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Pathology findings among women with alterations in uterine bleeding patterns in cameroon

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ABSTRACT

Purpose: Endometrial cancer is on the rise in high-income countries but it has not been adequately studied in low-and-middle income countries especially in sub-Saharan Africa (SSA), likely due to scarce pathology facilities. The purpose of this study was to characterize and quantify the prevalence of endometrial hyperplasia or cancer in a cohort of women with abnormal uterine bleeding (AUB) who underwent endometrial biopsy in Cameroon.

Methods: We designed a cross-sectional study using medical records to characterize women who underwent endometrial biopsy in the Cameroon Baptist Convention Health Services (CBCHS) from 2008 to 2019. Pathologic diagnoses were classified as either endometrial hyperplasia, endometrial cancer, or no endometrial hyperplasia/cancer. We reported the overall prevalence of endometrial hyperplasia or cancer. Bivariate analyses compared patient characteristics between women with endometrial cancer, endometrial hyperplasia, and neither.

Results: The average age was 46.2 years and women had an average of 5.1 parity. We found that, 61 [(36.7% of 166 women; 95% CI (27.6–47.0%)] had endometrial hyperplasia or cancer. There were no cases of hyperplasia with atypia and 13 women had endometrial cancer. The remainder were comprised of benign or infectious pathologic findings. In bivariate analysis, mean ages were statistically different among the three groups (hyperplasia, cancer, and no hyperplasia/cancer), $p < 0.001$, and women with cancer had the highest age. Parity was statistically significantly different among the three groups ($p = 0.002$) and women with endometrial cancer had higher parity.

Conclusion: We found that just over 1 in 3 women with AUB who underwent endometrial biopsy at a health system in SSA were found to have pathologic findings of endometrial hyperplasia or cancer, with no cases of hyperplasia with atypia. Women with endometrial cancer had higher mean age and parity.

1. Background

Alterations in uterine bleeding pattern such as abnormal uterine bleeding (AUB) and amenorrhea are among the most common gynecological problems worldwide (Soleymani et al., 2014; Al Nemer et al., 2019). AUB is a broad term used to denote all forms of uterine bleeding disorders irrespective of frequency, duration, and quantity. This includes menorrhagia, metrorrhagia, menometrorrhagia, polymenorrhoea, oligomenorrhoea, and dysfunctional uterine bleeding (DUB). It also includes any uterine bleeding that occurs one year or more after complete cessation of menses in postmenopausal women (Merrill et al., 2005; Sarvi et al., 2016).

Establishing the cause of alterations in uterine bleeding pattern requires a series of investigations including endometrial biopsy for

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histopathology. The histopathologic findings can reveal endometrial pathologies ranging from benign to malignant conditions, including endometrial cancer, endometrial hyperplasia (cancer precursor when atypia is identified), endometrial polyp, atrophic endometrium, endometrial tuberculosis (TB), and chronic endometritis. Even though ultrasound can aid in the diagnosis of AUB, histopathology remains the gold standard for diagnosing endometrial pathologies (Dueholm and Hjorth, 2017).

There are several pathologic findings that are important to rule out. The most important pathologic finding of endometrial histopathology to rule out is endometrial cancer, which is a common cancer among women and the most frequently diagnosed gynecological cancer in the United States (Jemal et al., 2005; Brüggmann et al., 2020). Even though the incidence and mortality rates of many cancers have been found to be stable or decreasing, endometrial cancer has risen in the recent decades (Boruta et al., 2009; Pessoaa et al., 2013). Endometrial cancer manifests with AUB in 90% of cases in pre- and post-menopausal women (Bakkum-Gamez et al., 2008) and 10–15% of women who suffer from post-menopausal bleeding have endometrial cancer (Elfayomy et al., 2012). The second most important pathologic finding to rule out is endometrial hyperplasia, particularly with atypia, since it is a major precursor to endometrial cancer (Bayer and DeCherney, 1993). Endometrial polyp, a benign focal hyperplastic growth of endometrial stroma and glands is one of the most common causes of AUB. Though they are not histologically malignant, its risk of malignant transformation is about 2–3% (Vázquez Mézquita, et al., 2019). Given an up to 20% risk of malignant components buried in their stalk, polypectomy is recommended to rule out malignancy (Sarvi et al., 2016). In addition, there are other endometrial conditions that are not associated with AUB but rather with chronic amenorrhea, such as endometrial TB and endometrial atrophy, that can be treated if diagnosed to improve patients' quality of life.

