26 (37.7)	1.44 (0.51–4.1), 0.49	39 (55.7)	0.94 (0.3–2.96, 0.3)
Insurance type						
Private Insurance*	23 (44.2)	10 (19.2)	19 (36.5)	Ref	32 (60.4)	Ref
Medicaid or Medicare	40 (44)	21 (23.1)	30 (33)	0.74 (0.33–1.63), 0.48	50 (53.2)	0.6 (0.26–1.39, 0.24)
Self-Pay	3 (60)	1 (20)	1 (20)	0.52 (0.07–3.68), 0.51	4 (80)	1.32 (0.12–14.98, 0.82)
Marital status						
Partnered*	36 (44.4)	18 (22.2)	27 (33.3)	Ref	47 (56.6)	Ref
Single	23 (46)	10 (20)	17 (34)	0.83 (0.41–1.7), 0.63	28 (53.9)	1.21 (056–2.63, 0.63).
Previous partnered	5 (41.7)	2 (16.7)	5 (41.7)	1.42 (0.42–4.72), 0.51	7 (58.3)	1.33 (0.34–5.38, 0.68) 0.8 (0.21–3), 0.74
Clinical Factors						
Obstetric History						
Nulliparous	32 (37.2)	18 (20.9)	36 (41.9)	Ref	44 (48.9)	Ref
Parous	34 (54.8)	14 (22.6)	14 (22.6)	**0.48 (0.25–0.94, 0.03)**	42 (67.7)	1.63 (0.75–3.5, 0.21)
Years of AUB prior to diagnosis						
<1y	31 (68.9)	9 (20)	5 (11.1)	Ref	35 (77.8)	Ref
1-2y	14 (53.9)	2 (7.7)	10 (38.5)	2.33 (0.82–6.58, 0.11)	16 (61.5)	0.64 (0.2–2.1, 0.45)
>=3y	20 (27)	19 (25.7)	35 (47.3)	**5.3 (2.39–11.75, <0.01)**	34 (45.3)	**0.29 (0.11–0.74, 0.01)**
Anovulatory bleeding	53 (42.7)	29 (23.4)	42 (33.9)	1.05 (0.37–3.01, 0.93)	72 (57.1)	1.97 (0.61–6.4, 0.26)
Transfusion	12 (48)	4 (16)	9 (36)	0.75 (0.3–1.88, 0.54)	16 (64)	1.73 (0.63–4.75, 0.29)
Body Mass Index						
Non-obese	25 (58.1)	9 (20.9)	9 (20.9)	Ref	33 (75)	Ref
Class I Obesity	10 (47.6)	4 (19.1)	7 (33.3)	1.08 (0.-3.06, 0.89)	12 (57.1)	0.42 (0.12–1.45, 0.17)
Class II Obesity	9 (42.9)	7 (33.3)	5 (23.8)	1 (0.34–2.97, 0.99)	13 (61.9)	0.39 (0.11–1.42, 0.16)
Class III Obesity	21 (34.4)	12 (19.7)	28 (45.9)	**2.2 (1.03–5.3), 0.048**	26 (40.6)	**0.2 (0.08–0.55, <0.01)**
Family Hx Endometrial Cancer	7 (36.8)	6 (31.6)	6 (31.6)	0.95 (0.35–2.6, 0.92)		1.12 (0.36–3.46, 0.84)
Health Systems Factors						
Pre-Cancer Health Care						
Emergency Department	21 (42.9)	8 (16.3)	20 (40.8)	1.59 (0.77–3.28), 0.21	27 (52.9)	0.69 (0.32–1.48), 0.34
Primary Care Provider	40 (39.6)	25 (24.8)	36 (35.6)	1.15 (0.54–2.43), 0.72	56 (53.9)	0.99 (0.44–2.22), 0.99
Subspecialty Care	39 (40.2)	25 (25.8)	33 (34)	1.03 (0.5–2.11), 0.94	57 (57.6)	1.23 (0.57–2.62), 0.6
Gynecology within 3y	23 (38.3)	13 (21.7)	24 (40)	1.79 (0.87–3.68), 0.11	40 (63.5)	1.45 (0.67–3.16), 0.35
Location of First Presentation for AUB						
Gyn	33 (52.4)	12 (19.1)	18 (28.6)	Ref	45 (69.2)	Ref
PCP	12 (27.9)	12 (27.9)	19 (44.2)	**2.83 (1.25–6.38), 0.01**	17 (38.6)	**0.28 (0.11–0.67, <0.01)**
ED	19 (61.3)	6 (19.4)	6 (19.4)	0.7 (0.26–1.88), 0.49	20 (64.5)	0.88 (0.31–2.5, 0.81)
Other/missing	2 (18.2)	2 (18.2)	7 (63.6)	**5.39 (1.42–20.5), 0.01**	4 (33.3)	**0.23 0.06–0.91, 0.04)**

