RESEARCH ARTICLE

Elevated Progestin-Related Immunoreactivity is Positively Associated with Bleeding Severity in Women with Intramural Uterine Fibroids

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Abstract

BACKGROUND: Uterine fibroids is an intentional cause of recurrent uterus bleeding. As a synthetic progestin, medroxyprogesterone acetate (MPA) is sequentially used as a medication for extensive uterine bleeding and have been broadly studied in gynecological field research. However, its role as a serum hormonal marker in fibroid-related bleeding remains poorly elucidated. Therefore, current study was conducted to evaluate serum progestin-related immunoreactivity (PRI) as biochemical parameter to examine its relation with the severity of bleeding in patients suffering from intramural uterine fibroids obtained among different menopausal statuses.

METHODS: A cross-sectional study including 90 individuals with intramural uterine fibroids was conducted. Subjects were classified into a reproductive-age and post-menopausal. Blood samples were collected for biochemical parameter analysis, and clinical as well as anthropometric assessments were performed. MPA, serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and Vitamin D3 were determined using enzyme-linked immunosorbent assay (ELISA). While fasting blood glucose (FBG) levels were determined using the glucose oxidase–peroxidase.

RESULTS: Circulating PRI, represented by MPA concentration, was markedly elevated in reproductive-age with mean of 4.57±1.45 compared with the postmenopausal group (1.30±0.59). In reproductive-age subjects, PRI levels showed a significant $p<0.001$ positive and strong association in comparison to bleeding duration, fibroid mass size, bleeding severity and body mass index (BMI) with r-values of 0.72, 0.53, 0.57, 0.67 respectively. A significant $p<0.001$ associations in postmenopausal group were seen between PRI and bleeding duration, bleeding severity, and BMI with r-values of 0.66, 0.53, 0.70 in that order. By contrast, the correlation between FBG and PRI was weak in both study groups, indicating a limited association between FBG and PRI.

CONCLUSION: This study demonstrates that higher levels of PRI markedly linked with increasing severity of bleeding and longer bleeding duration in patient with intramural uterine fibroids across both study group, indicating that PRI levels reflects progestin-related immunoreactive signals associated with fibroid-related bleeding severity therefore might be potential as biochemical parameter.

KEYWORDS: medroxyprogesterone acetate, intramural fibroids, uterine bleeding, reproductive age, postmenopause

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Introduction

Uterine fibroids is the most abundant tumors found in females, which trigger the female reproductive system and are described by uterine smooth muscle with high proliferation of cells.(1,2) Intramural fibroids are most likely observed with uterine bleeding pelvic pain, infertility, and anemia, specifically in patients who represent the greatest distribution of fibroid subtypes.(1–3) The pathophysiological mechanisms, in addition to their current understanding that fibroid-related bleeding severity has

been poorly understood. Prolonged and excessive menstrual bleeding is the main phenomenon of elevated fibroid burden, and disruption of proper endometrial architecture.(4,5)

Expansion of uterine fibroids is significantly affected by hormonal regulation, and this aspect plays an essential role in the progesterone-related signaling pathways progressively known as fibroid growth and bleeding patterns key contributors. In endometrial proliferation and vascular morphology, progestins play an essential regulatory role. Another important aspect is inflammation, which makes it a clinically important target in the management and treatment of fibroids as a source of uterine bleeding. Medroxyprogesterone acetate (MPA) is sequentially used in gynecologic practice as a synthetic progestin for the medication of extensive uterine bleeding.(6,7) The circulating MPA levels usually reflect the measured progestin-related immunoreactivity (PRI). Several studies have shown that MPA subsequent to exogenous administration, but regarding whether MPA is independent of therapeutic exposure and its importance of progesterone (progestin-related hormonal) or progestin-related immunoreactive signals in fibroid-associated bleeding remains insufficiently investigated.(8,9)