The prevalence of endometrial hyperplasia and endometrial cancer has not been adequately studied in Sub-Saharan Africa (SSA). Our primary aim was to describe the frequency and prevalence of endometrial hyperplasia or cancer in a cohort of women with AUB who underwent endometrial biopsy in Cameroon and our secondary aim was to describe potential risk factors for endometrial hyperplasia or cancer in this cohort.

2. Materials and methods

The study constitutes human subject research and received Institutional Review Board approval from the Cameroon Baptist Convention Health Services (CBCHS) and the University of Alabama at Birmingham (UAB).

2.1. Setting and procedures

We conducted a cross-sectional study involving patients who underwent endometrial biopsy by pipelle in the CBCHS Women's Health Program (WHP) from 2008 to 2019. The CBCHS is a large faith-based healthcare organization that has a network of 85 health facilities located in nine of the 10 regions of Cameroon (http://www.cbchealthservices.org). The CBCHS implemented the WHP in 2007 primarily to fight against cancer of the cervix. The WHP has become the largest cervical cancer prevention program in Cameroon and it operates in 12 of the CBCHS facilities (DeGregorio et al., 2016). In addition to cervical cancer prevention, WHP also provides services to women with other gynecological problems.

At WHP, women with abnormal uterine bleeding (AUB) without definitive diagnoses on ultrasonography are usually offered endometrial biopsy using the pipelle aspiration system. Women with chronic secondary amenorrhea whose underlying cause could not be identified by hormonal assays and ultrasonography are also offered endometrial biopsy. The pipelle, a clear, flexible, polypropylene sheath, is a disposable, sterile, single-use suction curette used for sampling the uterine lining. The device is marked with colored, graduated markings from 4 cm to 10 cm to help determine the length of the uterine cavity. After ensuring that the woman is not pregnant, a bi-valve vaginal speculum is inserted into her vagina to access the cervix. The device is then introduced into the uterus via the cervical canal with or without the aid of a tenaculum. The piston of the pipelle is then pulled backward to create a negative pressure or vacuum within the lumen of the sheath. The provider then moves the device in a backward and forward movements between the fundus and internal os while providing simultaneous 360° rotatory movements (by rolling or twirling between the fingers) within the uterine canal in order to scrape against the endometrial wall. This enables endometrial tissues to be aspirated through the pipelle opening into the lumen of the sheath. The provider examines the sheath to ensure that sufficient endometrial tissue is clearly visible within the sheath. The specimen is placed in 10% formalin solution, labeled, and shipped to a histopathology laboratory.

2.2. Histopathology

The specimens were analyzed at Yaoundé Gyneco-Obstetrics and Pediatric Hospital, Buea Regional Hospital, and Mbingo Baptist Hospital. Due to the fact that pathologists in Cameroon are not yet using the new classification of endometrial hyperplasia of the International Endometrial Collaborative Group, we used the WHO classification in this study. The different pathologic findings include endometrial cancer, endometrial hyperplasia, endometrial polyp, endometrial TB, endometritis, and endometrial atrophy. To facilitate analysis, the pathologic diagnoses were classified into three categories: (1) endometrial cancer (2) endometrial hyperplasia and (3) no endometrial hyperplasia or cancer (endometrial polyp, endometrial TB, and others which included endometritis, endometrial atrophy and normal endometrium).

