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# Insulin resistance and other risk factors of cardiovascular disease amongst women with abnormal uterine bleeding

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**Background:** Studies indicate the presence of cardiovascular disease risk amongst patients with uterine fibroids and polycystic ovarian syndrome.

**Aim:** The researchers aimed to examine the prevalence of cardiovascular disease risk factors and independent predictors of insulin resistance (IR) amongst women with abnormal uterine bleeding (AUB).

**Methods:** This observational study examined 77 premenopausal subjects with AUB. Their medical history, body mass index (BMI), waist–hip ratio (WHR), fasting insulin (FI), haemoglobin A1c, creatinine and lipids were evaluated. Subjects were subdivided using insulin levels and compared. Insulin resistance was defined at two FI levels: > 10 µU/mL and > 15 µU/mL.

**Results:** A total of 91% of participants had smoking history, 62% had a WHR > 0.80, 45% were obese and most had dyslipidaemia. In all, 38% – 66% were insulin resistant, depending on cut-off used. At FI > 10 µU/mL, subjects were significantly more likely to have a WHR > 0.8, be obese and have low HDL. At FI > 15 µU/mL, subjects were significantly more likely to have low HDL, elevated triglycerides, a WHR > 0.8 and be obese. Univariate analysis showed significant associations between IR in AUB and BMI, WHR and HDL for both FI cut-offs. Multivariate analysis using the lower FI cut-off revealed BMI and WHR were significant independent predictors of IR in AUB.

**Conclusion:** This study reveals the prevalence of IR (66%) and other predictors of cardiovascular disease are greater in AUB in this population than the general US population. Body mass index and WHR are independent predictors of IR in AUB. Low HDL, elevated triglycerides and ethnicity are also significantly associated with IR in AUB depending on the definition used.

**Keywords:** insulin; abnormal uterine bleeding; heavy menses; insulin resistance; gynecology; metabolic syndrome; cardiovascular disease.

## Introduction

The uterus responds to cardiovascular disease endothelial inflammation like other end organs, yet it is not typically viewed in this way. Insulin resistance (IR) and other markers of metabolic syndrome are well established risk factors of cardiovascular disease-related end organ damage.[1,2,3] Whilst IR and metabolic disorders are established risk factors for polycystic ovarian syndrome (PCOS),[4] they also play a role in other causes of abnormal uterine bleeding (AUB). Abnormal uterine bleeding is described as menstrual flow outside of normal volume, duration and regularity.[5] Historically, the focus of IR within the field of gynaecology is primarily dedicated to PCOS, yet gynaecologic literature indicates that risk factors for uterine fibroids, endometrial polyps and polycystic ovarian syndrome include obesity, hypertension and metabolic syndrome.[6] However, few studies have examined the presence of IR amongst women with abnormal uterine bleeding as a whole.

Insulin is a key anabolic hormone involved in multiple metabolic pathways in the body, including glucose uptake and lipid storage, cell growth and proliferation in the body and nitric oxide (NO) synthesis by endothelial cells.[2,7,8] Insulin resistance occurs when increasingly larger amounts of insulin are required to regulate the body's metabolic pathways, and even in the face of these increasing insulin levels, cellular activity is diminished compared with a normal person.[2,7,8] Insulin resistance is a multifactorial disease that has become an epidemic in the United States (US). Although the number of adults affected by IR is not known, one in three adults in the US has prediabetes and an additional 10.5% of adults has diabetes mellitus type 2 (DM2).[2,9] These numbers

are expected to double in the next 10 years because almost 90.0% of Americans have risk factors for IR.[9]

