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Evaluation of some physiological biomarkers among Egyptian women with uterine fibroids.

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ABSTRACT

Uterine fibroids are nonmalignant monoclonal neoplasms of the myometrium, constituting the most prevalent tumors among women globally**.** A total of one hundred women with fibroids and one hundred apparently healthy controls were evaluated for biochemical and hematological measurements including serum prolactin, CA 125, LDH levels and other biochemical parameters as well as complete blood picture. Relevant demographic, medical history and clinical presentation of studied subjects were obtained for all the participants. Fibroid women presented with specific characteristics**.** The median weight and BMI of fibroid patient were markedly superior than in the control group ($p<0.001$ for both). It was detected that 31% of women had a family history of fibroid, while 26% had previous abortion. In addition, 12% of women formerly underwent fibroid removal operations. Vaginal bleeding was present in 66% of the females. In addition, 34% of the cases suffered from abdominal and pelvic pain. Furthermore, the lab investigations revealed that the mean hemoglobin level in the fibroid group (10.66 ± 1.77 g/dl) was markedly inferior than the control group (11.63 ± 1.26 g/dl), $p<0.001$. The LDH activity was considerably elevated among the fibroid patients, whereas the serum albumin and total protein levels were considerably diminished compared to the controls ($p<0.001$ for all). The mean prolactin concentration was markedly elevated in the fibroid group than in the controls (43.05 vs.14.0 ng/mL, respectively, $p<0.001$). In conclusions, detection of serum some serum parameters such as serum prolactin, LDH, total proteins and CA125 levels are important markers characterizing uterine fibroids that can be served as possible biomarker for the occurrence of the disease.

Keywords: Uterine fibroids, risk factors, hormonal status, biomarkers.

1. INTRODUCTION

Uterine fibroids represent atypical neoplasms comprised of smooth muscle and fibrous connective tissue that arise within uterine fibroid. [1]**.** The term "uterine stone" was first used to describe uterine fibroid lesions. They were referred to as scleromas in the 2nd century AD, the term "fibroid "first appeared in medical writing during1860s .over than 70% of women round the world suffer with uterine fibroids. These are the most common pelvic tumors found in women of reproductive age [2]**.**

The amount of uterine fibroids varies and their composition varies among women and even within the same individual. Furthermore, a uterine fibroid is surrounded by a fibro-neurovascular structure known as the fibroid pseudo capsule, which isolates it from the healthy peripheral myometrium [3]**.**

Fibroids are characterized by the aggregation of extracellular matrix components and the benign growth of fibroblasts and smooth muscle cells from a single source. This monoclonal growth indicates that an internal factor, possibly an abnormal growth signal, drives their development. Changes in blood vessels can also influence this growth, potentially promoting both the formation and spread of fibroids [4]**.**

Fibroids are identified by looking at cell shape changes, tissue death, and how quickly cells divide. These features help tell them apart from leiomyosarcoma, which is a cancer of smooth muscle cells. They also help differentiate them from STUMP lesions, which are smooth muscle tumors with uncertain potential for becoming cancer [5]**.**

Fibroids are thought to develop due to an abnormal response in the uterus's muscle layer, known as the myometrium. This response involves increased growth and repair of tissue caused by poor blood flow or damage to blood vessels. Compared to normal myometrial cells, fibroid cells contain fewer parts that help muscles contract. Instead, they have more cellular structures involved in making proteins, such as the Golgi apparatus, free ribosomes, and rough endoplasmic reticulum. This change occurs at a very detailed level inside the cells [6]**.**

Fibroids are more changeable than static images might suggest. In the early stages of their growth, they are active and not just made of basic tissue. They go through four main phases. The first three phases focus on myocyte proliferation, where new muscle cells are formed[7]**.** This process is active mainly in phases 1 to 3. During phases 2 and 3, collagen production increases. Collagen is a key part of the fibroid structure. The fourth phase involves involution, which is when the fibroid shrinks. At this stage, collagen content is at its highest. As fibroids grow older, collagen levels tend to rise [4]**.**