2.3. Data management and statistical analysis

Information that was not available in the WHP database was abstracted from the paper registries at the WHP clinics. All study patients were assigned a unique study ID and de-identified data were entered into a stand-alone Redcap database (Vanderbilt University, TN). First, we estimated mean and percentage for the entire cohort. Means and standard deviations were estimated for continuous variables including age, gravida, parity, and years of education received. Counts and proportions were estimated for categorical variables including marital status, occupation, religion, residence, family planning method, HIV status, and menopause status. The 95% confidence intervals were included for primary and secondary outcomes. Bivariate analyses were performed to compare the mentioned characteristics between women with endometrial cancer, endometrial hyperplasia, and without endometrial hyperplasia/cancer. Analysis of variance (ANOVA) and chi-square tests were used to compare continuous and categorical variables, respectively. Statistical significance was evaluated at a 0.05 alpha level and all statistical analyses were performed by study statisticians at the Center for Women's Reproductive Health at UAB. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

Of the 166 women in the cohort, 15 (9.0%) did not have endometrial biopsy results due to insufficient tissue sample.

Sociodemographic and clinical characteristics of the entire study cohort are described in Table 1. The average age of women in the study was 46.2 years and the average gravidity was 5.1 gestations. A total of 66.1% were married/co-habiting, 17.8% were widowed, 10.5% were separated, and 3.7% were single or had never been married. For occupation, 80.2% of the study populations were unemployed. The average educational level was eight years of schooling. The majority of the women, 36.6% were of the Catholic religion. For family planning, most

Table 1
Sociodemographic and clinical demographic characteristics of the study cohort (N = 166).

	Entire cohort N = 166		
Variable	n	Mean (SD) or n (%)	95% CI
Age	163	46.2 (12.9)	44.2–48.2
Gravida	162	5.1 (3.1)	4.6–5.6
Parity	112	4.1 (3.0)	3.6–4.7
Marital status (%)	162		
Divorced	–	3 (1.9)	0.5%–7.0%
Married or domestic partnership	–	107 (66.1)	56.0%–75.0%
Single, never married	–	6 (3.7)	1.4%–9.7%
Separated	–	17 (10.5)	5.8%–18.3%
Widowed	–	29 (17.8)	11.5%–26.9%
Occupation (%)	162		
Employed	–	32 (19.8)	13.9%–26.7%
Unemployed	–	130 (80.2)	73.7%–86.1%
Education (years)	155	8 (5.0)	7.2%–8.8%
Religion (%)	112		
Baptist	–	19 (17.0)	9.5%–28.4%
Catholic	–	41 (36.6)	25.5%–49.3%
Jehovah's Witness	–	2 (1.8)	0.3%–9.1%
Muslim	–	6 (5.4)	1.9%–14.2%
Other	–	12 (10.7)	5.1%–21.1%
Pentecostal	–	10 (8.9)	4.0%–18.9%
Presbyterian	–	22 (19.6)	11.5%–31.4%
Residence (%)	160		
Live in city	–	67 (41.9)	33.5%–50.7%
Live out of city	–	93 (58.1)	49.3%–66.5%
Family planning method (%)	122		
IUD	–	2 (1.6)	0.3%–8.4%
Implant	–	1 (0.8)	0.1%–7.1%
Injection	–	2 (1.6)	0.3%–8.4%
Pills	–	1 (0.8)	0.1%–7.1%
Condoms	–	9 (7.3)	3.1%–16.4%
Natural methods	–	7 (5.7)	2.2%–14.3%
None	–	100 (82.0)	70.9%–89.4%
HIV status (%)	132		
Negative	–	121 (91.7)	84.6%–95.6%
Positive	–	11 (8.3)	4.4%–15.4%
Menopause status (%)	161		
Postmenopausal	–	47 (29.2)	21.9%–37.8%
premenopausal	–	114 (70.8)	62.2%–78.1%

of the women, 82% where non-users of any type of contraceptive method. A total of 8.3% of the study population were HIV positive and 29.2% were postmenopausal.