Notes: n/a, not applicable; Dx, diagnosis; Hx, history; PCP, primary care provider; ED, emergency department; pOR, proportional odds ratio. The collapsed "Other" race category includes groups with < 10 patients per category (Black or African American, n = 4; Native American or Alaskan Native, n = 6) and more than one race without specification or and self-identification as "other" race (n = 34). Body mass index < 30 is non-obese, class I 30–34.9, class II 35–39.9, class III 40 and greater.

their Gynecology and Gynecologic Oncology H&Ps. More than ninety percent (90.9 %) of individuals had at least one medical visit at any health care location before the appointment at which endometrial sampling diagnosed endometrial malignancy. The most common visits prior to malignancy diagnosis were to a primary care provider (PCP, 68 % of patients), followed by a non-gynecologic subspecialist (65.4 %), gynecologist (41.5 %), and the emergency department (ED, 33.3 %). Unsurprisingly, patients more often saw gynecologists for their first AUB-focused visit (42.5 % of patients) than other providers, including PCPs (28.8 %) and ED providers (20.3 %).

Even with health care access, few patients had timely and complete workup for AUB (Tables 1 and 2). Fewer than half (43.6 %) of individuals in this clinically high-risk cohort had either prompt endometrial sampling or ACOG–recommended AUB noninvasive management. Overall, only 41.9 % had endometrial sampling within 2 months of presentation with AUB, while more than a third of individuals (35.8 %) did not have endometrial sampling for more than 6 months after presentation with AUB; 22.3 % underwent sampling between 2 and 6 months. Of individuals who did not have endometrial sampling as the first step in AUB evaluation, only 12.5 % of patients had complete noninvasive evaluation and management with a pelvic exam, ultrasound, and progestin therapy within 2 months of presentation with AUB, and only 20.4 % of patients received complete noninvasive assessment within 3 years prior to malignancy diagnosis. This is despite AUB being identified months to years before malignancy diagnosis in many patients, as evidenced by underwent partial AUB evaluations: most patients had a pelvic ultrasound for AUB prior to malignancy diagnosis, but fewer than half had a pelvic exam prior to the visit of endometrial sampling or received progestin therapy. Unsurprisingly, patients with earlier endometrial sampling tended not to have complete noninvasive assessment – only 18 % of patients with sampling within 2 months of presentation had complete noninvasive assessment, versus 22.6 % and 34 % in those who underwent sampling within 2–6 or 6 months after of AUB presentation, respectively.

Of demographic factors, age 45 or older decreased the odds of complete noninvasive workup (OR 0.11, 95 % CI 0.03–0.34) but also reduced the odds of longer time to sampling (pOR 0.4, 95 % CI 0.2–0.8). There were no other significant differences in noninvasive workup by demographic factors (Tables 1 and 2).

