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Investigating the Relationship between Abnormal Uterine Bleeding and Insulin Resistance

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Abstract: Abnormal Uterine Bleeding (AUB) is a popular gynecological disease whose etiology is multifactorial, which includes metabolic dysregulation. The main study aim was to test the correlation between AUB subtypes and IR, with the hypothesis that IR is higher and more severe in AUB patients, especially those with heavy menstrual bleeding or comorbid with PCOS. The second set of objectives included the investigation of metabolic indicators (glucose, insulin) and the identification of independent predictors of AUB in a multivariate model**. Method:** This study was a cross-sectional analysis of 135 patients. We summarized all clinical outcomes of AUB subtypes and the prevalence of IR (HOMA-IR ≥ 2.5). The chi-square and ANOVA statistics were used to test the association between IR severity and AUB subtype. T-tests were used to compare metabolic markers, and multivariate logistic regression was done to correct for the effect of age and smoking. PCOS and non-PCOS patients were analyzed using a subgroup to compare the characteristics of the patients regarding their symptoms**. Findings:** IR was common among 54.1% of the participants, and much higher between AUB subgroups (heavy bleeding). AUB was also independently related to IR (adjusted OR=2.1, p=0.01). PCOS exacerbated IR risk (73.8% vs. 45.2%, p<0.001). AUB patients had a greater level of metabolic derangements (elevated glucose, insulin) (p<0.05). Multivariate analysis proved that IR is a predictor of AUB, as well as age and PCOS. Symptoms that were reported by patients (e.g., fatigue) were related to IR status**. Conclusion:** The research highlights the presence of a strong correlation between AUB and IR, regardless of the presence of PCOS, with metabolic dysregulation being a possible mechanism to support this association. The prevalence of IR is high in AUB subgroups, especially heavy bleeding, which indicates the need to screen the patients to avoid metabolic dysfunction.

Keywords: Abnormal uterine bleeding; age; polycystic ovary syndrome; and fasting insulin (μiu/ML).

INTRODUCTION

Abnormal Uterine Bleeding (AUB) is a condition that has abnormal menstrual patterns which is not observed to be normal [Faulds, M. H. *et al*., 2012]. It involves various problems, such as heavy menstrual bleeding (menorrhagia), irregular menstruation, and bleeding intervals. AUB should be understood because it affects a large number of women and can greatly have an influence on their quality of life quality [Lacey Jr, J. V. *et al*., 2009]. AUB is caused by a number of factors that can be blamed on hormonal imbalances, abnormalities in the uterus, medical complications, or some medications [Hecht, J. L., & Mutter, G. L. 2006]. A popular cause is hormone changes, especially of estrogen and progesterone, as in conditions such a condition as Polycystic Ovary Syndrome (PCOS). In addition, the menstrual cycle may become even more complicated by systemic factors, including thyroid disorders or medications. [Hecht, J. L., & Mutter, G. L. 2006]

Insulin resistance (IR) is a metabolic disorder; the cells in the body do not react to insulin as much, so that blood sugar levels increase [Zhang, Y. *et al*., 2010]. Such aspects as obesity, unhealthy lifestyle, hereditary tendencies, and unhealthy eating are the main causes of insulin resistance. Body weight is a major risk factor, especially when it is overweight, especially around the abdomen, because it might lead to an elevation of insulin and increased secretion of androgens, which can interfere with the normal hormonal balance [Mumusoglu, S., & Yildiz, B. O. 2020]. This interference is very vital to the health of women, especially in regard to the normalcy of their menstrual cycle and the overall reproductive capacity. [Amant, F. *et al*., 2005]

The AUB and insulin resistance relationship has been receiving growing interest over the past few years, particularly in women with PCOS. Increased insulin may result in disturbed hormonal responses with disrupted menstrual cycles and added to the AUB symptoms [Cust, A. E. *et al*., 2007]. The hormonal milieu in the female with insulin resistance is also changed, which, in most cases, leads to an increase in the number of male hormones, also increasing the abnormalities in the bleeding [Expert Panel on Detection, Evaluation, 2001]. Moreover, the conditions are often associated with the presence of metabolic syndrome, which involves the signs of obesity, high blood pressure, and dyslipidemia. Therefore, women who experience the combination of both AUB and insulin resistance can have complicated health risks, such as the possibility of contracting other diseases, such as type 2 diabetes and