Although angiogenesis is a relatively infrequent event in most adult tissues, it occurs repeatedly in the uterus in order to support the monthly cycle of growth, shedding and repair of the endometrial lining.[10] Both the process of angiogenesis and endometrial repair are tightly regulated by oestrogen and progesterone, which involve NO, platelets, immune cells and multiple growth factors.[6,10,11,12,13] Decreased NO production, because of IR, results in an increase in the shear stress on endothelial cells because of diffuse vasoconstriction.[2,8] Moreover, decreased NO, hyperglycaemia and the state of IR itself promote the release of inflammatory cytokines and free radical formation, which leads to further endothelial damage, surrounding tissue hypoxia, and, eventually, cellular apoptosis.[2,8] The resulting vascular permeability is worsened by high levels of circulating glucose that damages the endothelial cell glycocalyx.[2,8,14] Together, these vascular changes allow substrates to leave the blood and form plaques in the tunica intima layer of the blood vessel.[8] This thickening of the blood vessels leads to increased vascular resistance, chronic low-grade inflammation and atherosclerosis.[2] Atherosclerosis is a widely accepted cause of numerous microvascular and macrovascular diseases that are significantly associated with IR.[2,15,16,17,18] Studies have demonstrated that women with fibroids and PCOS are more likely to have risk factors for cardiovascular disease,[6] but AUB and its other causes are not currently thought of as an atherosclerotic-related end organ disease.

Applying this knowledge to the uterus, chronic low-grade inflammation likely reduces the spiral arteries' ability to meet the high metabolic demands of the endometrium. This leads to an overexpression of angiogenic cytokines and dysfunctional angiogenesis with excessive uterine vessel formation and dilation in an attempt to increase the amount of uterine blood flow.[10,12,19,20] It also results in functionally impaired proliferative and secretory phases of the menstrual cycle where the endometrial lining is not properly repaired during cyclical shedding.[20] Similar inflammatory cytokines and fibrosis-promoting growth factors seen in atherosclerotic disease encourage smooth muscle metaplasia and scarring in the uterus.[19,21,22,23,24,25,26,27] In fact, Moss and Benditt (1975) revealed the similar growth and behaviour of the atherosclerotic plaque cell with the leiomyoma cell.[28] The sentinel event postulated in both uterine leiomyoma and atherosclerotic plaque development reveal smooth muscle proliferation from a single progenitor myocyte.[29] Features suggesting related pathology were also highlighted in other studies that revealed similar clonality and ability to fibrose and calcify.[30,31]

This molecular and immunologic dysregulation leads to several forms of AUB that result in commonplace gynaecologic pathology. Abnormal uterine bleeding is the most common reason for outpatient gynaecologic consultation in the US.[32] In 2011, the International Federation of Gynecology and Obstetrics (FIGO) created a uniform system of classification to describe uterine bleeding disorders called PALM-COEIN (polyp, adenomyosis, leiomyoma, metaplasia, coagulopathy, ovulatory, endometrial, iatrogenic and not otherwise specified).[33] Whilst the approach to treating PCOS-related obesity and menstrual irregularity includes lifestyle changes by reducing cardiovascular risk factors, there is little information on how this management strategy can prevent or improve AUB from endometrial polyps, adenomyosis, leiomyoma or endometrial causes. On the other hand, the majority of treatment options for AUB caused by the development of morphologic pathologies such as endometrial polyps, adenomyosis and leiomyoma often include medical, hormonal or surgical management.[4,34]

The purpose of the present study is to describe the prevalence of IR and other predictors of cardiovascular disease amongst women overall with AUB in a suburban population in Southern California. Understanding this prevalence may point to relationships between metabolic and cardiovascular health and manifestations of gynaecologic disease that can lead to sustainable strategies for treatment and prevention.

# Methods

## Study population

This was a cross-sectional observational study conducted at Loma Linda University Heath outpatient obstetrics and gynaecology clinics. Potential study candidates were premenopausal, female and between the ages of 18 and 54 years old, presenting with a complaint of AUB between September 2018 and October 2019. A candidate was confirmed eligible for enrolment once the diagnosis of AUB was made in the outpatient clinic setting. Women with a history of gynaecologic cancer, prior hysterectomy, prior endometrial ablation, prior tamoxifen use, diabetes mellitus type 1, chronic steroid use or pregnancy were excluded. There were 117 subjects enrolled with a total of 77 complete subjects analysed for this study. The study was supported by the Department of Gynaecology and Obstetrics of Loma Linda University Health.

