The uterus is an end organ: a preliminary study of the association between abnormal uterine bleeding and hyperinsulinemia

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Abstract

Objective: This preliminary study aimed to conduct initial, exploratory analyses of the association between hyperinsulinemia and biomarkers of metabolic syndrome in reproductive-aged women with abnormal uterine bleeding (AUB), with the goal of motivating future hypothesis-driven research.

Methods: A cross-sectional study was conducted from June 2019 to August 2023 at a single institution's outpatient gynecology clinics. A total of 205 premenopausal women aged 18-54 were enrolled, including 116 with AUB and 89 with normal menstrual cycles. Participants underwent fasting insulin assessment with additional markers of metabolic syndrome, including body mass index (BMI), high-density lipoprotein, and waist-to-hip ratio. Logistic regression was used to examine the association between hyperinsulinemia and AUB, adjusting for confounders such as age, race, and low-density lipoprotein. Model selection prioritized low Akaike Information Criterion and model parsimony.

Results: Hyperinsulinemia was a significant predictor of AUB (OR = 3.009, 95% CI: 1.372-6.832; $P = 0.0085$). Including BMI in the model diminished the significance of hyperinsulinemia, suggesting overlapping or mediating pathways. The final model which included age, race, low-density lipoprotein , and waist-to-hip ratio achieved 73% concordance and improved model fit.

Conclusion: This study highlights an association between hyperinsulinemia and AUB, with BMI playing a unique role in this relationship. These exploratory findings underscore the need for larger, longitudinal studies to clarify causal mechanisms and evaluate the potential of addressing hyperinsulinemia and BMI as part of AUB prevention and treatment strategies. Limitations, including small sample size and cross-sectional design, should be considered when interpreting these results.

Key Words: abnormal uterine bleeding, endometrial polyps, hyperinsulinemia, insulin resistance, metabolic syndrome, uterine leiomyoma.

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Abnormal uterine bleeding (AUB) is the most common reason for benign gynecologic consultation in the United States utilizing more than $34 billion dollars in health costs per year.[1,2] Approximately 30% of women of reproductive age experience AUB, which may result in decreased quality of life, societal economic burden due to work absenteeism, and higher utilization of health care.[3] Trends in the prevalence of AUB appear to be increasing.[3] While the health care system largely focuses on diagnosis and treatment of AUB, focus on the prevention of the many common causes is lacking. There are several studies that associate cardiovascular disease risk factors such as chronic hypertension, diabetes mellitus, and obesity.[4-7]

Review of the medical literature supports the similar pathophysiologic development of both structural and nonstructural causes of AUB such as leiomyoma (AUB-L), endometrial polyps (AUB-P), and ovulatory/endometrial dysfunction (AUB-O/E) with end organ cardiovascular disease.[8-12] First, Moss and Benditt[8] reported progenitor myocytes found in human atherosclerotic plaques and from arterial media behave similarly to leiomyoma and myometrium with respect to growth behavior in cell culture. Mesquita et al[13] showed the involvement of reactive oxidative species in the development of uterine leiomyoma, similar to that observed in atherosclerotic plaques. Several studies have correlated the similarities of the development of atherosclerotic disease with leiomyomata, even noting carotid intima-media thickness as a potential clinical indicator for uterine fibroids.[10,11,14,15]

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Further, oxidative stress markers and angiogenic vascular endothelial growth factors were demonstrated in the development of endometrial polyps.[16,17]

The correlations between cardiovascular disease development and several common forms of AUB are well documented in the literature. Yet, despite this evidence, there is little attention toward reducing cardiovascular disease risk factors in the treatment of AUB outside of polycystic ovarian syndrome. The association of common causes of AUB such as leiomyoma or endometrial polyps with hypertension, diabetes, and obesity is well documented.[4,5,7,18] Insulin resistance and dyslipidemia are often precursors to these cardiometabolic diseases. Given the rise of chronic disease and obesity in the past several decades and a similar increase in AUB, it may be valuable to assess whether hyperinsulinemia leading to insulin resistance and metabolic syndrome may be associated with benign gynecologic pathology.