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cardiovascular diseases. [Furberg, A. S. *et al*., 2005]

It is demonstrated that in teens having PCOS characteristics, a chronobiological defect in LH secretion exists, which causes the LH peak to be shifted away as in the morning to afternoon [Furberg, A. S., & Thune, I. 2003]. This modification helps to prove that one of the focal points of the pathogenesis of this syndrome is the hypothalamic-pituitary area. This is an indication that tonic increase in LH secretion is not a primary occurrence but the outcome of androgen stimulation. Hyperinsulinemia can be used to clarify, at least partially, the rise in LH secretion [Bandera, E. V. *et al*., 2007]. It is possible that hyperinsulinemia can lead to PCOS since it enhances LH secretion; promotes ovarian androgen synthesis, either independently or in combination with LH; suppresses SHBG activity; suppresses IGFBPs; and promotes ovarian growth and cysts development in a synergistic relationship with LH [Lindemann, K. *et al*., 2009]. The synergistic impact of high LH and hyperinsulinemia induces stromal luteinization, which results in mild hyperandrogenism, which, consequently, results in follicular atresia. [Nikbakht, R. *et al*., 2021]

AUB should be managed holistically in the face of insulin resistance. The lifestyle changes are of paramount importance and involve dietary changes to decrease insulin concentration and to increase the amount of physical activity. The weight loss has been revealed to cause a significant increase in insulin sensitivity and can reduce the symptoms of AUB [Nikbakht, R. *et al*., 2021]. In some instances, hormonal treatment, such as birth control pills, may help to balance menstrual cycles and heavy bleeding. Insulin resistance and AUB have also been treated using medications such as metformin, which enhance insulin sensitivity. Frequent observation of the level of sugar level, menstruation, and general health are required to provide early intervention and improved results. [Abraham Gnanadass, S. *et al*., 2021]

METHOD

Study Design and Setting

In this study, the cross-sectional design was used in order to examine the possibility of a correlation between abnormal uterine bleeding (AUB) and insulin resistance (IR). The study was carried out at the outpatient gynecology and endocrinology departments in the period from July 2022 to July 2023. The cross-sectional design was chosen as a suitable approach of the first type to determine prevalence and define relations between these conditions in a specified clinical population at one time.

Study Participants

A consecutive sample of 135 premenopausal women (aged 24-39 years) who came with a primary complaint of abnormal uterine bleeding (AUB) according to the FIGO PALM-COEIN classification system was recruited. Women who were pregnant or lactating, six months after childbirth, known to have uterine malignancy, severe systemic disease (uncompensated thyroid, hepatic, or renal disorders), or taking medications that were known to have significant effects on glucose metabolism (metformin, glucocorticoids) or hormonal contraception/IUDs within the previous 3 months were excluded. A control population of 43 age-matched premenopausal women without AUB who presented themselves to the clinic with routine checkups or non-bleeding related problem (e.g. cervix cancer screening) was also recruited to act as controls.

DATA MEASURES AND DATA COLLECTION.

A structured proforma with three basic components was used in the collection of data:

Clinical and Anthropometric Assessment: It was a comprehensive interview wherein demographic data, menstrual history (characterization of AUB subtype: heavy menstrual bleeding, intermenstrual bleeding, prolonged bleeding, and amenorrhea), obstetric history, and symptoms suggestive of PCOS or metabolic dysfunction (fatigue, hirsutism) were collected. Polycystic Ovary Syndrome (PCOS) was defined based on the Rotterdam criteria, which required that the patient should have at least two of the following elements: oligo/anovulation, clinical/biochemical hyperandrogenism, and polycystic ovaries on ultrasound.