In hormone-dependent tumors, progesterone receptor–mediated pathways play an important role in fibroid development, which leads to abnormal bleeding, in addition to extracellular matrix accumulation, and symptom expression. Evidence shows that abnormal bleeding in fibroids is driven by progesterone signaling, not just estrogen. This suggests the needs to move beyond the traditional focus on estrogen alone when studying or treating fibroids. (10–12) In contrast, there is little information available to study it potential as a serum biochemical parameter that reflect progesterone activity and also distinguishes between the severity of bleeding in both reproductive-age and postmenopausal patients.(8,13,14)

In addition to PRI, several hormonal and metabolic parameters are mostly evaluated to better characterize the clinical and physiological context of a study population. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are measured as key reproductive hormones to confirm menopausal status and to reflect endocrine differences between reproductive-age and postmenopausal women.(10,11) Meanwhile fasting blood glucose (FBG) is often assessed to account for potential metabolic influences that could affect hormonal parameters. Vitamin D levels are also able to provide additional information regarding the metabolic status of the patients.(15)

Therefore, current study was conducted to evaluate serum PRI as biochemical parameter to examine its relation with the severity of bleeding in patients suffering from intramural uterine fibroids across different menopausal statuses. This biomarker may underscores that PRI represents an advancement beyond previous outcomes that focused on therapeutic results.

Methods

Subjects Recruitment

Ninety patients diagnosed with uterine fibroids, aged 25-65, were included in the current study. Subjects were recruited from November 2024 to February 2025 at Al-Alawiya Teaching Hospital, Baghdad, Iraq. Inclusion criteria involved woman patients with intramural uterine fibroids diagnosed by pelvic ultrasonography (USG). Subjects with cardiovascular disease (CVD), polycystic ovary syndrome, osteoporosis, diabetes mellitus, or other metabolic and/or endocrine disorders, were excluded. Individuals with recent or current use of MPA or any progestin containing therapy (oral or subcutaneous progestins), in addition to hormonal therapy, were also excluded.

The included subjects were then divided into two groups: reproductive-age women aged 25-45 years (n=45) and post-menopausal women aged 46-65 years (n=45). Blood samples of reproductive-aged group were taken on the 3rd day of their menstrual cycles. Meanwhile for post-menopausal subjects, with there was no set time for when blood samples collection. The protocol of the current study was ethically approved, and all paticipant have provided written informed consent before participating. To minimize selection bias, subjects were enrolled consecutively.

MPA and Vitamin D Enzyme-linked Immunosorbent Assay (ELISA)

Samples were collected at 8 hours of overnight fasting, and the serum aliquots were stored at stored at −20°C until time of assay. Serum MPA that represent the PRI level was determined using Human MPA using ELISA kit (Cat. No. MBS9349818; MyBioSource, San Diego, CA, USA). Blank, standard, and serum samples wells were prepared by adding 50 µL aliquot of samples or standards to wells, followed by 100 µL of conjugated horseradish peroxidase (HRP) to all except blank wells, next step involved for incubation for 60 min ant 37°C. After 4 washing cycles, 50 µL of chromogen solutions were added to all wells and incubated for 15 min at 37°C in darkness. Fifty µL stop solution was added, and the optical density was measured at 450 nm by using an ELISA reader. The assay detection range and sensitivity

was at 0.625–20 ng/mL and 0.1 ng/mL, respectively. The assay was intended to detect antibody-based PRI rather than structurally distinct endogenous hormones.(14,15) The obtained results reflect immunoreactive progestin-related signals detected and do not represent structurally confirmed endogenous MPA levels.(16) PRI was determined without influenced by therapeutic agents related confounding, due to that none of participants had received MPA or any progestin therapy before sample collection.

ELISA analysis was also performed using the collected serum for Vitamin D measurement. The serum Vitamin D3 concentrations were measured using a Human Vitamin D3 (VD3) ELISA kit (Cat. No. MBS9713731; MyBioSource) according to the manufacturer's instructions, which was similar to what have been performed for the measurement of MPA.

