



RESEARCH ARTICLE

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Prospective Correlation Study to Assess the Association of Serum Prolactin Levels in Cases of Fibroadenoma in Women of Reproductive Age Group

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ABSTRACT

Introduction: Fibroadenomas are one of the most common benign tumors of the breast in the adolescent population. They account for 68% of all breast masses and 44%-94% of all biopsied breast lesions. Fibroadenomas can range from asymptomatic masses to painful and rapidly growing tumors that can cause significant esthetic distortions of the breast. Benign breast disorders results from an imbalance or inappropriate target gland response to changing tide of circulating hormones. Several studies have shown that serum prolactin levels may be increased in benign breast diseases. Hence this study is intended to assess serum prolactin levels in patients presenting with fibroadenoma to our hospital. If a correlation is established between serum prolactin levels and incidence of fibroadenoma, a feasible drug treatment such as anti prolactin agents can be used which can reduce the anxiety and cosmetic problems associated with surgical interventions.

Aim and objectives: To estimate serum prolactin level in patients presenting with lump in the breast and proved to be fibroadenoma with Fine Needle Aspiration Cytology (FNAC). To assess whether prolactin level can be used as an indicator for incidence and progression of fibroadenoma.

Materials and methods: A prospective observational study of serum prolactin values of 95 female patients in the reproductive age group of 18-45 years who presented with lump in the breast proved to be fibroadenoma by FNAC and planning to undergo excision during the period of 2019-2021.

Results: Majority of the patients had no symptoms except lump in the breast. 34 participants had pain along with lump in the breast. Majority of the participants had lump in breast of size 3 cm in the greatest dimension in both right and left breast followed by 4 cm. 13 participants had lump of size 5 or more than 5 cm in right breast and 12 participants had lump of size 5 or more than 5 cm in left breast. In our study 44 out of 95 participants had lump in the right breast, 37 had lump in the left breast. 14 study participants had fibroadenomas in bilateral breast. 48 out of 95 participants had lump in the right upper quadrant followed by 44 participants with lump in left upper quadrant followed by 10 in right lower quadrant and 7 in left lower quadrant. Duration of lump in the breast ranged from 2 months to 24 months with majority of the participants having lump in the breast from past 8 months followed by past 9 months. All 95 patients had lump in the breast which was firm in consistency. FNAC was done in all 95 cases prior surgery and all cases were reported as Fibroadenoma. All 95 patients underwent excision of the lump which was sent for histopathology and all biopsy reports were consistent with FNAC findings prior to the surgery and were reported as fibroadenoma. Serum prolactin levels were measured in all 95 cases. The biological reference interval for serum prolactin in our study was 3.80 ng/ml to 23.20 ng/ml. Mean prolactin level in the study was found to be 24.29 ng/ml with standard deviation of 14.11 ng/ml. Minimum value of 5.72 ng/ml and maximum value was reported as 80.6 ng/ml. Out of 95 participants 42 had raised serum prolactin levels and remaining 53 had normal serum prolactin levels. Approximately 44% of the study population had raised serum prolactin values. Out of total study population, 81 patients had unilateral fibroadenomas and 14 had bilateral fibroadenoma. In the unilateral fibroadenoma group, serum prolactin levels were normal in 51 patients and elevated in 30 patients. Out of 14 patients in the bilateral fibroadenoma group 12 had elevated serum prolactin

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levels which accounted for approximately 85% in that group. Serum prolactin level was significantly higher in bilateral fibroadenoma group compared to unilateral fibroadenoma with p value <0.001 which is statistically significant with both chi square test and unpaired t test. Out of total 95 patients 68 patients had single lump in the breast including both unilateral and bilateral fibroadenoma groups and 27 patients had multiple lumps in both unilateral and bilateral group. Mean prolactin level in single lump group was 19.14 and in multiple lump group it was 37.27. Prolactin level was significantly higher among those with multiple lumps compared to those with single lump. (unpaired t test used) Out of the 14 patients with bilateral fibroadenoma, 9 patients had multiple lumps as compared to 5 patients who had single lump in each breast. Mean prolactin level was 19.36 in single lump group as compared to 39.87 in multiple bilateral fibroadenoma group. Prolactin level was significantly higher among those with multiple lumps compared to those with single lump in the bilateral fibroadenoma patients. In the unilateral fibroadenoma group, 63 patients had single lump in the breast as compared to 18 who had multiple lumps. Mean prolactin level in single lump group was 19.12 as compared to 35.96 in the multiple lump group. Prolactin level was significantly higher among those with multiple lumps as compared to those with single lump.

