The Interplay between Serum Adipocytokines and the presence of Uterine Leiomyoma and the severity of the presenting manifestations

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Abstract

Background: Uterine leiomyomas (ULs) are common female genital tract tumors causing significant morbidity. Adipocytes produce adipocytokines that are implicated in chronic inflammation and tumorigenesis.

Objectives: To estimate serum levels of adipocytokines in women diagnosed with uterine leiomyomas and to evaluate their relation to the presence and severity of the presenting symptoms.

Patients and methods: 90 women were clinically evaluated and categorized according to transvaginal ultrasonography as study group (S) included women who had symptomatic ULs; positive control group (PC) included women with incidentally diagnosed ULs and negative control group (CN) included women free of ULs. Blood samples were obtained for ELISA estimation of the studied markers.

Results: Serum levels of leptin and TNF-α were significantly higher in S than CN ($P < 0.001$) and CP (< 0.001 & 0.0002, respectively) groups with significantly higher ($P = 0.0014$ & < 0.001, respectively) levels in CP than in CN group. Serum adiponectin levels were significantly ($P < 0.001$) lower in groups S and CP than in Group CN with insignificant ($P = 0.212$) differences between CP and S groups. There were significant correlations between the serum levels of the three cytokines and the presence and multiplicity of ULs and the presence and number of symptoms. The correlations were negative with adiponectin and positive with TNF-α and leptin.

Conclusion: Obesity and multigravidity may serve as risk factors for the development and symptomatic nature of ULs, related to serum leptin and adiponectin equilibrium disturbances and high TNF-α levels, that contribute to ULs pathogenesis.

Keywords: Uterine leiomyoma; Leptin; Adiponectin; Tumor necrosis factor-α.

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Introduction

Uterine leiomyomas (fibroids; ULs) are benign mesenchymal neoplasms that originate from smooth muscle and represent the most common tumors of the female genital tract **(Lugata et al., 2024)**. Uterine leiomyomata are hormone-dependent neoplasms that can cause significant gynecologic morbidity in the form of abnormal uterine bleeding, pelvic pain, and infertility **(Guo et al., 2024)**.

Despite the significant clinical impact of ULs, the mechanisms responsible for leiomyoma growth remain poorly understood **(McWilliams et al., 2024)**. Mutations in mediator complex subunit 12 are the most prevalent alterations in leiomyomas and are associated with tumor size and number of leiomyomas **(Äyräväinen et al., 2024)**. A review of the literature documented the multiplicity of risk factors in UL development but found obesity to be the strongest risk factor for fibroid development and high intake of fruit and vegetables and vitamin D to be the strongest protective factors **(Keizer et al., 2024)**.

Adipokines are secreted from adipocytes and resident immune cells within adipose tissues to mediate lipid metabolism and are implicated in chronic inflammation and tumor formation and growth **(Zhang et al., 2024)**. Adipocyte-secreted hormones through activation of leptin receptor signaling pathways may contribute to leiomyoma development and growth **(Afrin et al., 2023b)**. Adipocytes release inflammatory, fibrotic, and angiogenic factors, and these factors were found to enhance leiomyoma cell proliferation mostly through increased abundance of the proliferating cell nuclear antigen **(Afrin et al., 2023c)**.

This study aimed to estimate serum levels of adipocytokines in women diagnosed with uterine leiomyomas and to evaluate their relation to the presence and severity of the presenting symptoms.

Patients and methods

Design: Prospective comparative observational study.

Setting: Obstetrics and Gynecology Department, Benha Teaching Hospital, Ministry of Health.

Inclusion criteria: The presence of UL, either symptomatizing or not, the absence of exclusion criteria, and acceptance to participate in the study.

Exclusion criteria: Intrauterine pathologies other than UL, endocrinopathy causing dysfunctional uterine bleeding, urinary pathologies causing mimicking symptoms, overt diabetes mellitus, coagulopathies, and inflammatory conditions elsewhere in the body.