Despite being benign, uterine fibroids have a high morbidity rate. They are the main reason for a hysterectomy and a major cause of reproductive and gynecologic problems, from pelvic pain and hemorrhage to infertility, repeated miscarriages, and premature childbirth. Accordingly, it has been estimated that uterine fibroids cost the United States of America over $34 billion in medical expenses each year. Thus, uterine fibroids pose a serious financial and health risk to society [8, 1]**.** Uterine fibroids can impact a person's physical and emotional health. Many fibroids cause no symptoms. However, some can result in severe issues like heavy bleeding during periods, pain in the pelvic area, and trouble getting pregnant. These symptoms can significantly affect daily life and well-being [9]**.**

`The size is ranging from microscopic to large masses that can distort the uterus[10]**.**.Fibroids are categorized into four types depending on their position: intramural fibroids (the dominant type which sited within the uterine wall); submucosal fibroids (found just beneath the inner lining of the uterus and can distort the uterine cavity); sub serosal fibroids (situated on the outer uterine surface of the uterus and

may extend outward) and pedunculated fibroids (These fibroids are connected to the uterine wall by a stem-like structure) [11]**.**

The diagnosis of uterine fibroids typically involves a combination of clinical evaluation, imaging tests, and sometimes biopsy. The treatment of uterine fibroids is based on the severity of symptoms, the size and position of fibroids, the woman's age, and her reproductive plans[12]**.**Treatment options range from conservative management to surgical intervention. Early diagnosis and a personalized treatment plan are keys to managing the condition and improving quality of life [13]**.** This study intended to examine the main serum biomarker and physiological abnormalities characterizing women with uterine fibroids in Egypt.

2. PATIENTS AND METHODS

The current case-control study was carried out on 100 females with uterine fibroids attended the obstetrics and gynecology department Mansoura University, after approval by the Ethics Committee of the Faculty of Medicine, Mansoura University (R.23.08.2288) and obtaining written informed consent from all participants. One hundred of unrelated healthy volunteers with matched age and sex were used as a control group. This study was conducted between October 2023 and June 2024. Relevant demographic, medical history and clinical presentation of studied subjects were retrieved from registered data archives. The inclusion criteria involved patients who underwent myomectomy or hysterectomy for symptomatic uterine fibroids during their reproductive years (18–50 years) and having regular menstruations. Patients with postmenopausal bleeding, neoplasm of the reproductive system, endometriosis and pregnancy were excluded from this study.

2.1. Methods

Five milliliters of blood were collected from all the participants. Each sample was separated into two partitions: the 1st part (2 ml) were placed in sterilized EDTA-tubes for the hematological evaluation, whereas the 2nd part (3 ml) were drawn in plain tubes for the biochemical assessments.

An end-point colorimetric assay**,** a biochemical method used to measure the concentration of total bilirubin, albumin, total proteins, and creatinine in the serum based on the intensity of a color that forms during a chemical reaction. The term "end-point" means the measurement is taken once the reaction has reached completion, not continuously over time using (BIOMED DIAGNOSTICS, Germany) kits according to the manufacturer's instructions.

Kinetic assay**,** a type of biochemical test that measures the rate of a reaction over time, rather than waiting for the reaction to reach an end point was performed using a spectrophotometer, this assay monitors changes in absorbance at a specific wavelength to calculate reaction velocity and, ultimately, enzyme activities of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) using (BIOMED DIAGNOSTICS, Germany) kits.

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Sandwich Enzyme-Linked Immunosorbent Assay (ELISA), an immunoassay technique used to detect and quantify a specific antigen (CA125) in serum and called "sandwich" because the target antigen is bound between two layers of antibodies—a capture antibody and a detection antibody**.** A human quantitative ELISA kit (Cat. No. # EHMUC16, Invitrogen, Thermo Fisher Scientific, USA) was used.

