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# A Study of Prolactin Hormone and other Factors in Relation to Uterine Leiomyomas among a Group of Iraqi Women

Maysaloun Muhammad Abdulla  
FICMS

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## Abstract:

**Background:** Uterine leiomyomas, commonly referred to, as "fibroids" are benign tumors arising from the myometrial compartment of the uterus. They are typically well differentiated, have a relatively low mitotic index, and retain their smooth muscle phenotype. Uterine leiomyomas are the most common gynecologic neoplasm, occurring with a remarkable frequency in more than 70% of women at their reproductive age. The female reproductive tract is known to be an extrapituitary source of the hormone prolactin. The endometrium, myometrium, and uterine leiomyomas (fibroids) all have been shown to secrete prolactin when cultured in vitro.

**Objectives:** To study the characteristics of patients with uterine leiomyomas (fibroid) in relation to some factors, and to estimate prolactin hormone level at different sites of leiomyomas patients

**Subjects and methods:** The study was conducted during the period from March 2004 to March 2006 at Obstetrics and Gynaecology departments of four hospitals in Baghdad city. It included a convenient sample of patients with leiomyomas. The circulating prolactin of those patients (n=53) as well as their tissues prolactin [(leiomyomas and myometrium)] was assayed using the Prolactin Kit (Biomérieux).

**Results:** Mean age of the patients was  $39.9 \pm 5.5$  years. Mean body mass index (BMI) was  $28.4 \pm 4.7$  kg/m<sup>2</sup>. Their mean age at menarche was  $13.1 \pm 0.6$  years. They weren't smokers neither hormonal contraceptive users. Eighty-three percent of patients were married and the rest (16.98%) were single. Parity for the married patients was ranging from nulliparous to 5 and the highest percentage was among those with 1-4 parity (70.5%). The prolactins mean for patient's serum was  $143.1 \pm 106.9$  ng/ml, leiomyomas was  $18.2 \pm 14.0$  ng/ml and for patients myometrium was  $8.0 \pm 3.3$  ng/ml respectively. A highly significant difference was found between the leiomyomas prolactin and patient's myometrium prolactin.

**Conclusion:** This study concluded that patients with leiomyomas are at late reproductive or premenopausal age and overweight with mean BMI  $28.4 \pm 4.7$  kg/m<sup>2</sup>. It was found that leiomyomas PRL is significantly higher than myometrial PRL of the same patient.

**Keywords:** leiomyomas, prolactin hormone

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## Introduction:

Uterine fibroids are tumors made of connective tissue and smooth muscle.

They grow slowly within the wall of the uterus or attach to the uterine wall. Most fibroids are non cancerous, although in some rare cases they may become cancerous. This occurs in less than 1% of fibroids<sup>[1]</sup>. Uterine leiomyomas, or fibroids, are the most common tumors of women in the United States; probably occurring in the majority of women by the time they reach menopause and becoming clinically significant in about one-third of these women. Despite their prevalence, little attention has been directed toward the causation and pathogenesis of fibroids until recent years because of the rarity of their malignant transformation. Regardless of their generally benign neoplastic character, uterine fibroids are responsible for significant morbidity in a large segment of the female population. The

## Methodology:

A cross sectional study was conducted during the period from March 2004 to March 2006 at Obstetrics and Gynaecology departments of four hospitals in Baghdad city (Al-Khadimiya teaching hospital, Al-Noor, Al-Kharck, and Al-Saadoon Hospital). It included a sample of female patients at their reproductive age who were

clinical effects of these tumors are related to their local mass effect, resulting in pressure upon adjacent organs, excessive uterine bleeding, or problems related to pregnancy, including infertility and repetitive pregnancy loss<sup>[2]</sup>. As a consequence of these local pressure effects and bleeding, uterine fibroids rank as the major reason for hysterectomy in the United States, accounting for approximately one-third of all hysterectomies<sup>[3]</sup>, or about 200,000 hysterectomies per year<sup>[4]</sup>.

## Objectives:

- 1-To study the characteristics of patients with uterine leiomyomas (fibroid) in relation to some factors.
- 2-To estimate prolactin hormone level at different sites of leiomyomas patients and to examine the difference in the hormonal level among these sites

diagnosed previously by their physicians as patients with uterine fibroids after proper physical and gynecological examination which was confirmed by ultrasound findings, they were prepared for laparotomy either for total abdominal hysterectomy or myomectomy. All patients were with normal pituitary image, none of them was on any drugs known to increase serum prolactin

level in the last six months. None of them was known to complain of diabetes mellitus, pituitary, thyroid, renal or psychiatric disease.