Clinical evaluation

Patients with symptoms of ULs were clinically evaluated including demographic data include age, weight, and height for calculating body mass index (BMI). History taking included family history of similar conditions, history of previous surgeries, medical disorders (especially bleeding-induced disorders), menstrual history with special regard to the age of menarche, regularity, and duration of the menstrual cycle, and obstetric history for the current fertility status, the number of previous pregnancies, modes of delivery, previous early pregnancy loss or abortion, and the number of living offspring.

Also, a detailed history of the presenting symptoms was taken, especially for the presence of pain, bleeding, and pelvic pressure manifestations.

Women and underwent transvaginal ultrasonography (TVS), and those diagnosed were eligible for study enrollment criteria.

Grouping

The Study Group (Group S) included women who had symptomatizing UL, Positive Control Group (Group CP) included

women who had non-symptomatizing UL that was discovered during routine TVS imaging, and Negative Control Group (Group CN) encompassed women who were free of UL clinically and on TVS imaging.

Laboratory investigations

Blood sampling: Blood samples (5 ml) were withdrawn under complete aseptic conditions in a plain tube, allowed to clot, and then centrifuged at 3000 rpm for 10 minutes to separate serum. Serum was collected in a sterile Eppendorf tube and stored at - 80 ºC till being assayed using the enzyme-linked immunoassay (ELISA) kit by quantitative sandwich enzyme immunoassay technique according to the manufacturer's instructions and was read using a 96-well microplate ELISA reader (Dynatech MR 7000).

Estimated parameters

1. Human tumor necrosis factor-α (TNF-α), Cat. No. ab181421, Abcam Inc., San Francisco, USA, with intra-assay C.V. of 2.5% and inter-assay C.V. of 3.1% **(Coughlan et al., 2001)**.
2. Human adiponectin, Cat. No. ab99968, Abcam Inc., San Francisco, USA, with intra-assay C.V. of 7.9% and inter-assay C.V. of 5.5% **(Yokota et al., 2000)**.
3. Human leptin,—Cat. No. ab179884, Abcam Inc., San Francisco, USA, with intra-assay C.V. of 5.8% and inter-assay C.V. of 9.9% **(Havel et al., 1996)**.

Study outcomes

The study outcome is the relation between estimated levels of the studied adipocytokines and the presence of UL, and their relation to multiplicity of ULs and the presence of their manifestations.

Ethical Registration

The Institutional Ethics Committee, Faculty of Medicine, Benha University, approved the study protocol by the approval number RC15-11-2024 and patients signed the written consent were enrolled in the study.

Statistical analysis

The Kolmogorov-Smirnov test of normality and the normal Q-Q plots were used to test the data normality. The data are presented as mean, standard deviation, numbers, and percentages. The intergroup differences were compared using a One-way ANOVA test including Tukey HSD, while data presented as percentages were compared using the Chi-square test. Correlation between the presence of ULs and its clinical and US character and patients' data and serum levels of the studied adipocytokines was evaluated using Pearson's correlation analysis and presented as Pearson's correlation coefficient. Statistical analyses were conveyed by the IBM® SPSS® Statistics software (Ver. 27, 2020; IBM Corporation; Armonk, USA). The significance of the analysis was evaluated at the cutoff point of P less than 0.05.

Results

Routine examination excluded seven of symptomatizing women and 30 women with ULs were included in the study. Another 60 asymptomatic women were included in after routine TVS, which detected ULs in 30 women (CP Group) and absence of ULs in the others (Group CN) as shown in (**Fig.1**). The demographic data of the enrolled women showed non-significant intergroup differences **(Table.1)**.