Biochemical Evaluation: All the participants had their venous blood sampled after 10-12 hours of an overnight fast. The standard laboratory procedures (glucose oxidase method and electrochemiluminescence immunoassay) were used to determine fasting plasma glucose (FPG) and fasting insulin (FI) in the serum. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was used to measure insulin resistance, which was calculated as

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[Fasting Insulin (μIU/mL) Fasting Glucose (mg/dL)/405]. The cutoff threshold of 2.5 was taken as the presence of IR, as determined by the study population demographic cutoffs.

Ultrasonographic Evaluation Each of the participants had a transvaginal or transabdominal ultrasound to determine the structure of the uterus and the thickness of the endometrium, as well as to determine the ovarian morphology to diagnose PCOS by Rotterdam criteria.

Statistical Analysis

The analysis of data was done in SPSS version 24.0. Continuous variables were reported in the form of mean, SD, and categorical variables in the form of frequencies and percentages. Continuous variables were compared by independent samples t -tests or Mann-Whitney U tests (according to necessity) to compare the differences between groups (AUB+ vs. AUB-; IR+ vs. IR-). The association between AUB (dependent variable) and the different predictors, including IR, was assessed with multivariate binary logistic regression analysis with consideration of the possible confounding variables, namely, age, BMI, and smoking status. The results were presented in terms of Odds Ratios (OR) with 95% confidence intervals (CI). All analyses were deemed to be significant at a two-tailed p-value of less than 0.05.

FINDINGS

Table 1. Enroll the Clinical outcomes of patients at the hospital.

Variables	Findings of patients [n = 135]
Age (years), mean ± SD	32.5 ± 7.2
BMI (kg/m²), mean ± SD	28.6 ± 5.1
Parity (≥1)	89 (65.9%)
Smokers	27 (20.0%)
PCOS Diagnosis	42 (31.1%)
ASA %	
II	80 (59.26%)
III	55 (40.74%)
Comorbidities	
Hypertension	34 (25.19%)
Diabetes	22 (16.3%)

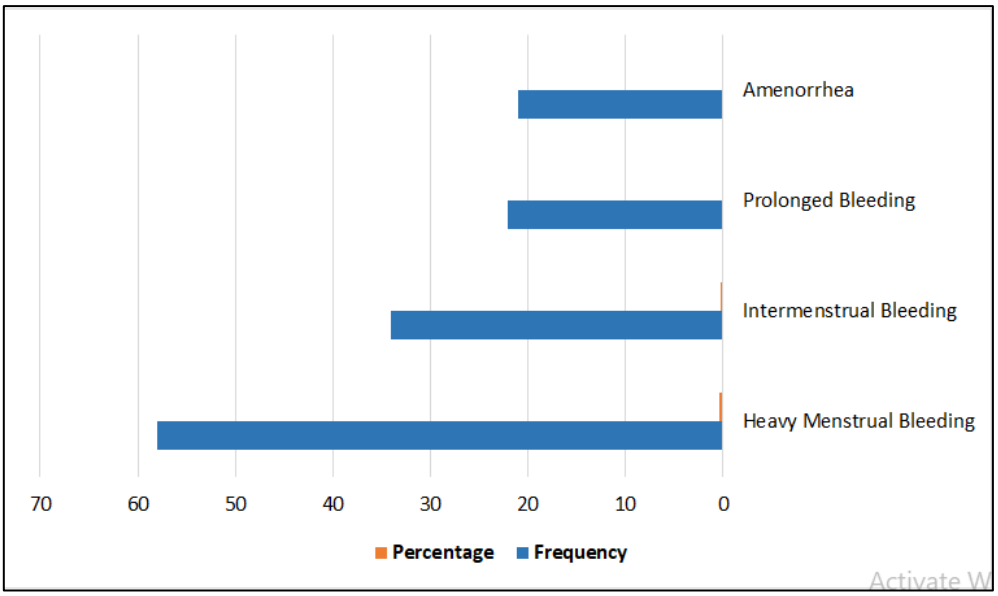

Figure 1. Determining the frequency of abnormal uterine bleeding types into patients.