Uterine Fibroids (leiomyomas) introduced in this study were identified grossly at surgery and confirmed by histological examination to be fibromatous leiomyomatous tissue.

Uterine leiomyoma were immediately immersed in ice-cold saline solution (0.9% NaCl) after recording their dimensions, types, and localized their position in the uterus. Leiomyomas were dissected free from surrounding myometrium. When two or more leiomyomas were present in the same uterus, samples from several

Of them were pooled and diced [5]

A myometrium sample from the same leiomyoma patient also was taken. These myometrium tissue samples were also immersed immediately in cold saline as the leiomyoma samples. Ten milliliters of venous blood were aspirated from leiomyoma patients just before operation, left to clot, and then centrifuged. Part of it was used for measuring the serum PRL level at the same day of operation by using the Prolactin Kit (Biomérieux); [measurement range of the VIDAS PRL kit is 0.5-200 ng/ml]. The range of expected values for the normal menstruating women is (5-35 ng/ml), Prolactin level was considered normal up to 35 ng/ml. Patients after operation with abnormal serum PRL level (>35 ng/ml) were sent to the Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT) to examine their pituitary, those with abnormal pituitary image were excluded from the study.

Patients with leiomyoma were questioned about their age, age at menarche, marital status, parity, hormonal contraception use and smoking. Their weight and height were measured and body mass index was calculated by using the equation

$$[BMI = \text{Weight (kg)} / \text{Height}^2 \text{ (m)}]$$

Analyses were done using SPSS computer program version 10.0, Statistical analysis included descriptive statistics (mean, standard deviation SD, frequencies and percentage), Student's t-test was used for comparing means of two variables. P value equals or less than 0.05 was considered significant.

### Results:

A total of 53 women patients with leiomyoma were included in this study. Their mean age  $\pm$  SD was (39.9 $\pm$ 5.5) years and age range was (31-49) years. Eighteen patients (33.96%) underwent hysterectomy while 35 patients (66.04%) had myomectomy.

Eighty-six leiomyoma samples with different uterine sites were harvested from those 53 women.

Table (1) shows different characteristics of the cases group (leiomyoma patients); their mean age at menarche was (13.1 $\pm$ 0.6) years.

All leiomyoma patients were more frequently overweight/ obese; their mean BMI was (28.4 $\pm$ 4.7) Kg/m<sup>2</sup>. None of them was smoker, and they did not use hormonal contraceptives.

Nine out of 53 leiomyoma patients (16.98%) were single, while 44 (83.02%) were married. About two thirds of married (70.5%) women had paragravidity of 1-4 while nulliparous represented (11.3%).

Regarding prolactin hormone level, table(2) shows that mean serum prolactin among leiomyoma patients (143.1 $\pm$ 106.9) ng/ml compared with normal serum PRL level range in women at reproductive age which is (5-35 ng/ml)

The mean PRL level of leiomyoma was greater than the PRL of myometrium in same patient group (18.2 $\pm$ 14.0) and (8.0 $\pm$ 3.3) ng/ml respectively, and it was found that the mean leiomyoma PRL was significantly higher than mean myometrium PRL (P<0.0001).

Table-1- Distribution of the liomyoma patients according to some variables.

|                              | Mean $\pm$ SD  | (%)                |
|------------------------------|----------------|--------------------|
| Age (years)                  | 39.9 $\pm$ 5.5 |                    |
| Age at menarche (years)      | 13.1 $\pm$ 0.6 |                    |
| BMI (Kg/m <sup>2</sup> )     | 28.4 $\pm$ 4.7 |                    |
| Smoking                      | -----          | -----              |
| Hormonal contraceptive users | -----          | -----              |
| Marital status               |                |                    |
| Single                       | -----          | 9 (16.98)          |
| Married                      | -----          | 44 (83.02)         |
| Total                        |                | <b>53 (100.0)</b>  |
| Parity                       |                |                    |
| Nulliparous                  | -----          | 5 (11.3)           |
| 1-4                          | -----          | 31(70.5)           |
| $\geq$ 5                     | -----          | 8 (18.2)           |
| Total                        |                | <b>44 (100.00)</b> |