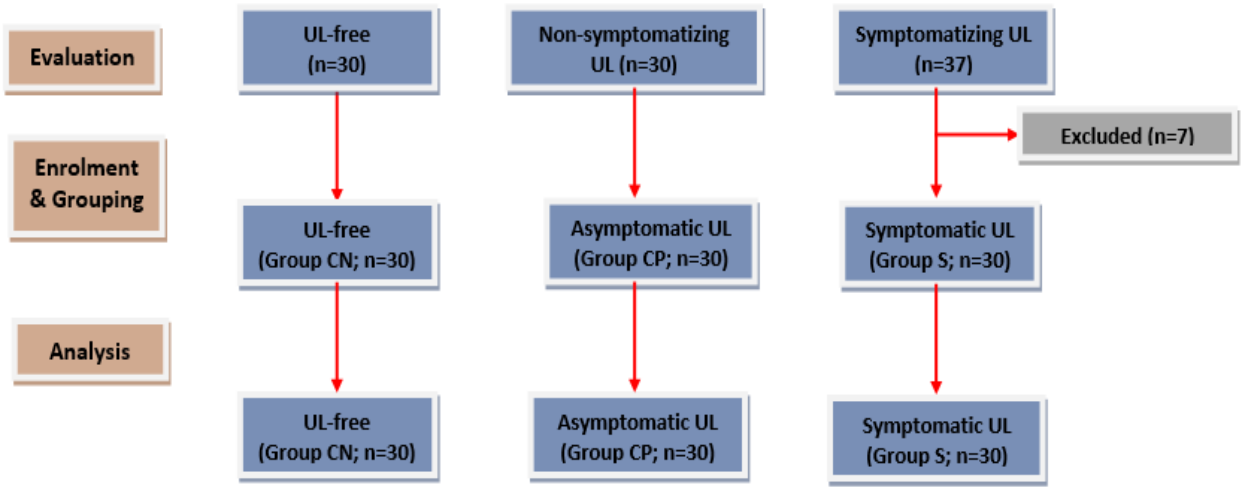

Fig. 1.The Study Flowchart.

Table 1. Demographic data of patients of the three groups.

Group Variable		UL-free (Group CN)	Asymptomatic UL (Group CP)	Symptomatic UL (Group S)	Intergroup difference
Age (years)		37.6±4.5	39.4±5.6	40±4.9	0.159
Weight (kg)		92.4±6.5	93.9±10.1	93±9.2	0.282
Height (cm)		170.2±2.5	169.5±3.5	169.4±3.5	0.509
BMI (kg/m^2)	30-35	27 (90%)	23 (76.7%)	22 (73.3%)	0.232
	>35	3 (10%)	7 (23.3%)	8 (26.7%)	
	Mean	31.9±2.5	31.2±3.7	32.4±3.1	0.345

BMI: Body mass index; One-way ANOVA test and Chi-square test

Women of S Group were more symptomatizing than women of other groups, especially the deregulated menstrual patterns **(Table.2)**.

Table 2. Menstrual and obstetric data of patients of the three groups.

Group Variable		UL-free (Group CN)	Asymptomatic UL (Group CP)	Symptomatic UL (Group S)	Intergroup difference
Age of menarche (years)		14.3±1.3	12.2±1.3	11±1.3	
Menstrual history	**Dysmenorrhea**	0	5 (16.7%)	9 (30%)	0.222
	Polymenorrhagia	0	0	13(43.3%)	0.0002
	Menorrhagia	0	0	10 (33.3%)	0.0027
	Spotting bleeding	0	0	7 (23.3%)	0.0227
Pelvic pressure symptoms	**No**	0	23 (76.6%)	17 (56.6%)	0.237
	Urinary troubles	0	5 (16.7%)	8 (26.7%)	
	Rectal troubles	0	2 (6.7%)	5 (16.7%)	
Fertility	**Fertile**	30	24 (80%)	23 (76.7%)	0.754
	Secondary	0	6 (20%)	7 (23.3%)	