End organ damage refers to the solid organ dysfunction stemming from endothelial inflammation seen in cardiovascular disease and diabetes. Typically, affected organs include the heart, kidneys, eyes, and lungs. However, using the same principles of end-organ damage, the uterus may also be susceptible to the effects of endothelial inflammation, leading to potential dysfunction seen in AUB. As such, the principles of cardiovascular disease prevention could apply to the prevention and treatment of abnormal uterine bleeding. Salcedo et al[19] in 2022 reported on the increased prevalence of insulin resistance among a prospective cross-sectional study of women with AUB. Therefore, measurements of fasting insulin levels could not only reveal impending cardiometabolic disease risk but could potentially predict abnormal uterine bleeding. If the uterus is a recipient of end-organ damage, an elevated fasting insulin level among women with AUB could indicate the current microvascular inflammatory effect commonly seen in hyperinsulinemia. We hypothesize elevated fasting insulin is associated with both structural and hormonal causes of AUB. Thus, the primary aim for this cross-sectional study is to evaluate the association of elevated fasting insulin among reproductive-age women with benign, non-iatrogenic AUB. In exploratory aims, we will also consider other biomarkers for metabolic syndrome. Because cross-sectional studies are difficult to interpret, this study is designed as a preliminary examination of the study hypothesis, with the goal of motivating future, rigorous, prospective studies recognizing the cross-sectional design does not allow for establishing causality or the sequence of events.

METHODS

Study population

We performed a convenience sampling of women with AUB and those with normal menstruation over a 4-year period. At the time of the enrollment we performed a cross-sectional evaluation of fasting insulin at a single institution, outpatient gynecology clinic system between June 2019 and August 2023. Other markers of metabolic syndrome were evaluated, including triglycerides, high-density lipoprotein (HDL), and waist-hip ratio, in an exploratory manner (Table 1). The study was expanded after a pilot cross-sectional study revealed the prevalence of hyperinsulinemia among women with AUB was 66%.[19]

TABLE 1. Patient characteristics among women with AUB and normal menses (No AUB), along with individual variable counts

					Univariate tests	CMH test	
Variable	**AUB (N = 116) Median (IQR)**	**Count (percent complete)**	**No AUB (N = 89) Median (IQR)**	**Count (percent complete)**	**Wilcoxson RS/χ^2 *P***	***P***	**VIF score**
Age	39.0 (30.0-43.0)	116 (100)	33.0 (28.0-38.0)	89 (100)	*0.0034*	*0.0003*	1.3
Triglycerides (mg/dL)	82.0 (67.0-123.0)	87 (75)	73.5 (56.0-116.0)	66 (74.2)	0.1263	0.0532	2.0
LDL (mg/dL)	95.0 (71.0-110.0)	87 (75)	95.0 (80.0–117.0)	66 (74.2)	0.4261	*0.0106*	7.9
HDL (mg/dL)	54.0 (44.0–63.0)	87 (75)	60.0 (50.0–70.0)	66 (74.2)	*0.0098*	*0.0224*	4.2
Cholesterol (mg/dL)	169.0 (143.0 -186.0)	87 (75)	172.5 (156.0–196.0)	66 (74.2)	0.1062	0.5102	*9.4*
BMI	29.9 (25.2–39.1)	115 (99.1)	24.8 (21.5–29.5)	83 (93.3)	*< 0.0001*	0.3173	1.8
Waist/hip ratio	0.86 (0.81-0.90)	100 (86.2)	0.85 (0.80-0.89)	87 (75.3)	0.4211	0.0833	1.3
	N (%)		N (%)		*P*		
Hypertension	30 (25.9)	116 (100)	11 (12.4)	86 (96.6)	*0.0198*	*0.0036*	1.4
Ever smoke	21 (18.1)	116 (100)	6 (6.7)	86 (96.9)	*0.0047*	*0.0020*	1.3
Migraines	36 (31.0)	116 (100)	8 (9.0)	86 (96.6)	*0.0001*	*0.0113*	1.2
Polyps or fibroids	53 (45.7)	103 (88.8)	8 (9.0)	86 (96.6)	*< 0.0001*	*0.0067*	1.35
Hyperinsulinemia	51 (44.0)	77 (66.4)	27 (30.34)	67 (75.3)	*0.0017*	—	1.6
Ethnicity		116 (100)		85 (95.5)	0.2550	*0.0047*	
Black	20 (17.2)		9 (10.1)				2.5
Hispanic	49 (42.2)		35 (39.3)				2.6
White	36 (31.0)		26 (29.2)				2.9
Other	11 (9.4)		15 (16.9)				.