## Measured variables

At the time of enrolment, a thorough history was performed. Each participant had her height, weight and waist-to-hip ratio (WHR) measured. Overnight fasting blood samples were then obtained to assess each participant's fasting insulin level (FI), haemoglobin A1c (HbA1c), creatinine (Cr) and lipid profile. A BMI $\geq$ 30 kg/m$^2$ was used as the cut-off for obesity and a WHR > 0.80 was considered abnormal.[35,36,37] The IR was assessed using two different FI cut-offs: > 10 µU/mL and > 15 µU/mL, which represented both the lower and higher end of the FI cut-offs of prior research.[7,18,38,39] Abnormal A1c values were defined by the prediabetic cut-off of $\geq$ 5.7%, whilst abnormal lipid levels were defined by the American Heart Association values of HDL < 50 mg/dL, total cholesterol levels > 150 mg/dL, LDL > 100 mg/dL and triglycerides levels > 150 mg/Dl.[9,40]

## Statistical analysis

Statistical analysis was performed using the online statistical software R version 3.5.1.[41] Assuming approximately 33% of the general population is IR, the minimum sample size was calculated to be approximately 27 subjects in each group to have 80% power and 5% Type 1 error.[9] Independent t-test, Mann–Whitney U test, and chi-square test were calculated with the statistical significance set as $p > 0.05$. Univariate regression analysis was performed using linear regression. Observed associations were expressed as odds ratios with 95% confidence intervals.

## Ethical considerations

This study was approved by the Institutional Review Board for Human Subjects at Loma Linda University Health (ref. no. 5180222).

The participants gave voluntary, informed, written consent prior to participating in the study. This research study was approved by the Institutional Review Board, 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 were handled only by the researchers participating in this study.

# Results

A total of 77 participants completed the measured variables and were included in the analysis. As shown in Table 1, the majority of participants were either Hispanic or white women, a mean age 37, with an average of two prior births. Interestingly, 90.0% of subjects were either current or former smokers. Approximately two-thirds of participants had a WHR > 0.80 with the average WHR being 0.86. Almost half of participants were obese, with the average BMI being 31.82 kg/m². Two-thirds of participants had a FI > 10 µiU/mL, with 38.0% having a FI > 15 µiU/mL, but only 22.0% of participants had an A1c ≥ 5.7%. The majority of participants also had dyslipidaemia, with 68.0% having high total cholesterol levels and an additional 38.0% of participants having high LDL levels.

Table 2 shows the difference in characteristics between the two groups when IR was defined as FI > 10 µiU/mL. Ethnicity was significantly related to IR, with all African-Americans and Middle Easterners being classified as IR, whilst none of the Asian participants were classified as IR ($p = 0.027$). The IR group was significantly more likely to be obese (60.8% vs 15.4%; $p < 0.001$) and have low HDL levels (41.2% vs 19.2%; $p = 0.03$) than the non-IR group. There were no statistical differences between the two groups with regard to the other variables analysed, but it is worth noting that no participants in the non-IR group had a history of DM2 or elevated triglycerides levels, and more than 62.0% of participants in both groups had high total cholesterol levels.