	infertility					
Obstetric history	**Gravidity**	**G1**	7 (23.3%)	5 (16.7%)	4 (13.4%)	0.491
		G2	11 (36.7%)	10 (33.3%)	7 (23.3%)	
		G3	12 (40%)	15 (50%)	19 (63.3%)	
	Parity	**P0**	2 (6.7%)	4 (13.4%)	7 (23.3%)	0.628
		P1	15 (50%)	12 (40%)	11 (36.7%)	
		P2	7 (23.3%)	9 (30%)	6 (20%)	
		P3	6 (20%)	5 (16.7%)	6 (20%)	
	Mode of delivery	**SV**	7 (23.3%)	8 (26.7%)	10 (33.3%)	0.392
		IV	4 (13.3%)	3 (10%)	5 (16.7%)	
		CS	17 (56.7%)	15 (50%)	8 (26.7%)	
	Number of living offspring	**0**	5 (16.7%)	6 (20%)	8 (26.7%)	0.624
		1	8 (26.7%)	11 (36.7%)	13 (43.3%)	
		2	13 (43.3%)	10 (33.3%)	7 (23.3%)	
		3	4 (13.3%)	3 (10%)	2 (6.7%)	
	EPL	**Yes**	1 (3.3%)	3 (10%)	6 (20%)	0.118
		No	29 (96.7%)	27 (90%)	24 (80%)	

G: Gravida; P: Para; SV: Spontaneous vaginal; IV: instrumental vaginal; CS: Cesarean section; EPL: Early pregnancy loss; One-way ANOVA test and Chi-square test

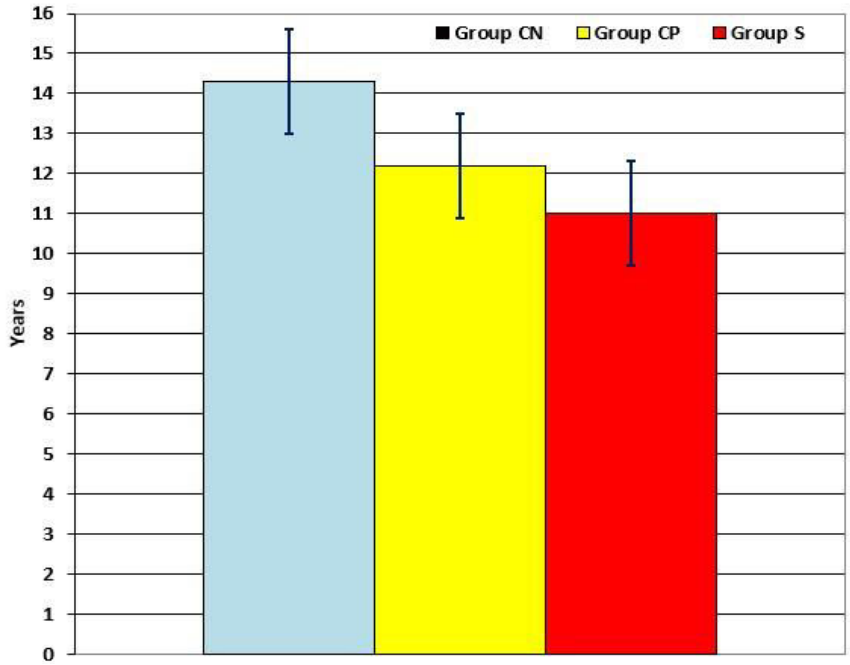

Fig. 2. The mean value (SD) of age of menarche of the women of the three groups.

Fourteen women had more than one UL on TVS imaging with insignificant (P = 0.184) difference between CP and S groups. Nine women had subserous ULs, 30 women had submucous ULs, and 21 women had intramural ULs with insignificantly (P = 0.483) higher frequencies of subserous ULs among women of group S. Twenty women

had pedunculated ULs with insignificantly (P = 0.273) higher frequency among women of group S than group CP **(Table.3)**.

Table 3.TVS characters of UL.