A complete blood count (CBC) was analyzed using an (Automated Analyzer, Cell-Dyn Ruby, USA). Coagulometer device (ERBA Coag UNO Blood Coagulometer) was used to measure INR).

2.2. Statistical analysis

The acquired data was categorized, and tabulated using the SPSS (IBM Corporation, IBM SPSS). Parametric numerical data was expressed by mean (± SD), non-parametric data was expressed by median (range) and the non-numerical data was expressed by percentage and frequency. Student-t test was applied to evaluate the significance of the difference between study group parametric variables. The Mann-Whitney U test was applied to explore the statistical significance of a non-parametric variable of study groups. Chi-Square test was used to examine the relationship between qualitative items. P-value is considered significant if < 0.05.

3. RESULTS

The median age of the women with fibroid is 50.0 years, ranging from 27 to 86 years**.** No significant difference was found between the fibroid and control group regarding age (p=0.065), **(Table 1).**

Table (1): Demographic data among fibroid patients.

	Fibroid group (N=100)	**Control (N=100)**	**p-value**
Age (years)			
Median (IQR)	50.0 (42.0 – 50.0)	44.0 (38.5 – 53.0)	p=0.065
Min. – Max.	27.0 – 86.0	20.0 – 68.0	

Data is expressed as median (IQR) with Min.-Max. z: Mann-Whitney U-test.

Table 2 details the past medical history of the studied patients **(Figure 1).** It was detected that 31% of women had a family history of fibroid **(Figure 2),** while 26% had previous abortion. In addition, 12% of women formerly underwent fibroid removal operations (10% myomectomy and 2% laparotomy). Notably, 47% of all the patients underwent previous operations such as myomectomy, breast lumpectomy, hernioplasty etc.,

Regarding gravidity 28%, 5%, 9% and 58% of women were gravida 0, 1, 2 and ≥ 3, respectively. For parity, 31%, 4%, 11% and 8% of women were para 0, 1, 2 and ≥ 3, respectively, as presented in **(Table 2).**

Table (2): Past history and of the studied cases.

	Fibroid group N = 100	
	n	**%**
Family history		
Yes	31.0	31
No	69.0	69
Abortion		
0	74.0	74
1	14.0	14
2	4.0	4
≥ 3	8.0	8
Gravidity		
0	28.0	28
1	5.0	5
2	9.0	9
≥ 3	58.0	58
Parity		
0	31.0	31.0
1	4.0	4.0
2	11.0	11.0
≥ 3	8.0	8.0
Previous fibroid removal		
Yes	12.0	12
No	88.0	88

Data is expressed as frequency (percentage).