Statistically significant results are highlighted in italics

Univariate results were derived using the Wilcoxon Rank Sum test for continuous variables and the χ^2 test for categorical variables. The CMH test refers to the Cochran-Mantel-Haenszel test, which was used to assess confounding, while VIF stands for Variance Inflation Factor, a measure used to test for multicollinearity.

AUB, abnormal uterine bleeding; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

The study was continued to investigate the association of hyperinsulinemia among women with AUB compared with those who reported normal menstruation. Participants were premenopausal females between the ages of 18 and 54 years old who presented with a complaint of AUB and were compared with women who reported regular menstrual cycles at the time of their visit. AUB status, blood samples, and measurements were collected at the time of enrollment into the study. Women with a history of gynecologic cancer, prior hysterectomy, prior endometrial ablation, prior tamoxifen use, diabetes mellitus type 1, chronic steroid use, hormonal contraceptive use, or pregnancy were excluded. There was a total of 89 women with normal menses and 116 with AUB.

The participants gave voluntary, informed, written consent before participating in the study. This research study was approved by the Loma Linda University Institutional Review Board (IRB #5180222) and it complied with all relevant national regulations, institutional policies, and the principles of the Declaration of Helsinki as they relate to human participants. All participant identifiers were replaced with identification codes and the data was handled only by the researchers participating in this study.

Measured variables

Participant demographics, clinical characteristics, and variables (Table 1) were taken from the electronic medical records and direct data collection from the participants by the study investigators at the time of enrollment. Each participant had height, weight, and waist-hip ratio (WHR) measured. The 5 factors for diagnosing metabolic syndrome were assessed.[20]

Fasting blood samples were then obtained to assess each participant's fasting insulin level (FI), complete metabolic panel, and lipid profile. Hyperinsulinemia was defined as an FI value of 10 μU/mL or greater based on prior research.[20,21] All variables studied, along with information on missing data are provided in Table 1. Potential confounders of obesity, as well as markers of metabolic syndrome, were intentionally retained within our analysis of hyperinsulinemia, due to the potential confounding effects.[22] All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC).

Statistical analysis

To test our hypothesis hyperinsulinemia is associated with AUB, independent of other biomarkers of metabolic syndrome, we performed a logistic regression analysis with AUB as the outcome variable and hyperinsulinemia as the main effect. Additional analyses evaluated how hyperinsulinemia affected AUB in the presence of covariables such as BMI, waist-to-hip ratio, and lifestyle factors while adjusting for potential confounders.

For the primary aim, we conducted 2 key analyses. First, we compared fasting insulin levels between women with normal menstruation and those with abnormal uterine bleeding in a series of univariate analyses (Table 1). Continuous variables were tested for normality and are presented as medians and interquartile ranges (IQR), reflecting their non-normal distributions. In exploratory analyses, the Wilcoxon rank-sum test was used to examine other components of metabolic syndrome (eg, BMI, waist-to-hip ratio, dyslipidemia, triglycerides) and to compare women with and without AUB. Categorical variables, including demographic characteristics and clinical conditions, are reported as counts and percentages and were compared using χ^2 (Table 1).

We evaluated the power of our model with respect to hyperinsulinemia, the primary variable of interest. Given an estimated prevalence of hyperinsulinemia of 33% in the general population and 66% among women with AUB (from our pilot study), we aimed to detect this significant difference with 80% power and a type 1 error rate of 5% [23,24]. The calculations indicated a minimum of 35 participants per group under the assumption of no confounders. Adjustments for 3-5 potential confounders were estimated to increase sample size requirements by 50%-100%, suggesting an adjusted range of 52-70 participants per group to maintain statistical power. The sample sizes in the AUB and non-AUB groups were approximately equal, with a sample ratio of 1:1.3, well within the acceptable threshold of 1:2.