**TABLE 1:** Description of the study population.

| Variable | Minimum to Maxium | Mean | s.d. | Category | *n* | % |
|---|---|---|---|---|---|---|
| Age | 18–53 | 37 | 9 | - | - | - |
| Gravity | 0–8 | 2 | 2 | - | - | - |
| Parity | 0–5 | 2 | 2 | - | - | - |
| Ethnicity | | | | White | 23 | 29.9 |
| | | | | African American | 10 | 13.0 |
| | | | | Hispanic | 36 | 46.7 |
| | | | | Native Alaskan | 2 | 2.6 |
| | | | | Middle Eastern | 2 | 2.6 |
| | | | | Asian | 4 | 5.3 |
| History of HTN | | | | Yes | 18 | 23.0 |
| | | | | No | 59 | 77.0 |
| History of DM2 | | | | Yes | 6 | 8.0 |
| | | | | No | 71 | 92.0 |
| Insulin (µiU/mL) | 2.7–112.7 | 17.8 | 16.4 | ≤ 10 | 26 | 34.0 |
| | | | | > 10 | 51 | 66.0 |
| | | | | ≤ 15 | 48 | 62.0 |
| | | | | > 15 | 29 | 38.0 |
| Hemoglobin A1c | 4.3–13.4 | 5.5 | 1.2 | < 5.7 | 60 | 78.0 |
| | | | | ≥ 5.7 | 17 | 22.0 |
| BMI | 17–57.9 | 31.8 | 9 | < 30 | 42 | 55.0 |
| | | | | ≥ 30 | 35 | 45.0 |
| WHR | 0.68–1.16 | 0.86 | 0.14 | ≤ 0.8 | 13 | 17.0 |
| | | | | > 0.8 | 48 | 62.0 |
| | | | | missing | 16 | 21.0 |
| Smoker | - | - | - | Yes or former | 70 | 91.0 |
| | - | - | - | No | 7 | 9.0 |
| Creatinine (mg/dL) | 0.5–1.4 | 0.7 | 0.2 | < 1 | 71 | 92.0 |
| | | | | ≥ 1 | 3 | 3.0 |
| | | | | missing | 3 | 3.0 |
| HDL (mg/dL) | 28–134 | 56 | 16.8 | ≥ 50 | 47 | 61.0 |
| | | | | < 50 | 26 | 34.0 |
| | | | | | 4 | 5.0 |
| LDL (mg/dL) | 22–185 | 94.2 | 27.2 | < 100 | 44 | 57.0 |
| | | | | ≥ 100 | 29 | 38.0 |
| | | | | missing | 4 | 5.0 |
| Cholesterol (mg/dL) | 97–228 | 166.6 | 28.7 | < 150 | 21 | 27.0 |
| | | | | ≥ 150 | 52 | 68.0 |
| | | | | missing | 4 | 5.0 |
| Triglycerides (mg/dL) | 39–341 | 101.3 | 49.8 | < 150 | 68 | 88.0 |
| | | | | ≥ 150 | 5 | 7.0 |
| | | | | missing | 4 | 5.0 |

s.d., standard deviation; HTN, hypertension; DM2, diabetes mellitus type 2; BMI, body mass index; WHR, waist to hip ratio; Smoker, former or current smoker.

Table 3 depicts the difference in characteristics between the two groups when IR was defined as FI > 15 µiU/mL. The IR group was significantly more likely to be obese (75.9% vs 27.1%; $p < 0.001$), have low HDL levels (48.3% vs 25%; $p = 0.016$) and have high triglycerides levels (13.8% vs 2.1%; $p = 0.032$) compared with the non-IR group. Although there were no statistical differences between the two groups regarding the other variables analysed, again, no Asian participants were classified as IR and more than 62.0% of participants in both groups had elevated total cholesterol levels.

By univariate regression analysis, factors significantly associated with IR in women with AUB were BMI, WHR and HDL levels. These associations persisted regardless of the FI

**TABLE 2:** Comparison of characteristics between IR and non-IR groups with IR defined as fasting insulin levels > 10 µiU/mL.