FSH, LH, and FBG Measurements

Other than MPA an Vitamin D concentration, the collected serum was also used for the measurement of hormonal parameters and blood glucose. Serum FSH and LH concentrations were measured using fluorescence immunoassay (FIA) method using commercially available kits (Cat. No. REF CFPC-35; i-CHROMA™, Boditech Med, Gangwon-do, South Korea and Cat. No. REF 13010; i-CHROMA™, Boditech Med, respectively) according to the manufacturer's instructions.

Meanwhile, the FBG levels were determined using the enzymatic colorimetric method of glucose oxidase peroxidase (GOD) based on the oxidation of glucose principle (17) with commercially available reagent kits (Cat. No. REF 87409; BIOLABO, Maizy, France). The FBG levels represented a continuous metabolic parameter rather than as a diagnostic indicator of diabetes.

Clinical and Anthropometric Assessments

Physiological parameter such as bleeding severity and duration of uterine, obtained during interviews of patient. Uterine fibroid mass was estimated by pelvic USG and fibroid spots were calculated by multiplying the peak of longitudinal and transverse diameters measured by ultrasound. Body mass index (BMI) was calculated, in accordance with standard anthropometric guidelines. Bleeding time was reported as the number of bleedings during days for each patient under study. According to the bleeding duration, its severity was classified as moderate (≤5 days), severe (6-8 days), and very severe (≥9 days).

Results

USG Characteristics of Intramural Uterine Fibroids

Intramural uterine fibroids were confirmed by pelvic USG performed by an experienced gynecologist. The diagnosis was based on the identification of well-defined intramural uterine masses with heterogeneous echotexture located within the myometrium. Compared with post-menopause group, the reproductive-age subjects exhibited significantly greater fibroid mass dimensions, which indicated more pronounced structural involvement in G1 group (Supplementary 1, Supplementary 2).

Distinct Metabolic and Hormonal Profiles between Reproductive-age and Post-menopausal Subjects

Both study groups represent a significant variation in demographic, metabolic, and hormonal parameters, supporting stratification for subsequent analysis as presented in Table 1. The mean age, BMI, FBG, FSH, and LH, in the post-menopause subjects were significantly higher compared

Table 1. Demographic and clinical characteristics in reproductive-age and postmenopausal subjects.

Variable	Mean±SD		*p*-value
	Reproductive Group (n=45)	Postmenopausal Group (n=45)	
Age (years)	35.36±6.81	58.51±5.89	<0.001
BMI (kg/m²)	23.08±3.55	26.74±5.61	<0.001
FBG (mg/dL)	81.47±9.48	98.6±12.38	<0.001
FSH (mlU/mL)	4.65±2.00	14.14±1.02	<0.001
LH (mlU/mL)	4.73±2.35	45.68±15.04	<0.001
Vit D3 (ng/mL)	35.11±3.45	32.62±2.72	<0.001

Data are presented as mean±SD. Group comparisons were conducted using the independent samples T-test after confirmation of normal data distribution (Shapiro–Wilk test). Significant if $p<0.05$.

to the reproductive-age subjects (all $p<0.01$). Meanwhile, Vitamin D3 levels showed a narrower distribution with generally lower concentrations in post-menopausal subjects (35.11±3.4511 *vs.* 32.62±2.716 ng/mL, respectively). These patterns highlight distinct metabolic and hormonal profiles associated with reproductive status.

Distinct Difference of Fibroid size, Bleeding Duration and MPA Levels

MPA status and bleeding records significant differences across reproductive-age and post-menopause groups. The ELISA analysis results exhibited significantly higher serum MPA in reproductive-age with mean of 4.57±1.45 in comparison to post-menopause subjects that records value of 1.3±0.59 with $p<0.01$, indicating higher PRI levels in reproductive-age subjects. Similar results were observed in the bleeding duration and fibroid sizes. Subjects in reproductive-age group showed longer bleeding duration and larger fibroid sizes compared to post-menopausal subjects (all $p<0.01$) (Table 2).