SD =Standard Deviation

Table-2- Mean  $\pm$  SD of prolactin (PRL) level in different sites of patients

| ITEMS   | No. | Mean $\pm$ SD*    | P-value (t-test) |
|---|-----|-------------------|------------------|
| Patient   | 53  |                   |                  |
| Leiomyoma PRL (ng/ml)                                 | 86  | 18.2 $\pm$ 14.0   |                  |
| Myometrium PRL (ng/ml)                                | 53  | 8.0 $\pm$ 3.3     |                  |
| Serum PRL (ng/ml)                                     | 53  | 143.1 $\pm$ 106.9 |                  |
| Uterine LIOMYOMA PRL + patient myometrium PRL (ng/ml) |     |                   | <0.0001          |

\*SD=Standard Deviation

**Discussion:**

In this study it was found that the mean age of patients with leiomyoma was 39.9 $\pm$  5.5 years which is considered as late reproductive age or premenopausal age. This result was in agreement with Cramer and Patel, 1990, who mentioned that uterine leiomyoma, is the most common gynecologic neoplasm, occurring with a remarkable frequency in more than 70% of reproductive age women [6]. Also Cheryl *et al.*

2001 reported that risk increases with age during the premenopausal years, but tumors typically regress and/or become asymptomatic with menopause [7]. Gordon *et al.* 2003; refers that estrogen has been traditionally proposed as the primary promoter of uterine leiomyoma growth. And this supposition was based in part upon the clinical observations that fibroids occur only after menarche and develop during the reproductive years [8].

Mean age at menarche was  $13.1 \pm 0.6$  years. This finding agrees with Cheryl 2002 who reported that at this early age there would be increase in overall exposure to circulating ovarian hormones and so increasing of risk associated with growth<sup>[9]</sup>.

Leiomyoma patients in this study had mean BMI  $28.4 \pm 4.7$  kg/m<sup>2</sup>. This mean value is approximately near the obese value  $\geq 29$  kg/m<sup>2</sup> [normal BMI=19-25 kg/m<sup>2</sup>], which is associated with an increasing level of circulating estrogen through aromatization of fat stores. Similar result was found by Cheryl 2002 who mentioned that obesity has been linked to an increased risk for leiomyomas<sup>[9]</sup>. Another study by Ross *et al.* 1986 concluded that risk of leiomyoma was strongly related to weight, women who weighed less than 55 kg had a particularly low risk, and overall the risk rose roughly 21% for each 10 kg<sup>[10]</sup>.

None of this study patient was smoker, or being a hormonal contraceptive user. This may be explained by the results of other study which identified smoking and hormonal contraceptives as protective factors.

About two thirds 70.5% of the 44 married patients had a paragravidity 1-4 while the lowest percentage 11.3% were nulliparous.

This finding was in disagreement with that of Ross *et al.* 1986 who referred to pregnancy as one of the factors that associated with a decreased risk of developing leiomyoma, and in case of pregnancy, the risk of developing leiomyoma in parous women is approximately half of nulliparous women and the risk of fibroid decrease with increased number of pregnancies<sup>[10]</sup>. But Cheryl *et al.* 2001 said that studies that report changes in existing leiomyoma during pregnancy are not consistent, some tumors grow, others shrink, but many show little change. Thus the mechanism(s) by which increasing parity might reduce the risk of fibroids are not understood, dissection of factors responsible is of importance, as the biological basis of this protective effect could yield valuable information with potential implications for therapy<sup>[7]</sup>. The highest percentage found among those with 1-4 parity in this study was similar to that of Cheryl.

Lauren *et al.* 2004 also reported that overweight or obesity appeared to attenuate the inverse association between parity and uterine leiomyoma. This agreed with the finding of this study in which leiomyoma patients were more likely overweight or obese<sup>[10]</sup>.

Mitchell *et al.* 1989 have reported that leiomyoma PRL secretion is significantly greater than myometrial PRL secretion for the same patient, and they found that leiomyoma PRL secretion increased with time whereas

myometrial PRL secretion did not. This finding agrees with the mean results of this study in which the mean PRL in leiomyoma was significantly higher than myometrium PRL of the same patient<sup>[11]</sup>.

Daly *et al.* 1984 said that leiomyoma has the ability to synthesize prolactin which increases the evidence that cells of mesenchymal origin that arise near the paramesonephric ducts have a latent ability to express the genome for prolactin synthesis, and the appearance of prolactin synthesis in leiomyoma *in-vivo* suggests that this potential genome expression is activated either in smooth muscle cells or stromal cells during the transformation of normal cells to leiomyoma cells<sup>[5]</sup>.

#### 4-Conclusion:

This study concluded that patients with leiomyoma are at late reproductive or premenopausal age and overweight with mean BMI  $28.4 \pm 4.7$  kg/m<sup>2</sup>. It was found that leiomyoma PRL is significantly higher than myometrial PRL of the same patient.

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