Conclusion: There is a significant association between raised serum prolactin levels and incidence of bilateral as well as multiple fibroadenomas. Multiple lumps which can't be excised can be managed with anti-prolactin therapy, requiring surgery only for symptomatic large lumps. Morbidity and anxiety due to surgery can be reduced.

Introduction

Fibroadenomas are one of the most common benign tumors of the breast in the adolescent population. They account for 68% of all breast masses and 44%-94% of all biopsied breast lesions. Fibroadenomas can range from asymptomatic masses to painful and rapidly growing tumors that can cause significant esthetic distortions of the breast [1]. Benign breast disorders results from an imbalance or inappropriate target gland response to changing tide of circulating hormones. Several studies have shown that serum prolactin levels may be increased in benign breast diseases [2]. Prolactin (also known as lactotropin and PRL) is a hormone that's responsible for lactation, certain breast tissue development and contributes to hundreds of other bodily processes. Bromocriptine and cabergoline are ergot derivatives with a high affinity for dopamine D 2 receptors [3]. Dopamine agonists suppress prolactin release very effectively in patients with hyperprolactinemia [4]. Fibroadenoma, a feasible drug treatment such as anti-prolactin agents can be used which can reduce the anxiety and cosmetic problems associated with surgical interventions.

Materials and Methods

Source of data

All patients presenting with lump in the breast with FNAC showing fibroadenoma in the reproductive age group of 18-45 years admitted in Department of General Surgery, Vydehi Institute of Medical Sciences and Research Centre Bangalore were included in our

study. The study was conducted during the period of October 2019 to September 2021.

Method of collection of data

A pretested proforma was used to collect patient information from all the selected patients. Each patient had a fasting blood sample taken. Prolactin was estimated by Immuno Radio Metric Assay. As far as could be ascertained, no patient was receiving phenothiazines, L-DOPA (known as levodopa and l-3,4-dihydroxyphenylalanine), monoamine oxidase inhibitors, or other drugs known to affect the secretion of prolactin.

Study design

A Prospective observational study.

Study period

October 2019 to September 2021.

Place of study

Vydehi institute of medical sciences and research Centre, Bangalore.

Sample size

$N = z^2 \times \sigma^2 / d^2$ $Z = 1.96$ at 95% confidence level
Standard deviation = 24.77, D = precision or margin of error (5)
 $N = (1.96)^2 \times (24.77)^2 / (5)^2$ $N = 95$
Serum prolactin levels of 95 patients who were diagnosed clinically with lump in the breast and proved to be fibroadenoma by FNAC was assessed.

Statistical analysis

The data collected was statistically analyzed using descriptive statistics namely mean, standard deviation,

percentage.

Inclusion criteria

Patients with breast lump proved to be fibroadenoma by FNAC in age group 18-45.

Exclusion criteria

Pregnant and lactating women of same age group Patients who have recurrent breast lumps. Patients on medications such as L-DOPA, Phenothiazines, monoamine oxidase inhibitors which alter the prolactin levels. Patients with breast lumps proved to be breast diseases other than fibroadenoma by FNAC.

Procedure for collection of data

Ethical clearance has been obtained from the "Ethical Clearance Committee" of the institution for the study. Prior Informed Consent was obtained before evaluating each patient. Data was collected on a pre-tested proforma. Based on the selection criteria, detailed history and clinical examination done in each patient. Serum prolactin values were analyzed of all the participating patient.

Investigation sent

Early morning fasting sample of Serum Prolactin.