Group Variable		Asymptomatic UL (Group CP)	Symptomatic UL (Group S)	Intergroup difference
Number of the detected ULs	**1**	26 (83.4%)	20 (66.7%)	0.184
	2	3 (10%)	7 (23.3%)	
	>2	1 (3.3%)	3 (10%)	
Site of the detected ULs	**Intramural**	10 (33.3%)	9 (30%)	0.483
	Submucous	18 (60%)	16 (53.3%)	
	Subserous	2 (6.7%)	5 (16.7%)	
Description of the detected ULs	**Sessile**	22 (73.3%)	18 (60%)	0.273
	Pedunculated	8 (26.7%)	12 (40%)	

Chi-square test

The estimated levels serum TNF-α and leptin were significantly higher in samples of women of Group S than samples of the CN (P < 0.001) and the CP (P 0.0002 and <0.001, respectively), and in samples of CP group than in samples of CN group (P <0.001 and 0.0014, respectively) as shown n (**Fig.3, Fig.4**). In contrast, serum adiponectin levels were significantly (P < 0.001) higher in samples of women of group CN compared to levels estimated in samples of women of other groups with insignificant (P = 0.212) differences between levels estimated in samples of women of CP and S groups **(Table.4, Fig. 5)**.

Table 4. Enrolment data of patients of the three groups

Group Variable	Data		UL-free (Group CN)	Asymptomatic UL (Group CP)	Symptomatic UL (Group S)
TNF-α (ng/ml)	**Serum level (mean ±SD)**		4.62±0.9	5.71±1	7.25±1.3
	Significance of difference versus	**CP**		<0.001	<0.001
		S			0.0002
Adiponectin (ng/ml)	**Serum level (mean ±SD)**		16.32±2.88	12.56±3.13	11.55±3.08
	Significance of difference versus	**CP**		<0.001	<0.001
		S			0.212
Leptin (ng/ml)	**Serum level (mean ±SD)**		5.795±1.86	7.34±1.7	12.898±2.23
	Significance of difference versus	**CP**		0.0014	<0.001
		S			<0.001

TNF-α: Tumor necrosis factor-α; One-way ANOVA test

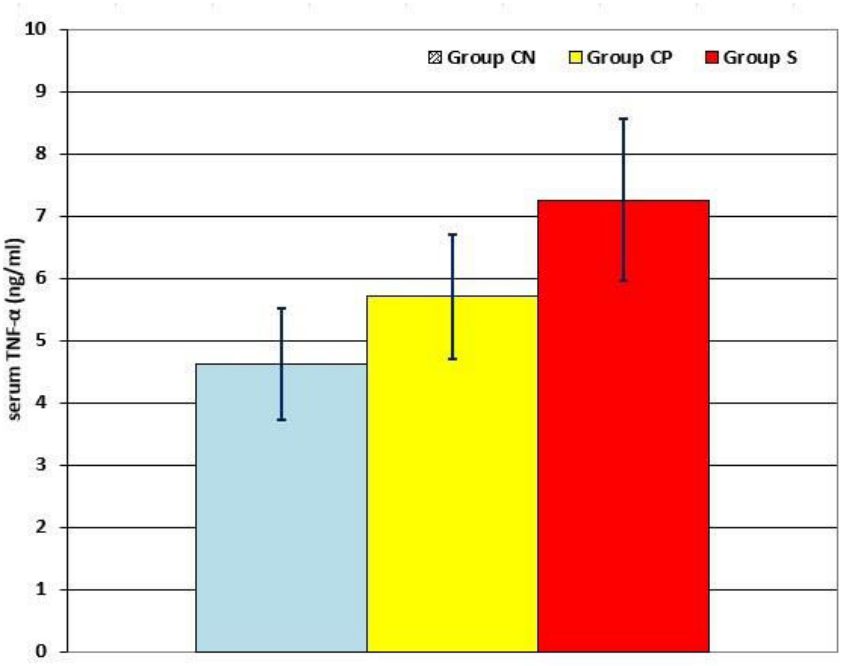

Fig. 3. The mean value (SD) of serum levels of TNF-α estimated in samples of the women of the three groups.