| Variable | Non-IR (*n* = 26) | | | IR (*n* = 51) | | | *p* |
|---|---|---|---|---|---|---|---|
| | *n* | % | s.d. | *n* | % | s.d. | |
| **Age†** | - | - | 9.4 | - | - | 8.4 | 0.714 |
| **Gravity** | 2 | - | 2.0 | 2.0 | - | 2.0 | 0.509 |
| **Parity** | 1 | - | 2.0 | 2.0 | - | 2.0 | 0.568 |
| **Ethnicity** | | | | | | | 0.027* |
| White | 10 | 38.5 | - | 13 | 25.5 | - | - |
| African American | 0 | 0.0 | - | 10 | 19.6 | - | - |
| Hispanic | 11 | 42.3 | - | 25 | 49.0 | - | - |
| Native Alaskan | 1 | 3.8 | - | 1 | 2.0 | - | - |
| Middle Eastern | 0 | 0.0 | - | 2 | 3.9 | - | - |
| Asian | 4 | 15.4 | - | 0.0 | 0.0 | - | - |
| **History of HTN** | 4 | 15.4 | - | 14 | 27.5 | - | 0.237 |
| **History of DM2** | 0 | 0.0 | | 6 | 11.8 | - | 0.069 |
| **Smoker** | 3 | 11.5 | - | 6 | 11.8 | - | 0.977 |
| **BMI (kg/m²)** | | | | | | | < 0.001* |
| < 30 | 22 | 88.5 | - | 20 | 39.2 | - | - |
| > 30 | 4 | 15.4 | - | 31 | 60.8 | - | - |
| **Hemoglobin A1c** | | | | | | | 0.111 |
| < 5.7% | 23 | 88.5 | - | 37 | 72.6 | - | - |
| ≥ 5.7% | 3 | 11.5 | - | 14 | 27.4 | - | - |
| **Creatinine (mg/dL)** | | | | | | | 0.301 |
| ≤ 1 | 25 | 80.8 | - | 46 | 90.2 | - | - |
| > 1 | 1 | 3.8 | - | 2 | 3.9 | - | - |
| missing | 0 | - | - | 3 | - | - | - |
| **HDL (mg/dL)** | | | | | | | 0.030* |
| ≥ 50 | 21 | 80.8 | - | 26 | 51.0 | - | - |
| < 50 | 5 | 19.2 | - | 21 | 41.2 | - | - |
| missing | 0 | - | - | 4 | - | - | - |
| **LDL (mg/dL)** | | | | | | | 0.245 |
| < 100 | 18 | 69.2 | - | 26 | 51.0 | - | - |
| ≥ 100 | 8 | 30.8 | - | 21 | 41.2 | - | - |
| missing | 0 | - | - | 4 | - | - | - |
| **Cholesterol (mg/dL)** | | | | | | | 0.424 |
| < 150 | 6 | 23.1 | - | 15 | 29.4 | - | - |
| ≥ 150 | 20 | 76.9 | - | 32 | 62.8 | - | - |
| missing | 0 | - | - | 4 | - | - | - |
| **Triglycerides** | | | | | | | 0.085 |
| < 150 | 26 | 100.0 | - | 42 | 82.4 | - | - |
| > 150 | 0 | 0.0 | - | 5 | 9.8 | - | - |
| missing | 0 | - | - | 4 | - | - | - |

IR, insulin resistance; s.d., standard deviation; HTN, hypertension; DM2, diabetes mellitus type 2; Smoker, current or former smoker.

*, significant *p*-value.

†, Non-IR: mean age = 36.1; IR: mean age = 37.3.

**TABLE 3:** Comparison of characteristics between IR and non-IR groups with IR defined as fasting insulin levels > 15 µiU/mL.