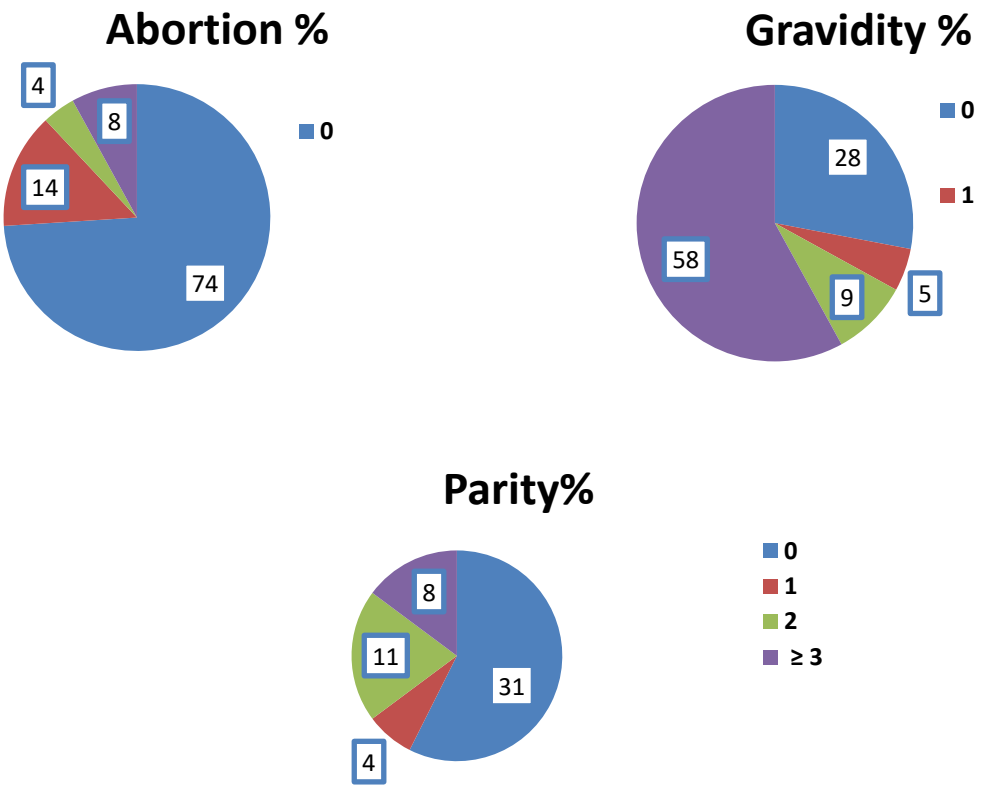

Figure (1): Past medical history of the studied patients

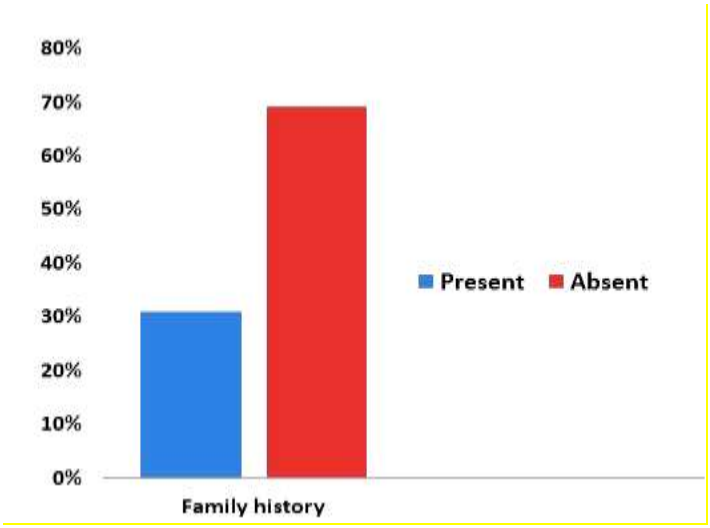

Figure (2): Family history of the studied patients.

Table 3 presents the comparison of anthropometric measures of the studied groups. The median weight of fibroid patients is 90.0 kg and the median height is 1.65 meters. The median BMI of fibroid patients is 31.25 and calculated by the formula: $BMI = \frac{\text{Weight (Kg)}}{\text{Height}^2(m2)}$. The median weight and BMI of fibroid patients were markedly higher than in the control group ($p<0.001$ for both).

Table (3): Comparison of anthropometric measures of studied group.

	Fibroid group N = 100	**Control N=100**	**p-value**
Weight (kg)			
Median (IQR)	90.0 (80.0 – 90.0)	70.0 (67.0 – 77.0)	**p<0.001****
Height (m)			
Median (IQR)	1.65 (1.62 – 1.67)	1.65 (1.62 – 1.67)	p=0.80
BMI (kg/m^2)			
Median (IQR)	31.25 (29.38– 33.46)	25.71 (24.7 – 28.08)	**p<0.001****

Data is expressed as median (IQR). z: Mann-Whitney U-test, *****:** Probability value was considered highly significant at $p<0.001$. BMI: body mass index.

Vaginal bleeding was present in 66% of the women. The symptoms presented by the studied patients were displayed in **(Table 4 and Figure 3).**

Table (4): Clinical presentation of the studied cases.