A total of 61 [(36.7% of 166 women; 95% CI (27.6–47.0%)] had endometrial hyperplasia or cancer. Overall, 13 [7.8% 95% CI (3.8–15.4%)] women had endometrial cancers, 48 [28.9% 95% CI (20.5–39.1%)] had endometrial hyperplasia, 11 [6.6% 95% CI (3.0–13.8%)] had endometrial polyps, 1 [0.6% 95% CI (0.06–5.3%)] had endometrial TB, 32 [19.4% 95% CI (12.4–28.7%)] had other benign endometrial conditions such as endometritis and endometrial atrophy, and 46 [27.7% 95% CI (19.4–37.8%)] had normal endometrium (Table 2). There were no cases of endometrial hyperplasia with atypia. Patient characteristics between the three comparison groups are shown in Table 3. Mean age was statistically different among the three groups ($p < 0.001$) with mean age of 59.7 years in the women with cancer. Parity was also different among the three groups ($p = 0.002$). Women with cancer had the highest average parity of 6.7 pregnancies. Marital status was statistically significantly different among the three groups ($p = 0.01$). As an exploratory analysis, we repeated the comparisons among postmenopausal women only. In this sub-analysis, mean education was statistically different among the three groups ($p = 0.016$).

Table 2
Endometrial Biopsy Results (N = 166)*

	Count	Percent (95% CI)
Cancer	13	7.8 (3.8%–15.4%)
Endometrial tuberculosis	1	0.6 (0.06%–5.3%)
Hyperplasia	48	28.9 (20.5%–39.1%)
Normal	46	27.7 (19.4%–37.8%)
Polyp	11	6.6 (3.0%–13.8%)
Other	32	19.4 (12.4%–28.7%)

* There were 15 women with insufficient endometrial biopsy results.

4. Discussion

In our study, the frequency of endometrial cancer among women with AUB was 7.8%. The main symptom of endometrial cancer is DUB especially in postmenopausal women. DUB in premenopausal women is quite common and usually associated with gynecological conditions such as uterine fibroids and endometrial polyps (Clarke et al., 2018). Though endometrial cancer is on the rise worldwide; it has not been adequately reported in SSA. The incidence, morbidity, and mortality of endometrial cancer rates have increased in the past 10 years at a time when other cancers are on the decline (Boruta et al., 2009; Pessoaa et al., 2013). From 2008 to 2012 alone, the incidence of endometrial cancer increased by 21% (Gaber et al., 2016) and the rates have continued to rise annually with a disproportional burden in high income countries (Brüggmann et al., 2020). This trend could be affected by the limited information on endometrial cancer in low-and-middle income countries (LMICs). There is also a projection that the rates will rise sharply in the next 10 years (Colombo et al., 2016). While there were 28.9% of women who had endometrial hyperplasia, it is interesting that no cases of endometrial hyperplasia with atypia, which is a premalignant condition, were identified in our cohort.

We found that higher age and higher parity were associated with endometrial cancer diagnosis. The mean age in our study population was higher in women with endometrial cancer, which is consistent with the literature that demonstrates endometrial cancer is more prevalent in older women(Bakkum-Gamez et al., 2008; Elfayomy et al., 2012). However, the analysis of menopausal status had no significant association with endometrial cancer. A recent *meta*-analysis on menopausal status and endometrial cancer has shown that it is not the menopausal status which matters per se but the age in which the woman entered menopause; for instance, women who entered menopause at 46.5 years or older had higher risk of developing endometrial cancer (Wu et al., 2019). In our cohort, women with endometrial cancer had the highest parity. The literature has rather found an inverse relationship between parity and endometrial cancer. In one study, nulliparous women had a 24% increased risk of developing endometrial cancer compared to uniparous women (95% CI:0.89, 1.74) (Karageorgi et al., 2010). It is thought that with pregnancy, the high levels of progesterone that oppose estrogen levels have a contributing role in making parous women less likely to develop endometrial cancer compared to nulliparous women (Chen et al., 2015). A large *meta*-analysis including 70 studies and a sample size of 69,681 women found that high parity is associated with reduced risk of endometrial cancer (Wu et al., 2015). In our cohort, HIV status was not associated with endometrial hyperplasia or endometrial cancer, which was unexpected as we hypothesized that HIV positive status would be associated with increased risk of cancer. The other collected variables, including occupation, religion, residence, gravidity, and family planning were not significantly associated with endometrial hyperplasia or cancer on endometrial biopsy in our cohort.