Higher PRI was Associated with Increased Bleeding Severity

Based on correlation analysis results, higher MPA levels were linked with longer duration of bleeding and its severity in both study groups (all $p<0.001$) (Table 3). The reproductive-age group indicated a significantly greater proportion of super severe bleeding cases (73.3%) compared with post-menopausal subjects. Meanwhile, moderate bleeding was more frequently observed in post-menopausal subjects (42.2%) compared to the reproductive-age group (Figure 1). The reproductive-age group indicate a markedly greater fibroid mass sizes and extended bleeding durations in comparison to the post-menopausal subjects, thereby the relation among elevated serum MPA levels and bleeding severity. These findings indicated a strong association was found between a high level of MPA and elevated bleeding severity, specifically in reproductive-age subjects (all $p<0.01$).

PRI was Positively Correlated with Clinical Variables

Correlation coefficient analysis demonstrated marked positive relationships between serum PRI and clinical assessments in both study groups (Table 3, Figure 2). In the reproductive-age, PRI levels showed a significantly strong ($p<0.001$) and positive correlations with duration of bleeding , fibroid size, bleeding severity and BMI with r-values of 0.72, 0.53, 0.57, and 0.67 respectively. In the reproductive-age subjects, serum PRI showed a significantly moderate and positive correlation with FBG (r=0.35). In post-menopausal subjects, the association between PRI and FBG was weak but statistically significant with r-value of 0.20. Additionally, PRI was significantly correlated ($p<0.001$) and have positive association with duration of bleeding, fibroid size, bleeding severity and BMI with r-values of 0.66, 0.43, bleeding severity 0.53, and 0.70.

Regression Analysis of PRI Predictors

Multiple linear regression analysis was performed to identify independent predictors of PRI in both groups understudy as illustrated in Table 4. In reproductive-age group, bleeding score, fiboid size, and BMI with β-values of 0.32,0.53, and 0.67, respectively, which emerged as significant independent predictors of PRI. FBG showed a weak but statistically significant contribution (β=0.12, $p<0.001$), while age didn't showed a significant association.

In the postmenopausal subjects, bleeding score were statistically significant ($p<0.001$) and had a greatest

Table 2. MPA level and bleeding characteristics in reproductive-age and postmenopausal subjects.

Variable	Reproductive Group (n=45)	Postmenopausal Group (n=45)	*p*-value
MPA Level (ng/mL), mean±SD	4.57±1.45	13.00±0.59	<0.001
DB (days), mean±SD	9.18±1.42	5.44±0.69	<0.001
BS (categorized), n (%)			
Very severe	33 (73.3)	9 (20.0)	<0.001
Severe	7 (15.6)	17 (37.8)	
Moderate	5 (11.1)	19 (42.2)	
FS (cm^2), mean±SD	5.00±1.38	2.89±0.71	<0.001

Continuous variables are presented as mean±SD and were compared between groups using the independent samples t-test after confirmation of normal data distribution (Shapiro–Wilk test). Categorical variables were compared using the chi-square test. Significant if $p<0.05$. DB: durations of bleeding; BS: bleeding severity; FS: fibroid size.

Table 3. Correlation between the clinical variables and serum MPA levels in reproductive-age and postmenopausal subjects.

Parameter	r	*p*-value
DB (days)		
Reproductive Group	0.72	<0.001
Postmenopausal Group	0.66	<0.001
FS (cm)		
Reproductive Group	0.53	<0.001
Postmenopausal Group	0.43	0.010
BS (Score)		
Reproductive Group	0.57	<0.001
Postmenopausal Group	0.53	<0.001
BMI (kg/m^2)		
Reproductive Group	0.67	<0.001
Postmenopausal Group	0.70	<0.001
FBG (mg/dL)		
Reproductive Group	0.35	<0.001
Postmenopausal Group	0.20	<0.001

Correlation coefficients (r) and corresponding *p*-values with MPA level were calculated using Pearson's correlation analysis. Significant if $p<0.05$. DB: durations of bleeding; BS: bleeding severity; FS: fibroid size.

independent association with serum PRI (which was represented by the MPA level), fibroid size and BMI with β-values of 1.20, 0.52, and 0.73 respectively. In contrast, FBG exhibited a minimal independent effect (β=0.04, $p<0.001$) (Table 4). These findings indicate that clinical and anthropometric parameters, rather than glycemic status, are the primary independent contributors to elevated PRI, particularly in the postmenopausal subjects.