	Fibroid group N = 100	
	n	**%**
Vaginal bleeding		
Present	66.0	66
Absent	34.0	34
Symptoms		
Lower abdominal & pelvic pain	31.0	31
Vaginal bleeding	45.0	45
Heavy menstrual bleeding	16.0	16
Menstrual pain	3.0	3
Post-menopausal bleeding	2.0	2
Abdominal swelling	2.0	2
Intestinal bleeding	1.0	1

Data is expressed as frequency (percentage).

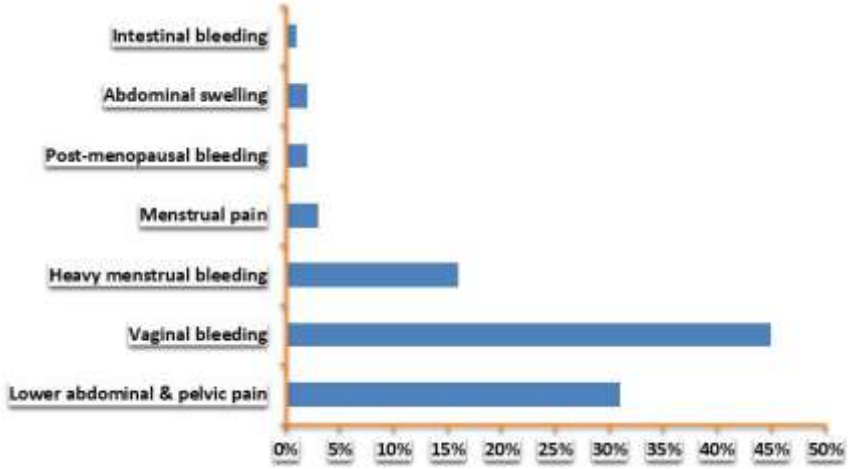

Figure (3): Clinical presentation of the studied cases.

The (**Table 5)** displays the results of laboratory investigations for fibroid patients and controls. The mean hemoglobin level in the fibroid group (10.66 ± 1.77 g/dl) was significantly lower than the control group (11.63 ± 1.26 g/dl), p<0.001.

For red blood cells, the mean count in the fibroid group was 4.18 $\times 10^3/mm^3$ with a standard deviation of 0.70, which was significantly less than in the control group 4.4 $X10^3/mm^3$, with a standard deviation of 0.52, (p=0.012).
The LDH activity was considerably elevated among the fibroid females, whereas the serum albumin and total protein concentrations were significantly less than in controls (p<0.001 for all). The average prolactin value was substantially raised in the fibroid females than the controls (43.05 vs.14.0 ng/mL, respectively, p<0.001).

Fibroid sizes were found to have size ≥5cm in 54% of patients. The intervention after diagnosis was hysterectomy in 74% for the cases and myomectomy in 26% of the cases, as shown in **(Table 6).**

Table (5): Comparison of lab measurements of the studied groups.

Parameters	**Fibroid group N=100**	**Control group N=100**	**p-value**
Hemoglobin (g/dl)	10.66 ± 1.77	11.63 ± 1.26	**p<0.001*** **
RBCs ($\times 10^{12}$/L)	4.18 ± 0.70	4.4 ± 0.52	**p=0.012***
WBCs ($\times 10^9$/L)	8.95 ± 4.1	7.99 ± 3.9	p=0.091
Neutrophils ($\times 10^9$/L)	5.46 ± 1.58	5.66 ± 0.92	p=0.27
Lymphocytes ($\times 10^9$/L)	1.83 ± 0.77	1.97 ± 0.75	p=0.19
Platelets ($\times 10^9$/L)	272.49 ± 72.01	276.24 ± 92.68	p=0.75
Creatinine (mg/dl)	0.7 (0.7 – 0.9)	0.75 (0.64 – 0.91)	p=0.60
ALT (U/L)	20 (18.0 – 23.0)	19 (16.0 – 32.0)	p=0.77
AST (U/L)	23.0 (21.0 –26.5)	23.0 (19.0 – 33.0)	p=0.96
INR	1.04 ± 0.03	1.04 ± 0.01	p=1.0
Bilirubin (mg/dl)	0.59 ± 0.29	0.52 ± 0.30	p=0.09
Albumin (g/dl)	4.0 (3.4 – 4.2)	4.5 (4.05 – 4.9)	**p<0.001*** **
Total proteins (g/dl)	6.72 ± 1.02	7.89 ± 0.62	**p<0.001*** **
LDH (U/L)	289.0 (268.5 – 300.5)	180.0 (152.0 – 194.5)	**p<0.001*** **
Prolactin (ng/ml)	43.05 ± 18.9	14.0 ± 3.98	**p<0.001*** **
CA.125 (U/mL)	10.5 (7.0 – 17.0)	10 (7.5 – 17.5)	p=0.49