Our study had several limitations. First, our sample has selection bias because the women who had endometrial biopsy were those patients for whom the provider decided to perform an endometrial biopsy. There were probably other women with AUB who did not present for care or whose providers elected not to perform endometrial biopsy and we do not have information about these patients. In addition, there were 15 patients in our cohort who underwent biopsy but did not have a recorded pathologic endometrial biopsy result due to insufficient tissue.

Table 3
Patients with and without endometrial hyperplasia or cancer (N = 151).

	No endometrial hyperplasia/cancer N = 90			Hyperplasia N = 48			Cancer N = 13			p-value
Variable	n	Mean (SD) or n (%)	95% CI	n	Mean (SD) or n (%)	95% CI	n	Mean (SD) or n (%)	95% CI	–
Age	88	46.0 (11.2)	43.6–48.4	47	41.6 (11.4)	38.2–45.1	13	59.7 (17.5)	53.2–66.2	<0.0001
Gravida	87	4.9 (3.0)	4.3–5.5	47	5.1 (3.3)	4.2–6.0	13	6.9 (3.1)	5.2–8.6	0.089
Parity	67	3.9 (2.7)	3.3–4.6	21	3.3 (3.1)	2.1–4.5	13	6.7 (2.9)	5.1–8.2	0.002
Marital status (%)	86			48			13			0.010
Divorced	–	1 (1.2)	0.1%-9.2%		1 (2.1)	0–15.6%		0	0–33.8%	
Married or domestic partnership	–	54 (62.8)	48.9%-74.8%		37 (77.1)	58.8%-88.8%		5 (38.5)	13.8%-70.9%	
Single, never married	–	4 (4.7)	1.4%-14.4%		4 (8.3)	2.5%-24.3%		0	0–33.8%	
Separated	–	13 (15.0)	7.7%-27.5%		2 (4.2)	0–0-18.6%		0	0–33.8%	
Widowed	–	14 (16.3)	8.5%-28.9%		4 (8.3)	0–0-18.6%		8 (61.5)	29.1%-86.2%	
Occupation (%)	88			47			13			0.497
Employed		19 (21.6)	13.5%-31.7%		9 (19.1)	9.5%-34.7%		1 (7.7)	1.1%-37.8%	
Unemployed		69 (78.4)	68.4%-86.5%		38 (80.9)	65.3%-90.5%		12 (92.3)	62.2%-98.9%	
Education (years)	82	8.5 (4.7)	7.4%-9.5%		9.0 (4.7)	7.6%-10.4%		2.7 (5.8)	0–5.6	0.0.030
Religion (%)	70				20			13		0.644
Baptist	–	14 (20.0)	10.2%-35.4%		1 (5.0)	0.6%–33.4%		4 (30.8)	9.2%-66.1%	
Catholic	–	28 (40.0)	25.9%-56.0%		7 (35.0)	14.1%-63.9%		3 (23.1)	5.7%-59.7%	
Jehovah's Witness	–	1 (1.4)	0.2%-11.8%		1 (5.0)	0.6%–33.4%		0	0–35.8%	
Muslim	–	4 (5.7)	1.6%-13.1%		1 (5.0)	0.6%–33.4%		0	0–35.8%	
Other	–	6 (8.6)	3.0%-21.9%		3 (15.0)	3.7%-44.9%		1 (7.7)	0.8%-44.8%	
Pentecostal	–	6 (8.6)	3.0%-21.9%		2 (10.0)	1.9%-39.4%		1 (7.7)	0.8%-44.8%	
Presbyterian	–	11 (15.7)	7.3%-30.5%		5 (25.0)	8.4%-54.9%		4 (30.7)	9.2%-66.1%	
Residence (%)	87				45			13		0.938
Live in city	–	37 (42.5)	31.4%-54.5%		18 (40.0)	25.4%-56.6%		5 (38.5)	15.8%-67.6%	
Live out of city	–	50 (57.5)	45.5%-68.6%		27 (60.0)	43.4%-74.6%		8 (61.5)	32.5%-84.2%	
Family planning method (%)	61				44			6		0.241
IUD	–	1 (1.6)	0.2%-13.4%		1 (2.3)	0.2%-17.8%		0	0–54.7%	
Implant	–	1 (1.6)	0.2%-13.4%		0	0–14.1%		0	0–54.7%	
Injection	–	1 (1.6)	0.2%-13.4%		1 (2.3)	0.2%-17.8%		0	0–54.7%	
Pills	–	0 (0)	0%-10.6%		1 (2.3)	0.2%-17.8%		0	0–54.7%	
Condoms	–	3 (4.9)	1.2%-18.2%		3 (6.8)	1.7%-24.2%		2 (33.3)	6.4%-78.5%	
Natural methods	–	3 (4.9)	1.2%-18.2%		1 (2.3)	0.2%-17.8%		1 (16.7)	1.9%-67.9%	
None	–	52 (85.4)	69.4%-93.6%		37 (84.1)	64.7%-93.8%		3 (50.0)	13.0%-87.0%	
HIV status (%)	72			42			11			0.883
Negative	–	67 (93.1)	83.2%-97.3%		39 (92.9)	78.7%-97.9%		10 (90.9)	57.5%-98.7%	
Positive	–	5 (6.9)	2.7%-16.8%		3 (7.1)	2.1%-21.3%		1 (9.1)	13.3%-42.5%	
Menopause status (%)	88			47			13			0.045
Postmenopausal	–	27 (30.7)	21.0%-42.5%		9 (19.1)	9.5%-34.7%		7 (53.9)	26.4%-79.1%	
Premenopausal	–	61 (69.3)	57.5%-79.0%		38 (80.9)	65.3%-90.5%		6 (46.1)	20.9%-73.6%	