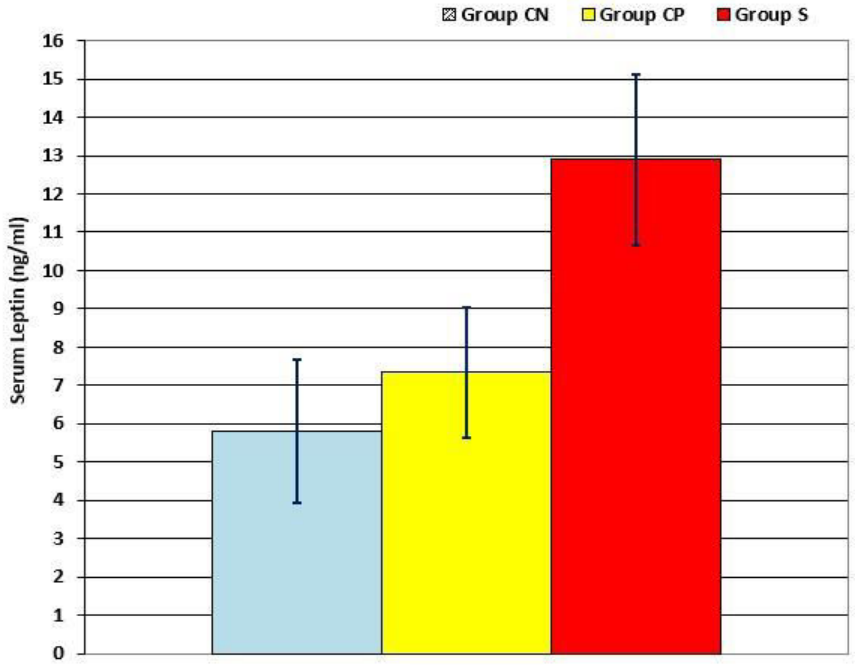

Fig. 4. The mean value (SD) of serum levels of leptin estimated in samples of the women of the three groups.

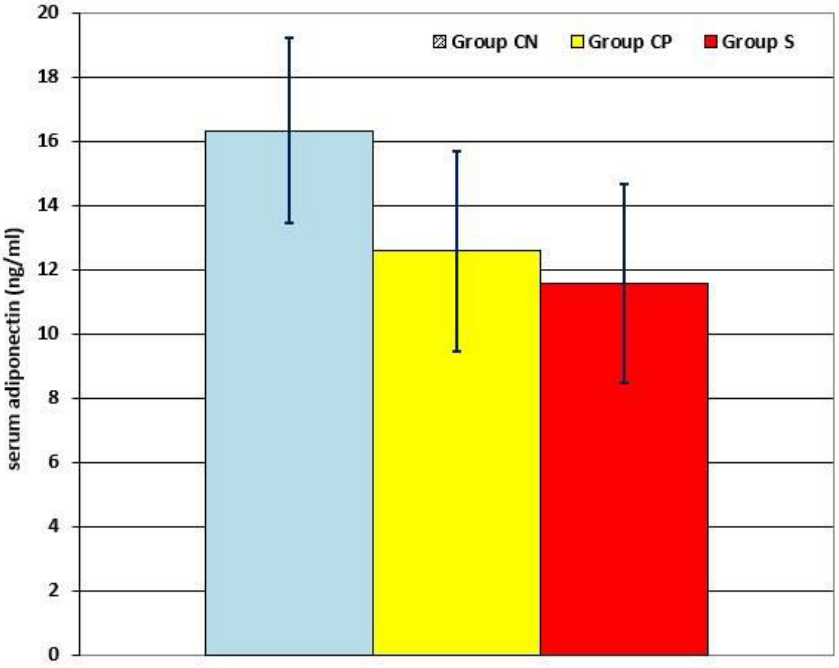

Fig. 5. The mean value (SD) of serum levels of adiponectin estimated in samples of the women of the three groups