:** P-value was considered significant at $p<0.05$; and **** highly significant at $p<0.001$.

Table (6): Intervention and pathological examination of the fibroids.

	Fibroid group N = 100	
	N	**%**
Intervention		
Hysterectomy	74.0	74
Myomectomy	26.0	26
Fibroid size		
<5	46.0	46
≥5	54.0	54

Data is expressed as frequency (percentage).

4. DISCUSSION AND CONCLUSION

The most prevalent benign uterine tumors in females are uterine leiomyomas, which are frequently asymptomatic but only present clinically in 20–25% of cases [14]**.**

Many determinants contribute to their development and growth. These include genetic, hormonal, and environmental influences [15]**.**

This work intended to explore the main serum biomarker and physiological abnormalities characterizing women with uterine fibroids in Egypt. This case-control study conducted on 100 females with uterine fibroids and 100 healthy individuals with matched age and sex were used as a control group.

The two main hormones that control the menstrual cycle, estrogen and progesterone, are essential for the growth of uterine fibroids. The smooth muscle cells inside fibroids expand as a result of these hormones. When estrogen and progesterone levels are high during the reproductive years, fibroids have a tendency to grow. When these hormone levels fall after menopause, fibroids may shrink. This reliance on hormones implies that hormonal abnormalities have a special impact on fibroids [16]**.**

The likelihood of having fibroids is greatly increased if there is a family history of them. In this investigation, it was detected that 31% of women had a family history of fibroid. Other risk factors include age as fibroids are most common in women aged 30 to 50, with the highest prevalence seen during the perimenopausal period. In the present study, the median age of the women with fibroid is 50.0 years, ranging from 27 to 86 years. Concerning ethnicity, African American women are susceptible to develop fibroids with more severe symptoms than women of other ethnic backgrounds. Fibroids often occur at a younger age and have larger, more numerous fibroids [**17**]**.**

Furthermore, the reproductive history is an important factor where the women who have never been pregnant or who experience delayed childbirth may have a greeted risk to get fibroids. Also, women with higher BMI are at an increased risk for fibroids, possibly due to the elevated levels of estrogen produced by adipose tissue [**18**]**,** In the current study the median weight and BMI of fibroid patients were significantly higher than in the control group ($p<0.001$ for both).

We found that the LDH activity was significantly higher among the fibroid patients, whereas the serum albumin and total protein levels were significantly lower compared to the controls ($p<0.001$ for all). The average prolactin level was significantly higher in the fibroid group compared to the control group ($p<0.001$).

Prolactin is a protein hormone involved in lactogenesis and other physiologic processes in mammals. By connecting with type-1 cytokine receptors and sending signals via the Janus kinase and activators of transcription (JAK/STAT) pathways, prolactin mediates its action. Prolactin is expressed in various tissues, including uterine leiomyomas, despite being isolated as a pituitary hormone [19]**.**

Measuring the serum total protein examines the total amount of albumin and globulin in the blood. A nutritional deficit, liver and renal illness, persistent bleeding, or anemia are typically linked to values below the normal threshold. Prior to undergoing a myomectomy or hysterectomy for leiomyomas, patients with uterine fibroids had decreased serum levels of total protein, according to a prospective study looking at total protein as a biomarker for fibroids [20]**.**