Second, the study used retrospective data which was collected for clinical purposes and not for research, which resulted in several variables of interest that could not be evaluated in our analysis. Exposure to unopposed estrogen is among the major risk factors for endometrial hyperplasia or cancer because of incessant endometrial proliferation (Pennant et al., 2017). Therefore, factors which influence estrogen exposure such as chronic anovulation, polycystic ovarian disease, obesity, nulliparity, and diabetes mellitus type 2 are risk factors for endometrial hyperplasia or cancer (Pennant et al., 2017). However, in our study, we could not measure several of these variables because our clinical database did not capture them. Third, as a cross-sectional study, incidence could not be calculated. Fourth, ultrasound or imaging information was not available. Fifth, there was no information on clinical outcomes after pathologic diagnosis was obtained. Sixth, the HIV status was self-reported.

We found that 7.8% of women who underwent endometrial biopsy at a single health system for AUB in SSA were found to have pathologic findings of endometrial cancer and 28.9% were found to have endometrial hyperplasia, although there were no cases with atypia. In this study, women with endometrial cancer had higher parity as well as mean age. Endometrial cancer is on the rise, but little is known about women who experience AUB and their risk for endometrial hyperplasia or cancer in SSA and other LMICs. Future studies are needed to prospectively incorporate body mass index, fasting blood sugar, and HIV status which are factors that may impact risk of endometrial cancer but are not always systematically collected in these settings. Established risk factors need to be prospectively collected in the health record to better understand how to mitigate risk factors that may be the same or different in patients in SSA where little is known about endometrial hyperplasia or malignancy.

Informed consent

The IRB waived requirements for informed consent because the study was based on review of secondary data.

CRediT authorship contribution statement

Simon M. Manga: Conceptualization, Methodology, Writing - original draft. **Yuanfan Ye:** Formal analysis, Writing - review & editing. **Jeff M. Szychowski:** Formal analysis, Writing - review & editing. **Kathleen L. Nulah:** Data curation. **Calvin Ngalla:** Conceptualization. **Kaitlyn Kincaid:** Data curation. **Teresa K.L. Boitano:** Data curation. **Alan T. Tita:** Writing - review & editing, Funding acquisition. **Isabel Scarinci:** Writing - review & editing. **Warner K. Huh:** Writing - review & editing. **Zacharie Sando:** Writing - review & editing. **Margaret I. Liang:** Methodology, Writing - original draft, Writing - review & editing.

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.

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