Prior to conducting the logistic regression, we tested all variables to ensure model assumptions were met and to verify the appropriate inclusion of potential confounders. Both standard variables (eg, age, smoking status, and race) and nonstandard variables (eg, HDL, LDL) were evaluated for their role as confounders of both AUB and hyperinsulinemia. The Cochran-Mantel-Haenszel test, specifically the General Association statistic, was used to test for confounding (Table 1). To assess potential multicollinearity, we calculated the variance inflation factor (VIF) for all independent variables. A VIF value above 5 indicates high multicollinearity and suggests the variable may need to be excluded from the analysis. In addition, the Pearson correlation coefficient was used to examine correlations between variables, and any variable with a correlation coefficient of 0.8 or greater with another variable was excluded from the analysis. Pearson residuals were examined to identify observations with large deviations from the model's predictions. Observations with residuals > 2 were reviewed but were not excluded from the analysis due to their small number and limited impact on model fit.

For model selection, we employed forward variable inclusion with AUB as the dependent variable and hyperinsulinemia as the main effect. Models were evaluated based on the Akaike Information Criterion (AIC), the total number of variables, and percent concordance to identify the best-fitting model. The model with the best balance of a low AIC, fewest variables, and highest percent concordance was selected as the final model. Variables identified as confounders in the Cochran-Mantel-Haenszel test were investigated to ensure that all core confounders remained in the analysis.

To account for the smaller sample size relative to the number of covariates, we applied Firth's correction for

penalized maximum likelihood estimates, providing more reliable coefficients and standard errors in the context of small sample sizes. In addition, the Fisher scoring likelihood was also implemented to enhance model stability and ensure better convergence for small sample sizes. In the final model, "White" was the reference category for race, and "not occurring" was the reference for binary categorical variables. Results are presented as odds ratios with 95% CIs to identify significant predictors of AUB.

As our regression revealed a strong association between BMI and hyperinsulinemia that influenced the results of the model, we further explored the relationship between these variables. This analysis assessed the strength and direction of their association and evaluated how this relationship might influence their roles in the primary model for abnormal uterine bleeding. To isolate the independent contribution of hyperinsulinemia to AUB after accounting for BMI, hyperinsulinemia was residualized against BMI. BMI was investigated as a potential confounder, mediator, or independent predictor based on its established biological relationship with hyperinsulinemia and metabolic health. We continued to examine the relationship between BMI and hyperinsulinemia, by testing an interaction term in the model (BMI×IR). However, the interaction did not significantly improve model fit or predictive ability, suggesting that BMI and hyperinsulinemia contribute independently to the risk of AUB.

Given the exploratory nature of this study, it was also essential to analyze hyperinsulinemia without BMI to isolate its direct association with AUB. This approach enables a clearer understanding of whether hyperinsulinemia independently contributes to the risk of AUB or whether its effects are largely mediated by BMI, a closely related metabolic factor. By examining these variables both jointly and independently, the analysis provides a more nuanced understanding of potential pathways and sets the stage for more in-depth, future hypothesis-driven research.

RESULTS

A total of 205 women were included in the study, with 116 participants diagnosed with abnormal uterine bleeding (AUB) and 89 participants with normal menstruation. Table 1 provides an overview of participant characteristics for women with AUB and those with normal menses. The table includes our exploratory analysis results, median values, and interquartile ranges (IQR) for continuous variables such as age, triglycerides, LDL, HDL, cholesterol, BMI, and waist-to-hip ratio. Categorical variables are also presented, including the prevalence of hypertension, smoking history, migraines, polyps or fibroids, hyperinsulinemia, and ethnicity distribution. In addition, the table displays the percentage of complete data for each variable in both groups, univariate test results (*P* values), and Cochran-Mantel-Haenszel (CMH) test results to evaluate associations with AUB. Variance inflation factor (VIF) scores are included to assess multicollinearity among the variables.

As shown in Table 1, the majority of participants in both the control and case groups identified as Hispanic (42% in the AUB group and 39% in the No AUB group). The racial distribution between the 2 groups was not statistically different in the univariate χ^2 analysis. However, race was identified as a potential confounder by the Cochran-Mantel-Haenszel (CMH) test. The median age of women with AUB was significantly higher than those without AUB (39.0 vs. 33.0 y). Age was statistically significant in the univariate analysis and identified as a confounder. Women with AUB had significantly higher BMI values compared with those without AUB (29.9 vs. 24.8), although neither group's median BMI fell into the obese category. While BMI was significantly associated with AUB, it was not identified as a confounder. Waist-to-hip ratio did not differ significantly between the 2 groups (0.86 vs. 0.83) and was not a confounder. Most participants did not identify as tobacco smokers, with 93% in the normal menstruation group and 82% in the AUB group.