Among clinical factors, duration of AUB for 3 or more years correlated to increased odds of complete noninvasive workup (OR 4.3, 95 % CI 1.53–12.03), as well as longer time from AUB presentation to endometrial sampling (pOR 5.3, (95 % CI 2.39–11.75). Notably, having class III obesity decreased odds of complete noninvasive workup (OR 0.37, 95 % CI 0.14–0.97), but also conferred increased time from presentation with AUB to sampling (pOR of time to sampling category 2.29, 95 % CI 1.03–5.26). In contrast, parity correlated to shorter time to sample (pOR 0.48, 95 % CI 0.25–0.94) Blood transfusion for severe AUB-related anemia, anovulatory bleeding pattern and family history of endometrial cancer did not improve likelihood of complete noninvasive care or early endometrial sampling after presentation with AUB.

. Health care access also impacted likelihood of both complete noninvasive workup and time from AUB identification to endometrial sampling. Having seen a gynecologist for any reason in the years prior to malignancy diagnosis significantly increased odds of having a pelvic exam, ultrasound, and progestin therapy (OR 10.9, 95 % CI 3.92–30.4), in contrast to other provider types. Similarly, presenting to a gynecologist for initial AUB evaluation correlated to timelier endometrial sampling: patients presenting to PCPs or other provider types, though not the ED, had higher odds of longer time to sampling (pOR 2.83, 95 % CI 1.25–6.38 and 5.39, 1.42–20.5, respectively). Having had contact with the health care system for visits not specific to AUB during the years prior to malignancy diagnosis did not improve time to endometrial sampling compared to patients without health care visits prior to the time of diagnosis.

Largely the same factors impacted the composite outcome of complete noninvasive management of AUB or sampling within 2 months of AUB presentation as they did complete noninvasive assessment and time to sampling individually (Table 2). Specifically, AUB duration of 3 or more years, class III obesity, and presentation to primary care or other/unidentified provider decreased odds of both complete workup and timely sampling.

Complete AUB workup by exam, ultrasound, and progestins, but not time to sampling, significantly corresponded to oncologic outcomes (Table 3). Having had complete noninvasive workup and management with pelvic exam, ultrasound, and progestin therapy correlated to lower disease grade and stage. With this combination of care, proportional odds of grade 1endometrial cancer versus hyperplasia with atypia/EIN, and of grade II or higher versus grade 1 endometrial cancer were 0.33 (95 % CI 0.14–0.76). Similarly, proportional odds of stage I cancer compared to hyperplasia or conservatively-managed cancer were 0.38 (95 % CI 0.17–0.85). Neither time to sampling alone or the composite outcome of time to sampling or adequate workup significantly impacted oncologic outcomes. Fig. 1 shows proportional odds of oncologic grade and stage by AUB care completeness.

4. Discussion

Much of this cohort faced insufficient identification and management of AUB prior to endometrial malignancy diagnosis, despite being high risk due to obesity, longstanding anovulatory AUB, and nulliparity, and despite contact with the health care system, with most individuals having had care concurrent with, but not addressing, their AUB.

The discrepancy between receipt of pelvic ultrasound and progestin therapy for AUB especially demonstrates deficient care. While most patients underwent ultrasound for AUB, demonstrating recognition of AUB as an issue by a provider, few were prescribed progestins to treat AUB and prevent endometrial malignancy. Furthermore, while ultrasound is important in determination of AUB type, it has poorer predictive value in some groups, including Black women and women with fibroids (Romano & Doll, 2020), and is not sufficient to rule in or out endometrial malignancy in premenopausal patients (Kim et al., 2016). Regardless of ultrasound, endometrial sampling needs to be expedited in high-risk individuals with AUB. Unfortunately, many of our cohort did not have endometrial biopsy until years after an ultrasound was done for AUB. Another key finding is that individuals most at risk of AUB-O and resulting endometrial malignancy, those with class III obesity, (Wise et al., 2016) were more likely to have incomplete noninvasive premalignant workup and longer time from AUB presentation to first endometrial sampling. Additionally, that only half of patients with AUB severe enough to require blood transfusion received progestin therapy highlights inadequate AUB management.