The detected TVS findings and clinical data of ULs showed positive significant (P<0.001) correlations with the estimated serum TNF-α and leptin while showing negative significant (P<0.001) correlations with the estimated serum levels of adiponectin. Additionally, the presence of ULs and being symptomatic were positively correlated with patients' age and BMI. The multiplicity of ULs was positively correlated with age, BMI, and gravidity. The number of presenting symptoms was found to be related to BMI **(Table.5)**. BMI showed a positive significant correlation with serum levels of leptin (r = 0.400, P < 0.001) and TNF-α (r = 0.333, P = 0.001) while showing a negative significant correlation with serum levels of adiponectin (r = -0.254, P=0.016).

Table 5. Pearson's correlation analysis for the clinical and TVS characters of ULs and patients' data.

Variates	Presence of ULs		Presence of symptoms		Number of symptoms		Number of ULs	
	"r"	P	"r"	P	"r"	P	"r"	P
Age	**0.235**	**0.026**	**0.231**	**0.029**	**0.185**	**0.081**	**0.327**	**0.002**
BMI	**0.315**	**0.003**	**0.299**	**0.004**	**0.241**	**0.022**	**0.265**	**0.012**
Gravidity	**0.127**	**0.231**	**0.103**	**0.334**	**0.151**	**0.155**	**0.242**	**0.022**
TNF-α	**0.574**	**<0.001**	**0.644**	**<0.001**	**0.636**	**<0.001**	**0.433**	**<0.001**
Adipokine	**-0.556**	**<0.001**	**-0.435**	**<0.001**	**-0.357**	**<0.001**	**-0.371**	**<0.001**
Leptin	**0.531**	**<0.001**	**0.698**	**<0.001**	**0.760**	**<0.001**	**0.505**	**<0.001**

BMI: Body mass index; TNF-α: Tumor necrosis factor-α; "r": Pearson's correlation coefficient

Discussion

There was high frequency of UL even among asymptomatic women and were accidentally detected during routine TVU, and four women of these asymptomatic patients had ≥2 ULs. These findings are coincident with the recent review documenting that ULs are often

asymptomatic; only 20-25% of women had ULs with clinical manifestation, so the diagnostic pathway must begin with clinical suspicion, US examination, and diagnostic hysteroscopy **(Centini et al., 2024)**. Also, the obtained results of the present study are in line with the Australian observational survey on women's health that found women with symptomatic fibroids are predominantly captured, while there is a potential to miss the asymptomatic women whose prevalence is underestimated **(Wilson et al., 2024)**. Also, **Don et al. (2023)** and **Vannuccini et al. (2024)** reported that ULs are asymptomatic in a large percentage of cases and are mostly identified incidentally during radiologic workups.

Among symptomatic ULs, the most common presentation was bleeding ranging between spotting and polymenorrhagia that affected most symptomatic women, pelvic pressure manifestations were also frequent and were reported in 43.3% of the studied women of Group S. These data are in hand with **Don et al. (2023),** who reported that most fibroids are asymptomatic, and when they symptomatize most often it cause heavy menstrual bleeding, pelvic pain and pressure complaints, infertility, and sexual dysfunction. Also, **Ahmad et al. (2023)** declared that symptoms of ULs include abnormal menstrual bleeding, abdominal protrusion, and bladder and/or bowel dysfunctions leading to urinary incontinence/retention with impaired fertility and adverse obstetric outcomes. Moreover, **Vannuccini et al. (2024)** documented that about 30% of women had UL, abnormal uterine bleeding, and heavy menstrual bleeding as the most common complaints, with an effect on the quality of life of the affected women.

Women harboring ULs had an earlier age of menarche than women, free of ULs, and those had symptomatic ULs rather than asymptomatic UL patients. In line with this finding, **Siegel et al. (2024),** found early menarche was associated with uterine fibroid risk, especially the symptomatic lesions, and attributed these findings to the prolonged exposure to estrogen, which may accelerate the tumorigenesis process.