Table 2. Evaluate diabetes prevalence (HOMA-IR 2.5 and over).

Existence of insulin resistance	Frequency	Percentage
IR Present	73	54.1%
IR Absent	62	45.9%

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Table 3. Identifying the extent of the correlation between abnormal uterine bleeding and insulin resistance in patients.

The existence of abnormal uterine bleeding	IR+ (n=73)	IR− (n=62)	p-value
Yes (n=92)	54 (58.7%)	38 (41.3%)	0.03
No (n=43)	19 (44.2%)	24 (55.8%)	

Table 4. Distribution the severity of insulin resistance according to abnormal uterine bleeding types.

AUB Types	HOMA-IR (mean ± SD)	p-value
Heavy Menstrual Bleeding	3.1 ± 1.2	0.01
Intermenstrual Bleeding	2.8 ± 1.0	0.04
No AUB	2.0 ± 0.8	—

Table 5. Classification of metabolic indicators based on abnormal uterine bleeding status.

Indicators	AUB+ (n=92)	AUB− (n=43)	p-value
Fasting Glucose (mg/dL)	98 ± 12	92 ± 9	0.02
Fasting Insulin (µIU/mL)	15.2 ± 6.1	10.4 ± 4.3	<0.001

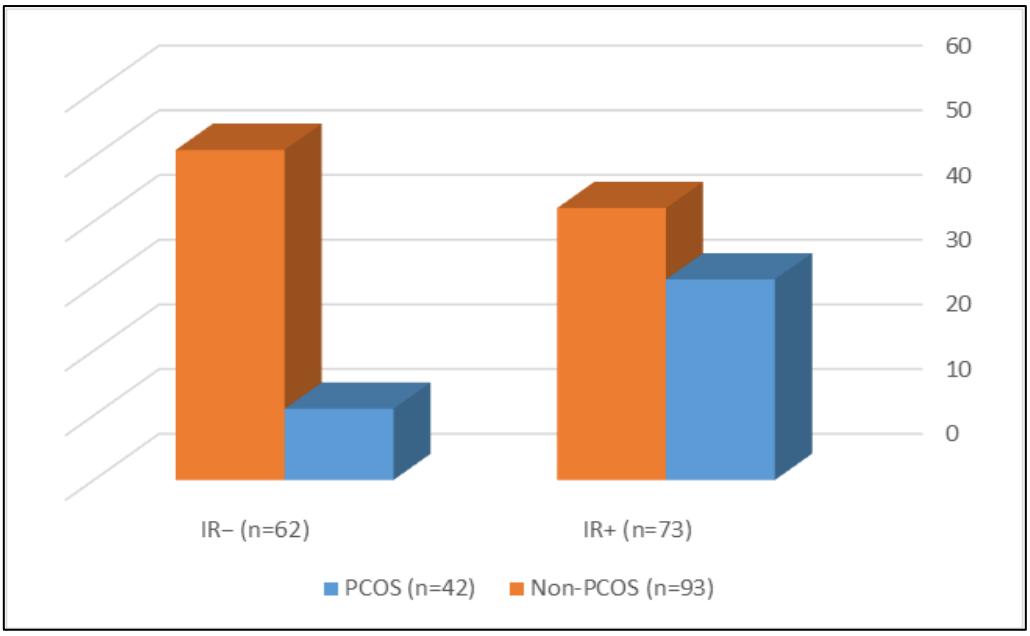

Figure. 2. Establishing the distribution of insulin resistance into both groups according to polycystic ovary syndrome (PCOS).

Table 6. Multivariable logistic regression performing in the prediction of abnormal uterine bleeding risk factors.

Variable	OR	95% CI	p-value
IR (HOMA-IR ≥2.5)	2.1	[1.2–3.8]	0.01
BMI ≥30	1.8	[1.0–3.2]	0.05
PCOS	2.5	[1.3–4.9]	0.006

Table 7. Assessment the clinical outcomes of patient-reported symptoms based on insulin resistance.