Not surprisingly, we found different practice patterns across specialties. As expected, patients who had seen gynecologists in the years prior to malignancy diagnosis were more likely to receive an adequate workup and to proceed sooner to endometrial sampling compared to patients who did not see a gynecologist until the visit at which endometrial sampling revealed malignancy. This may reflect under-identification of AUB by non-gynecologic clinicians as well as difficulty with patients accessing gynecologic services for further care. Indeed, neither the American College of Emergency Physicians (ACEP) nor the American Academy of Family Physicians (AAFP), which represent two of the specialties most likely to encounter patients with gynecologic complaints such as AUB, have current clinical practice recommendations or other society guidelines for AUB management. However, the majority of patients seen by gynecologists also received insufficient AUB care and faced endometrial sampling delays.

Overall, our results parallel previous findings of barriers to care for, and suboptimal management of, AUB, particularly with regards to under-recognition and undermanagement of AUB by providers (Henry et al., 2020; Cordasco et al., 2019; Matteson et al., 2011). The discrepancy between health care received and absent or incomplete AUB care in

Table 3
Correlation of Complete Noninvasive Premalignant AUB Care and Final Disease Grade and Stage.

	Highest Disease Grade				Highest Disease Stage			
	Hyperplasia with atypia N (percent)	Grade 1 N (percent)	Grade 2 or higher N (percent)	Proportional Odds Ratio pOR (95 % CI, p-value)	Not staged (hyperplasia with atypia or cancer treated medically)	Stage I N (percent)	Stage II or greater N (percent)	Proportional Odds Ratio pOR (95 % CI, p-value)
Total Premalignant Care	30 (19.7)	84 (55.3)	38 (25)	**n/a**	41 (27)	81 (53.3)	30 (19.7)	**n/a**
Complete	10 (33.3)	16 (19.1)	5 (13.2)	**0.36 (0.16–0.83, 0.02)**	13 (31.7)	13 (16.1)	5 (16.7)	**0.44 (0.2–0.9, 0.049)**
Incomplete	16 (53.3)	61 (72.6)	33 (86.4)	Ref	23 (56.1)	62 (76.5)	25 (83.3)	Ref
Missing	4 (13.3)	7 (8.2)	0	0.29 (0.08–1.07, 0.06)	5 (12.2)	6 (7.4)	0	0.35 (0.1–1.29, 0.12)
Time to Sample								
<2mos	9 (31)	39 (47)	18 (50)	Ref	13 (32.5)	37 (46.8)	16 (55.2)	Ref
2-6mos	6 (20.7)	19 (22.9)	7 (19.4)	0.82 (0.36–1.87, 0.64)	9 (22.5)	19 (24.1)	4 (13.8)	0.61 (0.27–1.37, 0.23)
>6mos	14 (48.3)	25 (30.1)	11 (30.6)	0.71 (0.34–1.5, 0.37)	18 (45)	23 (29.1)	9 (31)	0.59 (0.28–1.23, 0.16)
Complete or < 2mos	16 (18.6)	50 (58.1)	20 (23.3)	0.82 (0.44–1.53, 0.54)	22 (25.6)	44 (54.2)	20 (23.3)	0.93 (0.5–1.71, 0.81)

Notes: n/a, not applicable. Reference categories are not complete (compared to complete noninvasive workup and management or missing) and not complete or first sampling < 2 months (compared to composite predictor of complete workup or sampling < 2 months). Interpreting proportional odds ratios: For complete noninvasive workup, the odds of having grade 2 or higher disease versus the grade 1 or hyperplasia with atypia is 0.36 times the odds with incomplete workup, and 0.82 times the odds with complete workup or sampling < 2 months versus not having complete workup or sampling < 2 months. Likewise, the odds of having grade 1or grade 2 or higher disease versus hyperplasia with complete noninvasive workup is 0.36 times the odds with incomplete workup, and 0.82 times the odds with complete workup or sampling < 2 months versus incomplete or sampling < 2 months.