Results

Distribution of study participants based on age group Mean age of the study participants was 26.14 yrs (SD-7.645) majority of the study participants were from the age group of 18-24 years. 49 participants belonged to this age group followed by 25-34 years. 35-45 year group had least number of participants i.e 15 out of 95. Pie chart showing age group wise distribution. All of the study subjects presented with lump in the breast. (Figures 1 and 2).

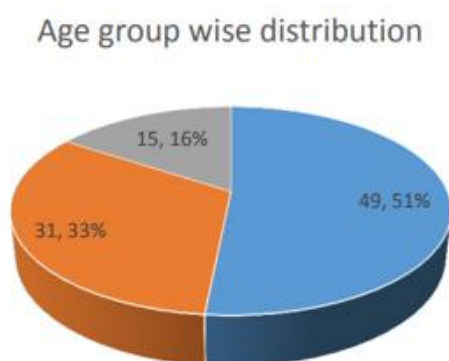


Figure 1. Age group wise distribution.

Note: (■)-18-24 years, (■)-25-34 years, (■)-35-45 years.

Distribution based on presence of pain

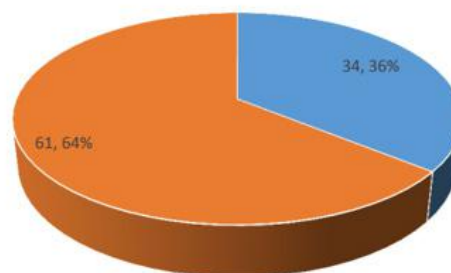


Figure 2. Distribution based on presence of pain.

Note: (■)-Present, (■)-Absent.

Distribution of study participants based on symptoms at the time of presentation. Out of 95 participants majority i.e, 61 patients had no symptoms except lump in the breast. 34 participants complained of pain along with lump in the breast (Table 1).

Table 1. Distribution of patients based on size of lump.

Size of the lump	Right side		Left side	
	Frequency	Percentage	Frequency	Percentage
3 cm	29	50%	27	52.94%
4 cm	16	27.59%	12	23.53%
5 cm	13	22.41%	12	23.53%
Total	58	100%	51	100%

Prolactin level was significantly higher among bilateral fibroadenoma group compared to unilateral fibroadenoma. (unpaired t test used) Mean prolactin levels in bilateral group was 32.55 as compared to unilateral group where it was 22.87 (Tables 2-4).

Table 2. Distribution of study participants based on prolactin level.

Prolactin level	Frequency	Percentage
Normal prolactin	53	55.79%
Raised prolactin	42	44.21%
Total	95	100%
100%	100%	100%

Table 3. Comparing mean prolactin level in bilateral vs. unilateral fibroadenoma.

	Unilateral fibroadenoma (n-81)		bilateral fibroadenoma (n-14)		P value
	Mean	SD	Mean	SD	
	Prolactin level	22.87	13.31	32.55	

In the bilateral fibroadenoma group out of 14 patients 12 had elevated prolactin levels as compared to unilateral fibroadenoma group where out of 81 patients 30 had high serum prolactin levels which was statistically significant (chi-square test) (Figure 3).

Out of total 95 patients 68 patients had single lump in the breast including both unilateral and bilateral

fibroadenoma groups and 27 patients had multiple lumps in both unilateral and bilateral group. Mean prolactin level in single lump group was 19.14 and in multiple lump group it was 37.27. Prolactin level was significantly higher among those with multiple lumps compared to those with single lump. (unpaired t test used) (Figure 4).

Table 4. Comparing prolactin level in bilateral vs. unilateral fibroadenoma.