Symptoms	IR+ (n=73)	IR− (n=62)	p-value
Fatigue	58 (79.5%)	35 (56.5%)	0.004
Acanthosis Nigricans	27 (37.0%)	8 (12.9%)	0.001

DISCUSSION & CONCLUSION

This was clinical research that examined the clinical records of 135 patients in assessing the relationship between abnormal uterine bleeding and insulin resistance. The fact that 54.1 percent of respondents had IR (HOMA-IR 2.5 and above) confirms that there was a high prevalence of metabolic disturbance among such an AUB cohort, far more prevalent than the general population estimates of the same age groups. Other reports reported more incidence of hyperinsulinemia and IR in women with menstrual irregularities than

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eumenorrheic controls. [Aldossary, K. *et al*., 2020; Brower, M. *et al*., 2013]

The sizeable correlation between the existence of AUB and IR (p=0.03) and the independent predictive worth of IR with AUB following the modifications of confounders (OR=2.1, p=0.01). This implies that IR is not just a comorbidity, but it might contribute to the pathogenesis of AUB in a mechanistic manner. Pathophysiological connection is probably the hyperinsulinemia. High levels of insulin may increase the production of ovarian theca cells androgens and reduce the production of sex hormone-binding globulin (SHBG) in the liver, leading to the production of more bioavailable androgens and estrogens [Carmina, E., & Lobo, R. A. *et al*., 2004; Ding, T. *et al*., 2017; Dumesic, D. A. *et al*., 2001]. This changed sex steroid environment may interfere with the hypothalamic-pituitary-ovarian axis, resulting in anovulation or oligo-ovulation, which is a frequent cause of AUB. Moreover, insulin and insulin-like growth factors might directly stimulate endometrial growth, which might be a cause of abnormal shedding and heavy menstrual bleeding (HMB). Our mean HOMA-IR findings was found in the HMB subtype (3.1 ± 1.2) and had the greatest statistical significance (p=0.01). [Dumesic, D. A., & Richards, J. S. 2013; Ezeh, U. *et al*., 2021]

Moreover, the high metabolic disarrays of the AUB patients are further reinforced with the fact that the levels of fasting glucose and insulin are quite high relative to controls. In our multivariate analysis, both independent predictors, IR and PCOS, had a positive association with PCOS, exhibiting a stronger relationship (OR=2.5). We also found that 73.8 percent of PCOS patients in our cohort resisted insulin as compared to 45.2 percent of the non-PCOS patients (p<0.001). This suggested a role of IR as a main cause of AUB symptoms in women with PCOS but as a secondary influence in women with non-PCOS by means of less pronounced endocrine abnormalities. [Garzia, E. *et al*., 2022; Harris, H. R. *et al*., 2017; Hatziagelaki, E. *et al*., 2020]

Clinical correlates of the biochemical data was provided by our results of patient-reported symptoms. The overwhelmingly better prevalence of fatigue and acanthosis nigricans in the IR+ group not only confirms our HOMA-IR classification but also highlights the multisystemic effect of IR [Jeanes, Y. M., & Reeves, S. *et al*., 2017]. Acanthosis nigricans is also another skin manifestation of excessive insulin levels, and the fact that it is associated with our core results strengthens the biological validity of the latter. The rates of fatigue reported by the IR+ women were the highest (79.5%), which could be explained by the overall systemic metabolic load, which might affect the quality of life, and the need to consider it in a holistic approach [Louwers, Y. V., & Laven, J. S. 2020].

To be conclude, the research proves that abnormal uterine bleeding (AUB) and insulin resistance (IR) have a strong connection in the studied sample. Over 54.1 percent of the respondents had IR, with a significantly higher prevalence rate among the respondents who had AUB, especially the heavy menstrual bleeding type. It was found that IR was positively related to AUB with confounding variables, which means that it could be a contributing factor through metabolic means. Moreover, it was discovered that polycystic ovary syndrome (PCOS) is a very potent effect modifier, which significantly increases the risk of IR. The co-occurrence of AUB and PCOS can determine a group of patients with severe metabolic impairment.

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