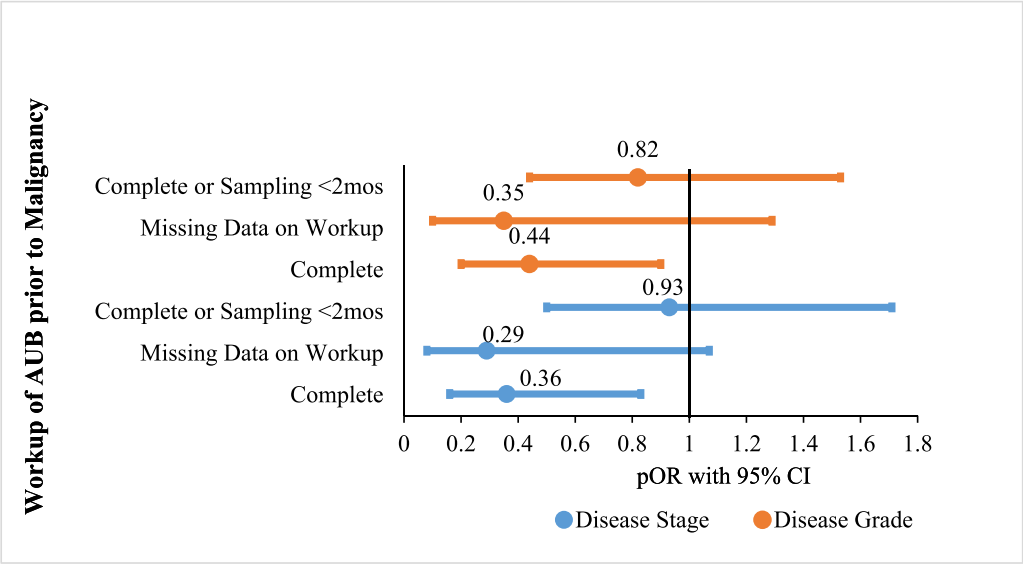

Fig. 1. Proportional Odds Ratios (pOR) of Malignancy Grade and Stage by Completeness and Timing of Noninvasive AUB Care Prior to Malignancy Diagnosis. Notes: Reference categories are incomplete workup (vs complete or missing) and not complete and/or first sampling ≥ 2 mos (vs complete workup and/or sampling < 2 mos). Interpreting pOR: With complete noninvasive workup, odds of grade 2 or higher disease vs grade 1 or hyperplasia is 0.36 times the odds with incomplete workup, and odds of grade 1 or grade 2disease vs hyperplasia is 0.36 times the odds of incomplete workup.

the same timeframe may also reflect patient-related delays, which are explored by Andersen, et al, in their model of "total patient delay:" insufficient patient knowledge of symptoms (appraisal delay), fear of disease and under-empowerment by patients to bring this up to their health care providers (behavioral delays), and barriers to timely care after presentation (scheduling delay) all contribute to delayed cancer diagnosis (Whetstone et al., 2022).

The geographic diversity of included patients adds to prior data on under-recognition of AUB, as patients' pre-diagnosis healthcare occurred at countless facilities across a large geographic area, demonstrating widespread insufficiency in AUB care. Our finding that incomplete noninvasive workup portends poorer oncologic outcome is also consistent with previous data finding that delayed diagnosis of endometrial malignancy portends worse prognosis (Gitsch et al., 1995; Dolly et al., 2016). Additionally, the correlation of obesity with poorer AUB care receipt adds to a growing body of literature on the subject and calls to action to improve care for this population (McAlpine et al., 2016). Class III obesity confers 9.8 times the odds of endometrial cancer as normal BMI, and BMI is more predictive of abnormal endometrial sampling than age (Wise et al., 2016). Beavis et al described a group of premenopausal women with AUB in the setting of overweight and obesity, of which only two thirds had discussed abnormal menses with a

gynecologist and one third received endometrial sampling (Beavis et al., 2020). Poorer care among obese subjects may reflect discrimination by health care providers, as individuals with obesity may self-delay care, including cancer evaluation, due to perceived negative attitudes and treatment (Amy et al., 2006).