Prolactin level	Unilateral fibroadenoma (n-81)		bilateral fibroadenoma (n-14)		P value
	Frequency	Percentage	Frequency	Percentage	
Normal	51	63.00%	2	14.30%	<0.001
High	30	37.00%	12	85.70%	
Total	81	100%	14	100%	

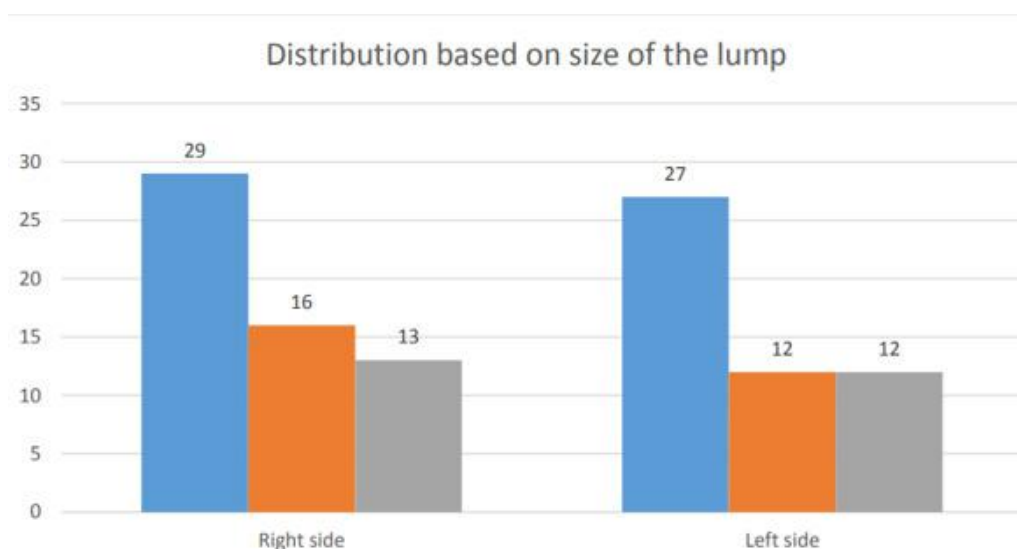


Figure 3. Distribution based on size of the lump.

Note: (■)-3 cm, (■)-4 cm, (■)-5 cm.

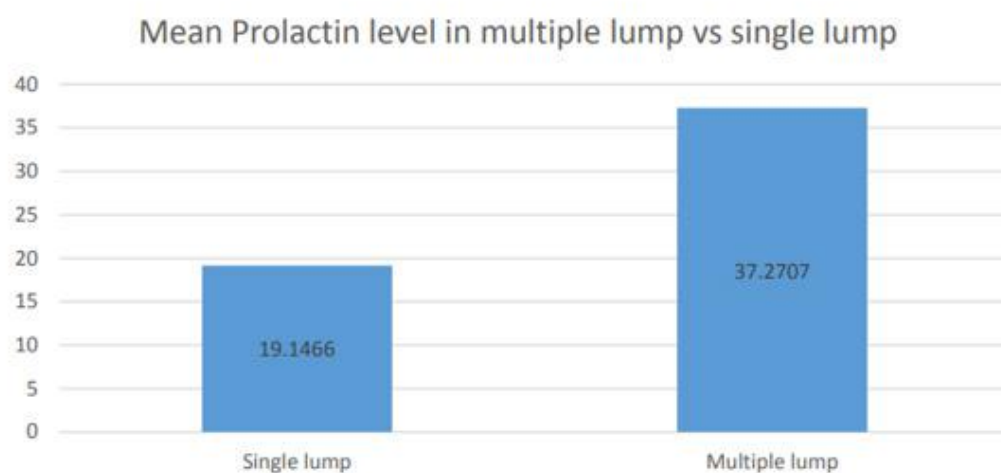


Figure 4. Mean prolactin level in multiple lump vs. single lump.

Note: (■)-prolactin level.

Discussion

95 female patients presenting with lump in the breast with FNAC showing fibroadenoma, in the reproductive age group of 18-45 years admitted in Department of General Surgery, Vydehi Institute of Medical Sciences and Research Centre Bangalore were included in the study. The study was conducted during the period of October 2019 to September 2021. Fibroadenoma tends to occur in early age. It is most commonly found in adolescents and less commonly in postmenopausal women [1].