Hypertension, LDL, HDL, smoking, migraines, and polyps or fibroids were all significantly associated with AUB and identified as confounders. Chronic hypertension was present in 12% of the control group compared with 26% of the AUB group. Among metabolic markers, LDL levels were similar between groups, while HDL levels were lower in women with AUB (54.0 vs. 60.0 mg/dL). Triglycerides showed a nonsignificant difference (82.0 vs. 73.5 mg/dL), and cholesterol levels also did not differ significantly between groups (169.0 vs. 172.5 mg/dL). Migraines were more prevalent in the AUB group (31.0% vs. 11.2%), as were polyps or fibroids (45.7% vs. 9.6%). Hyperinsulinemia, the main effect of interest, was significantly associated with AUB (44.0% vs. 33.7%).

Results from Table 1 highlighted 2 continuous variables—LDL and cholesterol—with high variance inflation factor (VIF) values, indicating potential multicollinearity. Total cholesterol had the highest VIF (9.4), likely reflecting its strong correlation with other lipid markers such as LDL and HDL, while LDL had a VIF of 7.9. The Pearson correlation coefficients showed that both LDL and cholestrol were highly correlated with each other ($r > 0.8$), meeting the threshold for exclusion. LDL was retained in the model due to its role as a confounder. Including cholesterol in the full model caused convergence issues in the logistic regression, whereas removing cholesterol resolved these issues and ensured model stability. These findings confirmed that excluding cholesterol effectively addressed multicollinearity concerns without compromising the model's interpretability or robustness.

The logistic regression analysis utilized forward model selection to identify a model that balanced low AIC, high concordance, and parsimony. The baseline model, which included only hyperinsulinemia (IR), had an AIC of 188 and a concordance of 40%. Variables were added iteratively and retained only if they substantially reduced AIC and increased percent concordance. Cholesterol was never added to the model due to its multicollinearity issues with LDL. Confounders and other covariates were added and assessed for their contribution.

TABLE 2. Forward logistic model selection.

Model (AUB = hyperinsulinemia +)	Additional covariates	AIC intercept	AIC covariates	Percent concordant	Hyperinsulinemia *P*
Base model	0	195	188	40	0.0024
BMI	*1*	*188*	*169*	*71*	*0.2938*
BMI×IR		*187*	*173*	*58*	*0.0002*
Age	1	187	179	67	0.0043
Age+race	2	181	179	68.3	0.0096
Age+race+migraines	3	180	165	73	0.0317
Age+race+PF	3	170	154	76	0.0127
Age+race+Waist_HipRatio	3	163	161	71	0.0080
Age+race+smoke	3	180	179	70	0.0083
Age+race+LDL	3	165	161	72	0.0123
Age+race+LDL+Waist_HipRatio	**4**	**147**	**145**	**73**	**0.0222**
Age+race+LDL+triglycerides	4	154	152	72	0.0246
Age+race+LDL+HDL	4	156	151	72	0.0410
Age+race+LDL+hypertension	4	163	162	72	0.0141
Age+race+LDL +HDL+triglycerides	5	145	142	73	0.0536
Age+race+LDL +Waist_HipRatio+hypertension	5	137	137	73	0.0227
Age+race+ LDL+Waist_HipRatio +trigyclerides	5	137	137	73	0.0092
Age+race+Waist_Hip Ratio+LDL+HDL	5	138	137	73	0.0222
Age+race+Waist_Hip Ratio+LDL+trigyclerides	*5*	*137*	*137*	73	0.0092
Age+race+Waist_Hip Ratio+HDL+trigyclerides	*5*	*138*	*138*	72	0.0193

AIC, Akaike Information Criterion; AUB, abnormal uterine bleeding; BMI, body mass index; HDL, high-density lipoprotein; IR, Insulin Resistance; LDL, low-density lipoprotein; PF, Polyps and Fibroids.

Models highlighted in bold are the final models discussed in the Results section. Models highlighted in bold and italics focus on BMI and represent a separate model selection also discussed in the Results section.

Adding age and race reduced the AIC from 195 to 181, with concordance increasing from 40% to 68%. Including LDL and waist-to-hip ratio further improved the model, resulting in a final AIC of 145 and a concordance of 73. This significant reduction in AIC highlights the importance of these covariates in capturing the relationship between hyperinsulinemia, metabolic health, and AUB.