Unlike others, we did not find statistically significant demographic differences between patients with adequate versus inadequate AUB management. This may likely be due to different demographic composition of our cohort compared to others studied, particularly with regard to race and ethnicity. Consistent with our regional demography, a larger proportion of our patients identified as Asian or Pacific Islander (27 %) and a smaller proportion (2.7 %) as Black or African American, compared to 15.4 % and 5.7 % of California residents and 6 % and 12.4 % of Americans overall (P8: RACE, 2023). Recent studies have similar uterine cancer death rates between Asian/Pacific Islander and white women; non-Hispanic Black women face more gynecologic health disparities, including disproportionately high uterine cancer deaths (Whetstone et al., 2022). We also did not find statistically significant differences in the impact of timing of diagnosis with endometrial sampling on oncologic outcomes, possibly due to our small sample size.

A major strength of this study is the inclusion of both pre-malignant and oncologic courses, and the detailed review of these courses, facilitating granular comparison of long-term consequences of varied AUB management. Efforts to limit bias include use of objective criteria for case selection through pathology diagnosis, and reduction of information bias through exhaustive medical record review by multiple authors. On the other hand, sample size is a main limitation of our study, particularly with regards to statistical power. For instance, while longer time from AUB presentation to sampling inversely correlated to cancer grade and stage, this did not reach statistical significance.

Overall, our findings imply that nonadherence to evidence-based evaluation and management of premenopausal AUB is widespread and contributes to avoidable cases and delayed diagnosis of endometrial malignancy. Our findings reveal specific missed opportunities for endometrial cancer prevention, particularly in the low rates of progestin therapy and timely endometrial sampling by clinicians who ordered pelvic ultrasound for identified AUB. Moreover, our study adds to calls for integrating menstrual health into preventative care (Matteson & Zaluski, 2019), as better identification of abnormal menses should improve AUB management and decrease endometrial cancer. Our study should propel evaluations of practice patterns in workup and management of AUB on a larger scale. Of particular research interest would be further investigation into provider knowledge and practices regarding AUB in order to identify targets of education and care improvement. Increased research, recognition and guideline-based care of AUB, particularly in high-risk individuals, is crucial to reduce the burden of endometrial malignancy.

Funding

No funding was received for this research project.

Project Presentation: Findings from this project were presented at the Society for Academic Specialists in General Obstetrics and Gynecology (SASGOG) 10th Annual Meeting, May 5, 2022, San Diego, CA.

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.

References

American College of Obstetricians and Gynecologists, 2013. Management of Abnormal Uterine Bleeding Associated With Ovulatory Dysfunction. Practice Bulletin No. 136. *Obstet Gynecol.* 122, 176–185.

American College of Obstetricians and Gynecologists. Diagnosis of abnormal uterine bleeding in reproductive-aged women: Practice Bulletin No. 12 *Obstet Gynecol.* 2012 (120):197-206. Accessed August 22, 2021. https://www.acog.org/en/clinical/clinical-guidance/practice-bulletin/articles/2012/07/diagnosis-of-abnormal-uterine-bleeding-in-reproductive-aged-women.

Amy, N.K., Aalborg, A., Lyons, P., Keranen, L., 2006. Barriers to routine gynecological cancer screening for White and African-American obese women. Int J Obes. 30 (1), 147–155. https://doi.org/10.1038/sj.ijo.0803105.