Mean age of the study participants was 26.14 yrs and majority of the study participants were from the age group of 18-24 years. Least number of participants were from the 35-45 year age group which was 15 out of 95. It can be concluded that incidence of fibroadenoma decreases with age and generally found before 30 years of age in females in general population which is consistent with the study done by Santen et al. [4].

Fibroadenoma presents as a painless, smooth, mobile, rubbery mass with distinct borders. 5 Out of 95 participants majority i.e 61 patients had no symptoms except lump in the breast. 34 participants complained of pain along with lump in the breast. Fibroadenomas usually range from 1 cm to 3 cm in size and most commonly in the upper outer quadrant of the breast [5]. This is consistent with our study where majority of the participants had lump in breast of size 3 cm in the greatest dimension in both right and left breast followed by 4 cm. Seventy to ninety percent of fibroadenomas are simple fibroadenomas. They are the most common type of fibroadenoma.

Giant juvenile fibroadenomas are a rare variant of fibroadenoma. They are rapidly enlarging encapsulated fibroadenoma with a diameter greater than 5 cm, weighing over 500 g, or displacing at least four fifths of the breast. The incidence of giant fibroadenomas is approximately 0.5%-2% of all fibroadenomas [5]. In our study 13 participants had lump of size 5 or more than 5 cm in right breast and 12 participants had lump of size 5 or more than 5 cm in left breast. In our study 44 out of 95 participants had lump in the right breast, 37 had lump in the left breast. Remaining 14 had lump in the bilateral breast. Most fibroadenomas present as single mass, however the presence of multiple fibroadenomas can be seen in 15-20% of patients. It has been reported that the average number of lumps in cases of multiple fibroadenomas is typically 3-4 in a single breast and occurrence of more than five fibroadenomas in an individual patient is much less common. 614 out of 95 patients had fibroadenomas in bilateral breast which is consistent with the study mentioned above.

In this study, duration of lump in the breast ranged from

2 months to 24 months in the study participants with majority of the participants having lump in the breast from past 8 months followed by past 9 months. Delay in presentation of lump can be either due to slow increase in size of the lump or patients may have noticed the lump very late. Fibroadenoma presents most commonly in the upper outer quadrant of the breast [5]. In our study population majority of the participants had lump in the right upper outer quadrant followed by lump in the left upper outer quadrant which is consistent with the study mentioned above. In our study all 95 patients had lump in the breast which was firm in consistency. FNAC was done in all 95 cases prior surgery and all cases were reported as fibroadenoma.

All 95 patients underwent excision of the lump which was sent for histopathology and all biopsy reports were consistent with FNAC findings prior to the surgery and were reported as fibroadenoma [6]. In a study done by Saravanan et al., which compared prolactin levels in women with fibroadenoma found that out of 13 patients with fibroadenoma 5 had elevated serum prolactin levels which is approximately 38% of the study population [7]. They had concluded in their study that number of cases are few to give an effective interpretation and thorough investigation in future was required with more number of patients which could open potential therapeutic approaches for fibroadenoma if a correlation can be established between the two [7].

In our study serum prolactin levels were measured in all 95 cases. The biological reference interval for serum prolactin in our study was 3.80 ng/ml to 23.20 ng/ml. Mean prolactin level in the study was found to be 24.29 ng/ml with standard deviation of 14.11 ng/ml. Minimum value of 5.72 ng/ml and maximum value was reported as 80.6 ng/ml. In our study, out of 95 participants 42 had raised serum prolactin levels and remaining 53 had normal serum prolactin levels. Approximately 44% of the study population had raised serum prolactin values.

Petronella et al, in their study showed that 70.83% of fibroadenoma cases displayed an increase in blood concentration of prolactin [2]. In another study conducted by Courtillot et al. and Zubor et al. elevated blood levels of serum prolactin showed a role in growth and development of benign breast diseases [8,9]. Further, study conducted by Kang et al. and Cercicatto et al., it was concluded that elevated blood concentration of prolactin lead to the development and growth of fibroadenomas [10,11].