Including BMI in the model (Table 2) alongside age and race increased collinearity and rendered hyperinsulinemia nonsignificant ($P = 0.3382$), suggesting an overlap between BMI and hyperinsulinemia. To investigate this relationship further, we examined a model that included BMI and residual hyperinsulinemia. The model showed a significant improvement in fit compared with the intercept-only model (AIC = 181.347 vs. AIC = 200.931, $P < 0.0001$). BMI was a significant predictor of AUB (OR = 1.122, 95% CI: 1.062-1.186, $P < 0.0001$), while residual hyperinsulinemia was not statistically significant (OR = 1.238, 95% CI: 0.872-1.759, $P = 0.2328$). The *c*-statistic for this model was 0.701, indicating fair discriminatory ability. BMI explained a substantial portion of the variance in the outcome, and its inclusion reduced the significance of IR, suggesting overlapping or mediating pathways between BMI and hyperinsulinemia in relation to AUB. As these are exploratory analyses, it was important to evaluate BMI and IR both jointly and independently to better understand their distinct and overlapping contributions.

The final model retained age, race, LDL, and waist-to-hip ratio, with a 25.5% reduction in AIC compared with the base model. Beyond the final model, additional covariates offered diminishing returns, as they did not substantially reduce AIC or improve concordance. Smoking, migraines and polyps, and/or fibroids were removed from the final model due to their rarity in the dataset, making reliable estimation difficult, while hypertension, despite being identified as a confounder in the CMH test, did not improve AIC or model fit.

Subsequent steps tested additional covariates, including triglycerides, HDL, and waist-to-hip ratio, but these did not meaningfully reduce AIC beyond the final model. In Table 2, we document the forward selection process used to build the final logistic regression model for AUB, including the progressive addition of covariates and their impact on model fit (AIC, percent concordant, and hyperinsulinemia *P*-value). This table illustrates the rationale for the final model and highlights the contributions of individual covariates to overall model performance.

In our final model (Table 3), hyperinsulinemia was the only statistically significant predictor of abnormal uterine bleeding (Table 3). Hyperinsulinemia was associated with increased odds of AUB (OR = 3.009, 95% CI: 1.372-6.832, $P = 0.0085$), suggesting a strong positive relationship between hyperinsulinemia and AUB. Age

TABLE 3. Odds ratios for IR-focused model

Effect	Unit	*P*	Odds ratio	95% CIs
Age	1	0.0884	1.047	0.995-1.104
LDL	1	0.1407	0.989	0.975-1.003
Waist hip ratio	0.1	0.9791	1.008	0.588-1.780
Insulin resistance[a]	1	0.0085	3.009	1.372-6.832
Race (African American)[b]	1	0.7622	1.231	0.340-4.691
Race (Hispanic)[b]	1	0.8977	1.059	0.447-2.510
Race (Other)[b]	1	0.5531	0.676	0.182-2.303

LDL, low-density lipoprotein

[a]No is the reference level (event of outcome not occurring).

[b]White is the reference variable for race (event this happens to someone not White).

showed a borderline effect (OR = 1.047, 95% CI: 0.995-1.104, $P = 0.0884$), indicating older age might slightly increase the odds of AUB, although this was not statistically significant at the conventional $P < 0.05$ threshold. Other predictors, including LDL, waist-to-hip ratio, and race categories were not statistically significant. The correlation matrix revealed limited multicollinearity among the predictors, with generally weak correlations observed between variables (all under 0.4) suggesting the variables are largely independent in the model.

From these exploratory analyses, the additional variables in the model while not all individually significant contributed meaningfully to the overall fit and predictive power of the model. Controlling for age and race was essential to account for potential confounding effects, ensuring the relationship between hyperinsulinemia and AUB was not influenced by these demographic factors. Furthermore, although covariates such as LDL and waist-to-hip ratio were not statistically significant in this model, their inclusion markedly improved the model's fit and discriminatory ability compared with the base model with only hyperinsulinemia. In addition, the model's ability to predict outcomes improved substantially with their additional variance, with concordance increasing from 40% in the base model to 73% in the full model. This demonstrates the additional variables in the final model improved its ability to estimate outcome probabilities, enhance predictive accuracy, and account for confounding effects. By explaining variability in the data, these covariates made the model more reliable in estimating the probability of the outcome. Furthermore, the likelihood ratio test ($\chi^2 = 16.04$, $P < 0.02$) confirmed the addition of covariates significantly improved model fit.