Discussion

The present study investigated the association between circulating PRI, detected using an antibody-based MPA ELISA assay, and the severity of bleeding in women with intramural uterine fibroids across different menopausal statuses. Strong association of elevated PRI with increased bleeding severity, longer bleeding duration, larger fibroid size, and higher BMI in both reproductive-age and postmenopausal women suggest that PRI may reflect progesterone-responsive biological activity associated with fibroid-related bleeding severity rather than exposure to exogenous MPA.

The positive association between PRI levels and fibroid size was in consistent with previous investigations demonstrating the important role of progesterone signaling in the development and progression of uterine fibroids. Progesterone-mediated pathways contribute significantly to fibroid growth and symptom development.(3) Similarly, activation of progesterone receptors stimulates fibroid cell proliferation and extracellular matrix accumulation within uterine tissue.(7) In addition, another study also demonstrated that progesterone signaling contributes to vascular remodeling within fibroid tissue, which may influence abnormal uterine bleeding.(8)

The strong positive correlation between PRI levels and bleeding severity was also supported by previous studies examining the role of progestogens in endometrial physiology. Progestogens regulate endometrial vascular stability and tissue remodeling, processes that may directly influence menstrual bleeding patterns.(18) Furthermore, progestogens also can alter endometrial morphology and vascular responsiveness, thereby contributing to abnormal uterine bleeding in hormonally responsive tissues.(12) The use of molecular and biochemical biomarkers has been increasingly explored to improve the understanding of disease mechanisms and clinical outcomes in biomedical research. Similar biomarker-based approaches have also been applied in recent studies investigating cellular signaling pathways and disease progression.(19)

Another important observation in the present study was the significantly higher PRI levels detected in

Figure 1. Sankey diagram illustrating the distribution of bleeding severity categories between reproductive-age and postmenopausal subjects. Bleeding severity (BS) was categorized as: 2=Moderate, 3=Severe, and 4=Very Severe. The width of each flow represents the proportion of participants transitioning between severity categories across the two study groups.