| Variable | Non-IR | | | IR | | | *p* |
|---|---|---|---|---|---|---|---|
| | *n* (48) | % | s.d. | *n* (29) | % | s.d. | |
| **Age†** | - | - | 8.4 | - | - | 8.9 | 0.158 |
| **Gravity** | 2 | - | 2.0 | 2 | - | 2.0 | 0.120 |
| **Parity** | 2 | - | 2.0 | 1 | - | 2.0 | 0.127 |
| **Ethnicity** | | | | | | | 0.027* |
| White | 16 | 33.3 | - | 7 | 24.1 | - | - |
| African American | 6 | 12.5 | - | 4 | 13.8 | - | - |
| Hispanic | 20 | 41.7 | - | 16 | 55.2 | - | - |
| Native Alaskan | 1 | 2.1 | - | 1 | 3.5 | - | - |
| Middle Eastern | 1 | 2.1 | - | 1 | 3.5 | - | - |
| Asian | 4 | 8.3 | - | 0 | 0.0 | - | - |
| **History of HTN** | 9 | 18.75 | - | 9 | 31.0 | - | 0.217 |
| **History of DM2** | 3 | 6.25 | - | 3 | 10.3 | - | 0.618 |
| **Smoker** | 4 | 8.3 | - | 5 | 17.2 | - | 0.238 |
| **BMI (kg/m²)** | | | | | | | < 0.001* |
| < 30 | 35 | 72.9 | - | 7 | 24.1 | - | - |
| > 30 | 13 | 27.1 | - | 22 | 75.9 | - | - |
| **Hemoglobin A1c** | | | | | | | 0.141 |
| < 5.7% | 40 | 83.3 | - | 20 | 69.0 | - | - |
| ≥ 5.7% | 8 | 16.7 | - | 9 | 31.0 | - | - |
| **Creatinine (mg/dL)** | | | | | | | 0.699 |
| ≤ 1 | 45 | 93.8 | - | 26 | 89.7 | - | - |
| > 1 | 1 | 2.1 | - | 1 | 3.5 | - | - |
| missing | 2 | - | - | 2 | - | - | - |
| **HDL (mg/dL)** | | | | | | | 0.016* |
| ≥ 50 | 35 | 72.9 | - | 12 | 41.4 | - | - |
| < 50 | 12 | 25.0 | - | 14 | 48.3 | - | - |
| missing | 1 | - | - | 3 | - | - | - |
| **LDL (mg/dL)** | | | | | | | 0.404 |
| < 100 | 30 | 62.5 | - | 14 | 48.3 | - | - |
| ≥ 100 | 17 | 35.4 | - | 12 | 41.4 | - | - |
| missing | 1 | - | - | 3 | - | - | - |
| **Cholesterol (mg/dL)** | | | | | | | 0.779 |
| < 150 | 13 | 27.1 | - | 8 | 27.6 | - | - |
| ≥ 150 | 34 | 70.8 | - | 18 | 62.1 | - | - |
| missing | 1 | - | - | 3 | - | - | - |
| **Triglycerides** | | | | | | | 0.032* |
| < 150 | 46 | 95.8 | - | 22 | 75.9 | - | - |
| > 150 | 1 | 2.1 | - | 4 | 13.8 | - | - |
| missing | 1 | - | - | 3 | - | - | - |

IR, insulin resistance; s.d., standard deviation; HTN, hypertension; DM2, diabetes mellitus type 2; Smoker, current or former smoker.

*, significant *p*-value.

†, Non-IR: mean age = 38.0; IR: mean age = 35.0.

level used to define IR (see Table 4). Ethnicity, Cr, triglycerides levels, total cholesterol levels, LDL, history of DM2, history of hypertension, history of migraines and smoking were not significantly associated with IR in women with AUB in either of the univariate regression analyses. When multivariate regression analysis was performed using FI > 10 µiU/mL to define IR, BMI (standardised coefficient β: 1.07, $p = 0.015$) and WHR (standardised coefficient β: 1.94, $p = 0.045$) were independent predictors of IR in women with AUB. Regression analysis was not performed using FI > 15 µiU/mL.

## Discussion

This study shows that the prevalence of IR and other predictors of cardiovascular disease are higher amongst women from this diverse suburban community with overall AUB (66%) than amongst the general female US population.[9] The BMI and WHR were shown to be independent predictors of IR in women with AUB. The odds of a woman with AUB having IR were seven times higher for every one-unit increase in BMI over 30 kg/m² when controlling for other variables. By the same convention, the odds of a woman with AUB having IR were nearly four times higher for every 0.1 unit increase in WHR after 0.8. Low HDL levels, elevated triglycerides levels and ethnicity were also significantly associated with IR in women with AUB, depending on how IR was defined.