DISCUSSION

To our knowledge, this is the first study examining the association between AUB and fasting insulin levels. Many studies and organizational bodies have examined and asserted a relationship between polycystic ovarian syndrome (PCOS) and elevated insulin levels[25-27]; however, many patients have AUB before a diagnosis of PCOS is made. The decision to include all classifications of AUB in this study was done intentionally to capture causes that may not always be apparent by clinical, radiologic, or pathologic sources. Chronic low-grade inflammation, seen in hyperinsulinemia, is an important contributor to metabolic disease.[28] Elevated insulin levels, or hyperinsulinemia, is an independent predictor of impending prediabetes or cardiovascular disease risk.[29-31] It is well documented that those affected with uterine leiomyoma, endometrial polyps, and ovulatory dysfunction have increased cardiovascular disease risk.[4,5,7,32]

Research indicates various sources of chronic low-grade inflammation play a role in the structural and non-structural causes of AUB.[8,10,13,17,27,33] Therefore, it is possible for hyperinsulinemia, as an indicator of chronic low-grade inflammation, to be a unifying factor in the structural and non-structural causes of AUB. Furthermore, it is important to acknowledge the concept of metabolically obese normal weight individual (MONW). This indicates the presence of hyperinsulinemia but other biomarkers of metabolic syndrome in the normal-weight individual.[22] Clinically, screening women with AUB with a fasting insulin level may reveal current undiagnosed cardiometabolic disease. Taken further, screening reproductive-age women with a fasting insulin level may identify those who are either at risk of metabolic syndrome, AUB, or both. Therefore, the evaluation of fasting insulin may be more clinically useful than monitoring hemoglobin A1c, given elevations of insulin levels precede the diagnosis of type 2 diabetes mellitus.[21,34,35] Hyperinsulinemia leading to insulin resistance will later lead to hyperglycemic changes that result in elevations in hemoglobin A1c.[21,36,37] Awareness of hyperinsulinemia as a predictor of cardiovascular disease will translate into significant quality of life improvement and health cost savings.

Our findings suggest future research could focus on further exploring the relationship between hyperinsulinemia, BMI, and AUB, particularly to determine causality and the sequence of events. The results highlight the complex interplay between BMI, hyperinsulinemia, and AUB, as BMI appears to mediate or dominate the relationship between hyperinsulinemia and AUB. The strong association observed between hyperinsulinemia and BMI has important implications for the primary model examining the relationship between hyperinsulinemia and abnormal uterine bleeding. When BMI was included as a covariate, hyperinsulinemia's significance as an independent predictor diminished or became nonsignificant in several models. This suggests BMI mediates or absorbs part of hyperinsulinemia's effect on AUB, reflecting its role as a key contributor to metabolic syndrome and other pathways linked to abnormal uterine bleeding.

Specifically, BMI emerged as a significant predictor of AUB, while the residualized component of hyperinsulinemia was not, indicating BMI and hyperinsulinemia may share explanatory power over the outcome variable (AUB). This finding aligns with BMI's established role as a marker of adiposity and metabolic health. Furthermore, when an interaction term between BMI and hyperinsulinemia was tested, it did not significantly improve model fit or predictive ability, suggesting these variables contribute independently to the risk of AUB. When BMI was excluded from the model, hyperinsulinemia became significantly associated with AUB, underscoring hyperinsulinemia alone is linked to AUB, but its effects are largely captured by BMI when both are included. Notably, none of the other variables analyzed in this study demonstrated a similar relationship with hyperinsulinemia and AUB as BMI. This highlights BMI's unique role in this interplay, suggesting BMI may influence AUB through specific metabolic or physiological pathways that are distinct from those of other variables. Acknowledging the overlap between hyperinsulinemia and BMI is crucial, as it reflects the complex interplay of metabolic and endocrine factors contributing to AUB.

These findings underscore the importance of BMI as a modifiable risk factor for AUB and metabolic health.