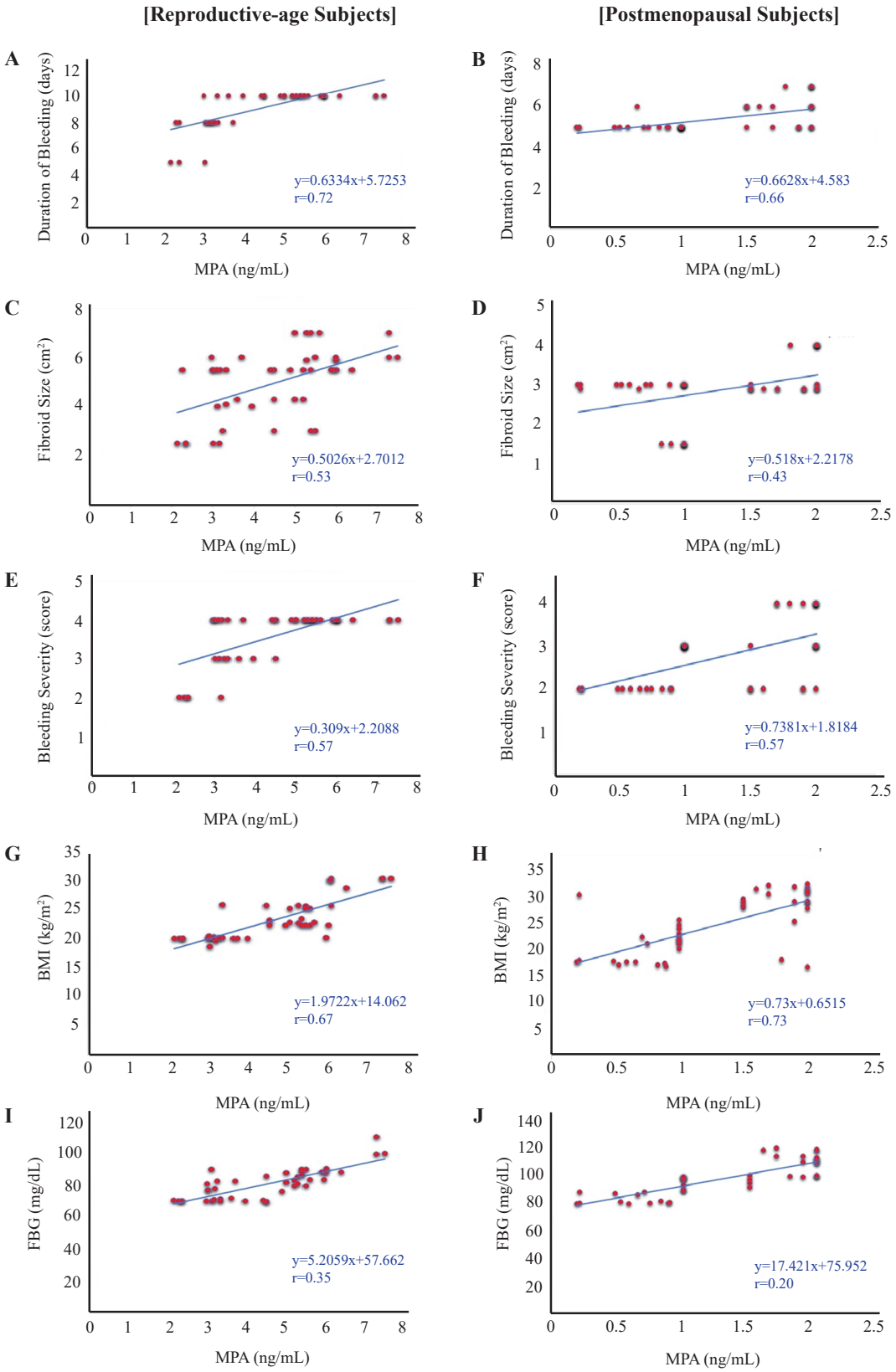

Figure 2. Correlation between serum MPA levels and clinical parameters in reproductive-age and postmenopausal subjects with intramural uterine fibroids. Scatter plots show linear correlations between serum MPA concentrations and duration of bleeding (A,B), fibroid size (C,D), bleeding severity score (E,F), BMI (G,H), and FBG (I,J) in reproductive-age (left) and postmenopausal (right) subjects. Lines represent least-squares regression fits, and r represent the correlation coefficients. All variables are significantly correlated with $p<0.05$.

Table 4. Regression analysis between study parameters in reproductive-age and postmenopausal subjects and fibroid-associated bleeding.

Parameter	β coefficient	95% CI	*p*-value
BS (Score)			
Reproductive Group	0.32	0.22–0.43	<0.001
Postmenopausal Group	1.20	0.99–1.42	<0.001
Age (year)			
Reproductive Group	1.25	-0.08–2.58	0.066
Postmenopausal Group	0.24	-0.63–5.37	0.110
FS (cm^2)			
Reproductive Group	0.53	0.25–0.75	<0.001
Postmenopausal Group	0.52	0.18–0.86	0.010
BMI (kg/m^2)			
Reproductive Group	0.67	0.36–1.77	<0.001
Postmenopausal Group	0.73	0.06–0.79	<0.001
FBG (mg/dL)			
Reproductive Group	0.12	0.09–0.15	<0.001
Postmenopausal Group	0.04	0.03–0.05	<0.001

Regression coefficients (β), 95% confidence intervals (CI), and corresponding *p*-values were calculated using multiple linear regression analysis.