In our study we have also compared serum prolactin levels of unilateral and bilateral fibroadenomas. Out of total study population, 81 patients had unilateral fibroadenomas and 14 had bilateral fibroadenoma. In

the unilateral fibroadenoma group, serum prolactin levels were normal in 51 patients and elevated in 30 patients. Out of 14 patients in the bilateral fibroadenoma group 12 had elevated serum prolactin levels which accounted for approximately 85% in that group. So we have concluded that Prolactin level was significantly higher in bilateral fibroadenoma group as compared to unilateral fibroadenoma group with p value <0.001 which is statistically significant with both chi square test and unpaired t-test.

It has also been inferred that elevated blood concentration of prolactin causes, through a link with its receptors, an abnormal activation of these receptors that, in turn, produces "cellular upregulation" thus initiating a series of intracellular reactions that eventually lead to the development and growth of fibroadenomas [12].

According to Gill et al., higher expression of prolactin receptors is noted in cells of most benign and malignant breast lesions, compared with normal cells. Most benign lesions show more intense positive staining than that seen in normal ducts and acini. Thus, in addition to luminal staining, intense cytoplasmic staining is also noted in many cases. All fibroadenomas were prolactin receptor positive in their study [12]. In the study done by Courtillot et al., there was an explosive response (>100 ng/ml) of PRL to stimulation test in 31.2% of the cases of multiple fibroadenomas which was one third of the study population [8].

Out of total 95 patients 68 patients had single lump in the breast including both unilateral and bilateral fibroadenoma groups and 27 patients had multiple lumps in both unilateral and bilateral group. Mean prolactin level in single lump group was 19.14 and in multiple lump group it was 37.27. Prolactin level was significantly higher among those with multiple lumps compared to those with single lump (unpaired t test used). Out of the 14 patients with bilateral fibroadenoma, 9 patients had multiple lumps as compared to 5 patients who had single lump in each breast. Mean prolactin level was 19.36 in single lump group as compared to 39.87 in multiple bilateral fibroadenoma group. Prolactin level was significantly higher among those with multiple lumps compared to those with single lump in the bilateral fibroadenoma patients. In the unilateral fibroadenoma group, 63 patients had single lump in the breast as compared to 18 who had multiple lumps. Mean prolactin level in single lump group was 19.12 as compared to 35.96 in the multiple lump group. Prolactin level was significantly higher among those with multiple lumps as compared to those with single lump.

Antiprolactin agents such as Bromocriptine is highly

effective in most conditions of aberrations of normal development and involution of which fibroadenoma is a part. In a study conducted by Memon et al, in patients with multiple fibroadenomas, 72% responded quite remarkably to the treatment in a way that most of the small fibroadenomas disappeared and only 1-2 of large fibroadenomas remained which were excised with better cosmetic results [13].

In study conducted by Parlati et al, significant reduction of mastodynia and significant improvement of the breast lesions were observed in the group given bromocriptine. Moreover breast lesions appeared to be reduced in size and became softer in patients with who received bromocriptine [14].

Conclusion

From our study we have concluded that patients with with bilateral fibroadenomas have raised serum prolactin levels as compared to patients with unilateral fibroadenomas. We also concluded that patients having multiple lumps in both unilateral and bilateral group had raised serum prolactin levels as compared to those with single lump. We can ascertain from our findings that there is an association between raised serum prolactin levels and incidence of bilateral as well as multiple fibroadenomas. In patients with multiple fibroadenomas in single breast, lumps which are too small to excise surgically can be managed with antiprolactin therapy along with excision of lumps which are large enough and are symptomatic.

In this way multiple scars can be avoided and morbidity and anxiety due to surgery can be reduced. Same can be applied for patients having multiple lumps in unilateral breast as well as in bilateral breast. There is a possibility that antiprolactin therapy can also reduce the chance of recurrence of fibroadenomas. But there are very few studies where anti prolactin therapy has actually been given and where favourable results were obtained in terms of reduction in size of lumps and disappearance of lumps after initiation of anti prolactin therapy. Further studies have to be done to ascertain the effectiveness of anti prolactin therapy, its side effects, dosage and duration of treatment.

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