Beavis, A.L., Najjar, O., Cheskin, L.J., et al., 2020. Prevalence of endometrial cancer symptoms among overweight and obese women presenting to a multidisciplinary weight management center. Gynecol Oncol Rep. 34, 100643 https://doi.org/10.1016/j.gore.2020.100643.

Brinton, L.A., Berman, M.L., Mortel, R., et al., 1992. Reproductive, menstrual, and medical risk factors for endometrial cancer: Results from a case-control study. Am. J. Obstet. Gynecol. 167 (5), 1317–1325. https://doi.org/10.1016/S0002-9378(11)91709-8.

Clarke, M.A., Long, B.J., Sherman, M.E., et al., 2020. Risk assessment of endometrial cancer and endometrial intraepithelial neoplasia in women with abnormal bleeding and implications for clinical management algorithms. Am. J. Obstet. Gynecol. 223 (4), 549.e1–549.e13. https://doi.org/10.1016/j.ajog.2020.03.032.

Cordasco, K.M., Yuan, A.H., Danz, M.J., et al., 2019. Guideline adherence of veterans health administration primary care for abnormal uterine bleeding. Womens Health Issues 29 (2), 144–152. https://doi.org/10.1016/j.whi.2018.12.004.

Doll, K.M., Khor, S., Odem-Davis, K., et al., 2018. Role of bleeding recognition and evaluation in Black-White disparities in endometrial cancer. Am. J. Obstet. Gynecol. 219 (6), 593.e1–593.e14. https://doi.org/10.1016/j.ajog.2018.09.040.

Dolly, D., Mihai, A., Rimel, B.J., et al., 2016. A delay from diagnosis to treatment is associated with a decreased overall survival for patients with endometrial cancer. Front. Oncol. 6 https://doi.org/10.3389/fonc.2016.00031.

Ely, J.W., Kennedy, C.M., Clark, E.C., Bowdler, N.C., 2006. Abnormal uterine bleeding: A management algorithm. J. Am. Board Fam. Med. 19 (6), 590–602. https://doi.org/10.3122/jabfm.19.6.590.

Franceschi, S., Vecchi, C.L., Gallus, G., et al., 1983. Delayed diagnosis of endometrial cancer in Italy. Cancer 51 (6), 1176–1178. https://doi.org/10.1002/1097-0142(19830315)51:6<1176::AID-CNCR2820510634>3.0.CO;2-O.

Gitsch, G., Hanzal, E., Jensen, D., Hacker, N.F., 1995. Endometrial cancer in premenopausal women 45 years and younger. Obstet. Gynecol. 85 (4), 504–508. https://doi.org/10.1016/0029-7844(95)00001-8.

Henry, C., Ekeroma, A., Filoche, S., 2020. Barriers to seeking consultation for abnormal uterine bleeding: systematic review of qualitative research. BMC Womens Health 20 (1), 123. https://doi.org/10.1186/s12905-020-00986-8.

Kim, M.J., Kim, J.J., Kim, S.M., 2016. Endometrial evaluation with transvaginal ultrasonography for the screening of endometrial hyperplasia or cancer in premenopausal and perimenopausal women. Obstet. Gynecol. Sci. 59 (3), 192. https://doi.org/10.5468/ogs.2016.59.3.192.

Levy-Zauberman, Y., Pourcelot, A.G., Capmas, P., Fernandez, H., 2017. Update on the management of abnormal uterine bleeding. J. Gynecol. Obstet. Hum. Reprod. 46 (8), 613–622. https://doi.org/10.1016/j.jogoh.2017.07.005.

Lortet-Tieulent, J., Ferlay, J., Bray, F., Jemal, A., 2018. International patterns and trends in endometrial cancer incidence, 1978–2013. JNCI J. Natl. Cancer Inst. 110 (4), 354–361. https://doi.org/10.1093/jnci/djx214.