Cancer antigen 125 (CA125) is not unique to ovarian cancer; rather, it is a diagnostic of nonspecific peritoneal diseases. Zhou et al . discovered that the median CA125 levels in adenomyosis, leiomyomas, and controls were 102.1 kIU/L, 34.6 kIU/L, and 33.1 kIU/L, respectively, in a research involving 55 patients with either condition [21]**.**

Anaerobic glycolysis involves the enzyme lactate dehydrogenase, which changes pyruvate into lactate. Cancer patients frequently have elevated serum levels of it. The LDH gene is frequently overexpressed and has been connected to a bad prognosis for a number of malignancies**.** Koukourakis et al**.** showed that fibroid females had considerably higher LDH (310 ± 81 vs. 256 ± 68; $P=.05$) when comparing 24 leiomyoma patients to controls. However, same examination was carried out alongside patients who had endometrial cancer, and it was discovered that their LDH levels were nearly the same as those of the leiomyoma patients[22].

According to major epidemiological research, parity and uterine fibroids have an inverse relationship, which may indicate a preventive effect. Uterine fibroids are more prevalent in nulliparous women than in multiparous women. The chance of this condition may decrease with each additional child. Uterine fibroid production may be reduced as a result of steroid hormone exposure during pregnancy and the

significant remodeling of the uterine tissues following each pregnancy [23] . We did not detect any woman having a previous history of hypertension in this study.

Uterine fibroids and arterial hypertension are directly correlated. Regardless of antihypertensive medication use, uterine fibroids are more likely to occur in people with elevated diastolic blood pressure. Uterine fibroids are five times more common in women with hypertension, and early detection of hypertension is a major contributing factor. Lesions are thought to develop as a result of the myometrium's ongoing deterioration brought on by elevated blood flow and cytokines released by damaged myometrial cells [24].

In the current work, 28%, 5%, 9% and 58% of women were gravida 0, 1, 2 and ≥ 3, respectively and 31%, 4%, 11% and 8% of women were para 0, 1, 2 and ≥ 3, respectively.

Uterine fibroids are the main reason for a hysterectomy and a major cause of reproductive and gynecologic problems. We found that fibroid sizes were ≥5cm in 54% of patients and vaginal bleeding was present in 66% of the women. In addition, 34% of the cases suffered from abdominal and pelvic pain.

In this study, the mean hemoglobin level in the fibroid group (10.66 ± 1.77 g/dl) was significantly lower than the control group (11.63 ± 1.26 g/dl), ($p<0.001$). For red blood cells, the mean count in the fibroid group was 4.18 $\times 10^3/mm^3$ which was significantly less than controls 4.4 $X10^3/mm^3$ ($p=0.012$).

Moreover, we found that 26% had previous abortion. In addition, 12% of women formerly underwent fibroid removal operations. The intervention after diagnosis was hysterectomy in 74% for the cases and myomectomy in 26% of the cases.

In conclusion, detection of serum some serum parameters such as serum prolactin, LDH, total proteins and CA125 levels are important markers characterizing uterine fibroids that can be served as possible biomarker for the occurrence of the disease.

Author Contributions

Yasmeen M. Elsayed and **Ali H. Abu Almaty** contributed to project administration, investigation, and the performance of the statistical analysis. **Yasmeen M. Elsayed** and **Afaf M. Elsaid** contributed to methodology, formal analysis, and supervision. **Ahmed K. Hasan** and **Mohamed I. Eid** were involved in validation, writing, and editing..

Data Availability
The data will be available upon reasonable request.

Declarations
Conflict of interest The authors declare that they haven't financial relationships, or potential conflicts of interest on the subject of this study.

Ethical Approval All procedures involved in this work are in accordance with the ethical guidelines of the institutional research committee and with the 1964 Helsinki Declaration and its adjustments.

Consent to participate Written informed consent was attained from all participants (Approval No. R.23.08.2288)

Consent for publication The manuscript does not contain any personal data
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