Similar to prior studies on AUB, the present study's participants had a high prevalence of risk factors for cardiovascular disease, including smoking (90%), obesity (45%), an elevated WHR (62%) and dyslipidaemia.[16,24,26,42,43,44,45,46]

**TABLE 4:** Univariate analysis of risk factors for IR in women with AUB.

| Variable | IR defined as FI > 10 µiU/mL | | | IR defined as FI > 15 µiU/mL | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | *p* | Odds ratio | 95% CI | *p* |
| Age (years) | 1.02 | 0.96–1.07 | 0.589 | 0.96 | 0.91–1.02 | 0.160 |
| BMI (≥ 30 kg/m$^2$) | 7.68 | 2.38–24.77 | < 0.001* | 7.89 | 2.76–22.56 | < 0.001* |
| WHR | 5.72 | 1.81–18.05 | 0.003* | 3.55 | 1.41–8.90 | 0.007* |
| Creatinine (> 1 mg/dL) | 2.74 | 0.06–11.65 | 0.598 | 1.72 | 0.10–28.60 | 0.710 |
| Hemoglobin A1c (≥ 5.7%) | 2.60 | 0.70–9.61 | 0.153 | 2.21 | 0.74–6.59 | 0.160 |
| LDL (≥ 100 mg/dL) | 1.77 | 0.65–4.83 | 0.268 | 1.50 | 0.57–3.97 | 0.410 |
| HDL (≥ 50 mg/dL) | 0.32 | 0.10–0.96 | 0.042* | 0.30 | 0.11–0.83 | 0.021* |
| Cholesterol (≥ 150 mg/dL) | 0.67 | 0.22–1.89 | 0.463 | 0.85 | 0.30–2.43 | 0.760 |
| Triglycerides (≥ 150 mg/dL) | 6.86 | 0.28–169.98 | 0.240 | 6.20 | 0.77–49.95 | 0.090 |
| **Ethnicity** | | | | | | |
| White (reference ethnicity) | - | - | - | - | - | - |
| Hispanic | 1.73 | 0.58–5.10 | 0.325 | 1.77 | 0.59–5.32 | 0.310 |
| African American | 16.33 | 0.75–35.80 | 0.076 | 1.52 | 0.33–7.09 | 0.590 |
| Other | 0.50 | 0.096–2.56 | 0.401 | 0.85 | 0.14–5.02 | 0.850 |
| History of DM2 | 7.57 | 0.33–175.43 | 0.207 | 1.72 | 0.32–9.13 | 0.530 |
| History of HTN | 1.93 | 0.63–6.97 | 0.285 | 1.93 | 0.66–5.61 | 0.230 |
| Smoker | 0.96 | 0.25–4.34 | 0.955 | 2.22 | 0.55–9.04 | 0.270 |

IR, insulin resistance; AUB, abnormal uterine bleeding; FI, fasting insulin; CI, confidence interval; WHR, waist to hip ratio; DM2, diabetes mellitus type 2; HTN, hypertension; Smoker, current or former smoker.

*, signficant *p*-value.

The majority of participants did not have an elevated A1c or a history of hypertension or DM2, but this lack of association has been observed in prior studies on overall AUB as well.[28,29,43,44] This may indicate that whilst subjects may not have current diabetes or hypertension, elevated fasting insulin levels may be a precursor to abnormal uterine bleeding. Prior studies have found a relationship between AUB and elevated triglycerides levels, but this relationship was only significant in the present study when participants were IR using the higher FI cut-off of > 15 µiU/mL.[37,44] Interestingly, the significant inverse relationship between IR and HDL levels in women with AUB in the present study was not seen in prior studies on overall AUB.[43,44] Subjects with normal HDL levels, which are considered cardioprotective, were almost 70% less likely to be IR.[40]

In addition, although a significant relationship between BMI and WHR and AUB has been reported in multiple prior studies, the relationship between BMI and WHR, IR and AUB has previously only been shown to be significant in prior studies on AUB because of PCOS.[24,42,43,44,45,46,47]

There were strengths and limitations of this study. One strength was the inclusion of the ethnically diverse patient population, which can improve generalisability of the findings. Another strength was the broad definition of AUB used intentionally to evaluate the overall prevalence of IR and metabolic risk factors amongst women with this problem. However, this broad term also made it difficult to compare the present study's results with the results of prior studies, which often only evaluated one specific cause of AUB. However, it is worth noting that although the developmental causes of AUB (polyps, leiomyoma, PCOS, etc.) may be different, the inflammatory factors that lead to each manifestation may be related. One potential weakness of the study was the large population of smokers or former smokers in the study, which on its own carries the risk of IR.