reproductive-age women compared with postmenopausal women. This difference likely reflects the distinct hormonal environments between these groups. Reproductive-age women exhibit active ovarian steroid production and cyclic progesterone secretion, which may enhance progesterone-responsive signaling pathways in fibroid tissue. Similar observations have been reported earlier that progesterone-related pathways play a major role in fibroid development and symptom expression in hormonally active women.(20)

Interestingly, although PRI levels were lower in postmenopausal women, the association between PRI and bleeding severity remained significant. This observation suggests that uterine fibroids may retain local steroid responsiveness even after menopause. Previous studies have suggested that fibroid tissue can maintain sensitivity to steroid signaling independent of systemic hormone levels, indicating that local progesterone-related pathways may continue to influence fibroid behavior and bleeding patterns in postmenopausal women.(13)

The present study also found a significant positive association was observed between PRI levels and BMI in both study groups. This finding is consistent with previous observations that reported that obesity and metabolic disturbances can alter steroid hormone metabolism and bioavailability. Increased adiposity may modify peripheral steroid conversion and hormonal clearance, thereby indirectly influencing circulating immunoreactive hormonal signals.(13)

In contrast, FBG showed only a weak association with PRI levels in both reproductive-age and postmenopausal groups. This observation suggests that glycemic status may not be a primary determinant of PRI in women with uterine fibroids. It is important to note that patients with known diabetes mellitus, polycystic ovary syndrome (PCOS), and osteoporosis were excluded from the present study to minimize potential metabolic and endocrine confounding factors that could influence hormonal measurements. Therefore, the weak association observed between FBG and PRI likely reflects minor metabolic variability within a non-diabetic population rather than pathological alterations in glucose metabolism. Similar conclusions have been reported in previous studies examining metabolic influences on reproductive hormones.(6,12,13) The measurement of vitamin D partly supported the exclusion of patients with osteoporosis, which was one of the predefined exclusion criteria in the study design. Although vitamin D levels were not directly associated with PRI levels, previous studies suggested that vitamin D deficiency may contribute to fibroid development through mechanisms involving extracellular matrix remodeling, inflammation, and cellular proliferation.(21-23)

Unfortunately, the cross-sectional design of current study limits causal interpretation of the observed associations. In addition, the relatively modest sample size and single-center recruitment may restrict the generalizability of the findings. Another methodological limitation relates to the use of antibody-based immunoassays, which detect immunoreactive signals rather than structurally confirmed endogenous hormones. As reported by previous studies, immunoassay-based steroid measurements may be subject to

cross-reactivity with structurally related steroid molecules. (24-26) Future studies involving larger multicenter populations and advanced steroid profiling techniques such as mass spectrometry are required to further clarify the biological origin and clinical significance of circulating PRI in uterine fibroids. Longitudinal investigations may also help determine whether PRI could serve as a predictive biomarker for fibroid-associated bleeding severity.

Conclusion

In women whom suffering intramural uterine fibroids, elevated circulating PRI are positively linked with raised bleeding severity and longer bleeding duration in both reproductive-age and postmenopausal women. Reproductive-age showed greater PRI in comparison with postmenopausal women, reflecting differences in hormonal activity between the two physiological states. These findings demonstrate that circulating PRI is positively associated with the clinical severity of fibroid-related bleeding and may serve as a biochemical indicator reflecting disease severity in intramural uterine fibroids.

Authors Contribution

TAA and MJJ were involved in planning and concepting the proposal. MMS performed the data collection acquisition and analysis. TAA drafted and designed the figures. MJJ interpreted the results. All contributors took parts in giving critical revision of the current work and have approved the final draft.

Ethical Statement

The current study protocol was approved by the Iraqi Ministry of Health (Approval No. 10911/ع, dated 29 January 2024), and all procedures performed in this study were in accordance with the approved protocol. The research adhered to all the principles of the Declaration of Helsinki. Subjects provided written informed consent before participating.

Conflict of Interest

Authors declare no conflict of interest.

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