Excluding BMI allowed for a clearer assessment of hyperinsulinemia's total effect on AUB, providing a more nuanced understanding of the relationship. While this study highlights these dynamics, additional research with larger sample sizes and formal mediation testing is needed to disentangle the direct and indirect effects of hyperinsulinemia on AUB through BMI. Future research could explore whether addressing adiposity through lifestyle interventions could mitigate AUB in populations with insulin resistance. Incorporating additional markers of metabolic health in future studies may also provide a more comprehensive understanding of these interactions.

Migraines, polyps and/or fibroids, and smoking were excluded from the final model due to rarity in the dataset. Future studies with larger, more balanced datasets are needed to better understand the roles and interactions of these factors in the context of IR and AUB. Interactions between migraines, polyps and/or fibroids, AUB, and hyperinsulinemia also warrant further investigation.

These findings highlight important associations between hyperinsulinemia and AUB; however, due to the cross-sectional nature of the study, causality and temporal relationships cannot be determined. It is important to note these analyses are exploratory and the relatively small sample size of 205 participants may amplify the variability in the results and limit the generalizability of the findings. The primary purpose of this study was to gain new knowledge and generate hypotheses for further investigation, rather than to draw definitive conclusions. However, thorough and meticulous analyses were performed to ensure robust conclusions, incorporating thorough evaluations of various scenarios and model adjustments to inform our findings. While these analyses provide valuable insight into potential mechanisms linking hyperinsulinemia, BMI, and AUB, they should be interpreted cautiously and serve as a foundation for future hypothesis-driven research.

There are limitations in this study. First, the study was conducted over a span of 4 years where the normally menstruating group was enrolled after the AUB group. The normally menstruating group was enrolled during the COVID-19 pandemic. The identification and enrollment of normally menstruating women was challenging in this gynecology clinic setting through the COVID-19 pandemic as very few preventive examinations were performed during this period due to the limited personnel resources during the public health emergency. Second, enrollment of controls was also a challenge as there were few patients who were seen in the gynecology clinics who were normally menstruating without the use of hormonal contraceptives. Furthermore, the study relied on participants' assertions and menstrual pattern documentation from intake questionnaires to confirm the normalcy of their menstrual cycle.

In this study, the presence of polyps was identified via physical examination, pathology report or through identification on pelvic sonogram. Women with AUB of unexplained causes may have had endometrial/cervical polyps that were not identified with biopsy or imaging modalities. In addition, while the participants agreed to enroll in the study, a small percentage did not complete their laboratory analysis, and thus, certain indicators could not be analyzed. Advancing age may also play a role in the findings, as aging increases the risk for cardiometabolic and gynecologic disease. Finally, the generalizability of the study is limited, as the population was limited to a suburban, academic health care system in southern California.

It is important to acknowledge the association of hyperinsulinemia in this study evaluating its relationship to AUB does not imply predictability. It is not possible to know what risk factor preceded the other given the exploratory design of the study. Although no clinical conclusions can be drawn from this preliminary study, it highlights the potential for future research to lead to clinically relevant outcomes. While this study identifies an association between hyperinsulinemia and AUB, it does not imply predictability or causality, as the cross-sectional design does not allow for determining the sequence of events.

However, these findings underscore the need for larger, prospective studies to address these questions and further explore the role of hyperinsulinemia in gynecologic conditions. Hyperinsulinemia has been linked to other gynecologic inflammatory conditions, such as endometriosis and adenomyosis, which are also associated with cardiovascular disease. Although this study cannot provide clinical recommendations, it serves as an important foundation for generating hypotheses and guiding rigorous future research aimed at advancing gynecologic and metabolic health.

Few studies and treatment recommendations focus on potential preventive strategies for AUB, with most management centered around standard medical and surgical treatments familiar to gynecologists. However, lifestyle and dietary modification is noted to be the best approach for modifying cardiovascular disease risk and PCOS.[25] Fasting insulin levels are part of laboratory studies to consider in the evaluation of PCOS.[25] Future research could incorporate fasting insulin level measurements and markers of metabolic syndrome into larger, prospective cohort studies focused on gynecologic health. In addition, interventional studies investigating targeted lifestyle approaches may help identify strategies for preventing and managing both AUB and metabolic health conditions.

CONCLUSION

This study highlights the association of hyperinsulinemia with common causes of abnormal uterine bleeding. This data, although preliminary, may demonstrate promise for future research in examining potential relationships between cardiovascular disease risk factors and the potential development of benign gynecologic disease.

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