Furthermore, as this was a cross-sectional study, conclusions can only be made between IR and other cardiovascular disease risk factors amongst women with AUB. Another limitation of this study was the high attrition rate, with 41 (35%) of the participants excluded from the analysis because of incomplete laboratory values. Although still included in the analysis, an additional four (3%) of the participants did not complete the required lipid panel and an additional 16 (13.6%) of the participants did not undergo evaluation of their WHR. This selection bias likely affects how generalisable the results from the present study are to women with AUB. Finally, attempts to limit investigator bias were made by using retrospective self-reports to diagnose AUB, but prior studies have shown these may not be accurate.[48]

## Implications for research

This study highlights the need for further investigation related to AUB and IR. Originally conceptualised to be an observational study, the goal was to determine the prevalence of IR and cardiovascular disease risk factors amongst women with AUB. A follow-up case-control study is currently underway to evaluate the association of IR and other cardiovascular disease risk factors in women with AUB with normally menstruating women within this same diverse suburban community.

Further research is needed on the relationship between ethnicity and IR, as ethnicity has been shown to be an important predictor of cardiovascular disease in the general population.[49] Although ethnicity was shown to be significantly related to IR in women with AUB when IR was defined as FI > 10 µiU/mL, it may not have been significantly related to IR using the higher FI cut-off because of a small sample size.

## Conclusion and implications

The high prevalence of risk factors for cardiovascular disease seen in these women suggests that AUB may be a sentinel

finding for DM2 and cardiovascular disease in women later in life. Specifically, elevations in insulin may lead to AUB. This study also confirms the finding that women with metabolic risk factors correlate with IR amongst those with abnormal uterine bleeding. It is well-established that elevations in insulin levels are an associated sign of endothelial dysfunction,[1,2,7,15] which may lead to common causes of abnormal uterine bleeding. There are several studies indicating that angiogenic dysregulation and endothelial dysfunction may lead to the development of uterine leiomyoma, endometrial polyps and endometrial inflammation.[21,29,50,51] Whilst each of these gynaecologic pathologies develop uniquely, their clinical result is abnormal uterine bleeding. As such, monitoring cardiovascular and metabolic disease risk factors may lead to early prevention or treatment of AUB. Evaluation of fasting insulin levels, in particular, can guide the clinician to impending or current gynaecologic disorders.

Recognising cardiovascular disease risk factors and elevated insulin levels in women can guide the clinician toward primary and secondary prevention and treatment of abnormal uterine bleeding. Clinicians may be able to counsel patients before gynaecologic pathologies develop by screening for these risk factors. Gynaecologists can inform patients of their potential underlying risk of cardiovascular disease when medical or surgical treatment is performed to treat AUB. Whilst medical management is most prescribed to treat cardiovascular disease, the role for lifestyle modifications is of utmost importance in long-term management. Therefore, if the development of AUB may be related to metabolic disease risk such as hyperinsulinemia, then lifestyle changes such as carbohydrate reduction may play a vital role in treatment. It is vital for clinicians to screen women from diverse communities with AUB for cardiovascular disease risk factors.

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### Competing interests

Dr Andrea Salcedo is a medical consultant for the Nutrition Network.

### Authors' contributions

A.S. was the principal investigator who conceptualised the study design, executed the methodology, obtained informed consent of subjects, participated in writing of the original draft, curated the data, reviewed data analysis, wrote, edited and reviewed the final manuscript, as well as supervised the project. H.S. assisted in investigation, subject consent and writing of the original draft. A.B. and C.R. obtained informed consent of subjects, and curated data, as well as assisted in review of the original draft of manuscript.

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### Data availability

The raw de-identified data are available for review upon expressed written consent from the corresponding author, A.C.S.

### Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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