Women who had ULs, especially the symptomatic women were more obese than women who were free of ULs. Moreover, correlation analysis showed positive relations between BMI, the presence and multiplicity of ULs, and the presence and number of the presenting symptoms. These findings are coincident with **Samantaray et al. (2024)** who reported that visceral obesity, which is characterized by excess fat around internal organs, is a risk factor for benign ULs and malignant uterine leiomyosarcoma, and bioinformatic analyses detected 14 genes to present significant differential expression across the three conditions. Further, **Okunade et al. (2024)** found a relationship between maternal obesity, the presence of ULs, a history of antepartum bleeding in the current pregnancy, and the development of severe postpartum bleeding, and considered the coexistence of ULs and obesity significant risk factors of severe postpartum hemorrhage. Moreover, **Dai et al. (2024)** epidemiologically evaluated the global burden for the potential risk factors for ULs at the national level and found the incidence of ULs was positively correlated with overweight and obesity.

The blood samples of symptomatic women showed significantly higher serum levels of TNF-α and leptin with significantly lower serum adiponectin than blood samples of women free of ULs or with asymptomatic ULs. Additionally, similar significant differences in serum levels of these cytokines were detected between samples of women who had asymptomatic ULs and women who were free of ULs. Moreover, correlation analysis defined significant correlations between the serum levels of the

three cytokines and the presence and multiplicity of ULs and the presence and number of symptoms, but such correlations were negative in the case of adiponectin and positive in the case of TNF-α and leptin.

Also, the estimated levels of these adipocytokines were significantly correlated with BMI. Similarly, **Harmon et al. (2024)** reported that repeated measures of BMI and ultrasound assessments of fibroid incidence and growth detected a nonlinear association between BMI and ultrasound findings; such an association was attributed to the effects of obesity on inflammation and reproductive hormones.

Multiple experimental studies tried to explore the relationship between adipocytokines and the growth, progress, and systematization of ULs. Physiologically, there is an equilibrium between the tumorigenesis action of leptin and the anti-tumorigenesis actions but this equilibrium was disturbed by increased serum levels of TNF-α in the direction of leptin-induced UL development and enlargement through insulin-dependent or estrogen-dependent pathways **(Strzałkowska et al., 2021)**. Also, increased TNF-α expression levels activate dysregulation of macrophage proliferation, accumulation, and infiltration, leading to uncontrolled tissue repair with pathological fibrosis, which represents a typical feature of UL **(Zannotti et al., 2021)**.

An in-vitro study found leptin induced a proliferative response and extracellular matrix deposition in HuLM cells and suggested that leptin, acting through the JAK2/STAT3 and MAPK/ERK pathways, is involved in the development of uterine leiomyomas, which may partly explain their increased incidence in obese women **(Reschke et al., 2022)**.

Experimentally, co-culture of myometrial stem cells with adipocytes resulted in increased expression of the leptin receptor and production of reactive oxygen species production, and increased expression of makers of DNA damage; the expression of these markers was decreased after adiponectin treatment, but increased after leptin treatment secondary to binding of leptin to its receptor, leading to inducing signal transduction, resulting in the transcription of genes involved in cellular proliferation and angiogenesis, and concluded that obesity may mediate initiation of tumorigenesis in myometrial cells, resulting in leiomyomas mostly through increased expression of leptin receptor **(Afrin et al., 2023a,b)**.

Limitations: Estimation of serum levels of other adipocytokines to explore its role in UL development is a limitation. Also, being a single-center study limited the case collection and reduced the sample size.

Recommendations: Large multicenter studies are required to verify the riskiest adipocytokines and to determine cutoff points for their diagnostic cutoff points.

Conclusion

Obesity and multigravidity may serve as risk factors for the development and symptomatic nature of ULs, related to serum leptin and adiponectin equilibrium disturbances and high TNF-α levels, that contribute to its pathogenesis.

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