Marnach, M.L., Laughlin-Tommaso, S.K., 2019. Evaluation and management of abnormal uterine bleeding. Mayo Clin. Proc. 94 (2), 326–335. https://doi.org/10.1016/j.mayocp.2018.12.012.

Matteson, K.A., Anderson, B.L., Pinto, S.B., Lopes, V., Schulkin, J., Clark, M.A., 2011. Practice patterns and attitudes about treating abnormal uterine bleeding: a national survey of obstetricians and gynecologists. Am. J. Obstet. Gynecol. 205 (4), 321.e1–321.e8. https://doi.org/10.1016/j.ajog.2011.05.016.

Matteson, K.A., Zaluski, K.M., 2019. Menstrual health as a part of preventive health care. Obstet. Gynecol. Clin. N. Am. 46 (3), 441–453. https://doi.org/10.1016/j.ogc.2019.04.004.

McAlpine, J.N., Temkin, S.M., Mackay, H.J., 2016. Endometrial cancer: Not your grandmother's cancer. Cancer 122 (18), 2787–2798. https://doi.org/10.1002/cncr.30094.

Moyer, D.L., Felix, J.C., 1998. The effects of progesterone and progestins on endometrial proliferation. Contraception 57 (6), 399–403. https://doi.org/10.1016/S0010-7824(98)00047-X.

Munro, M.G., Critchley, H.O.D., Broder, M.S., Fraser, I.S., for the FIGO Working Group on Menstrual Disorders, 2011. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int. J. Gynecol. Obstet. 113 (1), 3–13. https://doi.org/10.1016/j.ijgo.2010.11.011.

National Cancer Institure Surveillance, Epidemiology, and End Results Program. Corpus and Uterus Cancer, Recent Trends in SEER Age-Adjusted Incidence Rates, 2000-2017. seer.cancer.gov/explorer/application.html. Accessed March 20, 202https://seer.cancer.gov/explorer/application.html?site=58&data_type=1&graph_type=2&compareBy=race&chk_race_1=1&hdn_sex=3&age_range=62&stage=101&rate_type=2&advopt_precision=1&advopt_display=2.

Onstad, M.A., Schmandt, R.E., Lu, K.H., 2016. Addressing the role of obesity in endometrial cancer risk, prevention, and treatment. J. Clin. Oncol. 34 (35), 4225–4230. https://doi.org/10.1200/JCO.2016.69.4638.

P8: RACE - Census Bureau Table. Accessed July 27, 2023. https://data.census.gov/table?q=race&tid=DECENNIALDHC2020.P8.

Romano, S.S., Doll, K.M., 2020. The impact of fibroids and histologic subtype on the performance of US clinical guidelines for the diagnosis of endometrial cancer among black women. Ethn. Dis. 30 (4), 543. https://doi.org/10.18865/ed.30.4.543.

StataCorp, 2021. Stata Statistical Software: Release 17. StataCorp LLC, College Station, TX.

von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., 2014. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Int. J. Surg. 12 (12), 1495–1499. https://doi.org/10.1016/j.ijsu.2014.07.013.

Whetstone, S., Burke, W., Sheth, S.S., et al., 2022. Health disparities in uterine cancer. Obstet. Gynecol. 139 (4), 645–659. https://doi.org/10.1097/AOG.0000000000004710.

Wise, M.R., Gill, P., Lensen, S., Thompson, J.M.D., Farquhar, C.M., 2016. Body mass index trumps age in decision for endometrial biopsy: cohort study of symptomatic premenopausal women. Am. J. Obstet. Gynecol. 215 (5), 598.e1–598.e8. https://doi.org/10.1016/j.ajog.2016.06.006.

Wise, M.R., Jordan, V., Lagas, A., et al., 2016. Obesity and endometrial hyperplasia and cancer in premenopausal women: A systematic review. Am. J. Obstet. Gynecol. 214 (6), 689.e1–689.e17. https://doi.org/10.1016/j.ajog.2016.01.175.