

Original Research Article

Clinical spectrum and hormonal profile of patients with non-inflammatory benign breast disorders: a cross-sectional study

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ABSTRACT

Background: Benign breast disorders (BBD) are one of the most common problems seen in women. Since development of the breast is under the influence of various hormones, this study was done to document the clinical spectrum of females with BBD, and to understand if any association exists between serum levels of various hormones and BBD.

Methods: This was a cross sectional study of 134 patients who presented to the surgical OPD with non-inflammatory BBD. These patients were evaluated for serum levels of 8 hormones-estrogen, progesterone, follicle stimulating hormone (FSH), luteinising hormone (LH), prolactin, thyroid stimulating hormone (TSH), testosterone and prostate specific antigen (PSA). The levels of these hormones were correlated with the type of BBD.

Results: Breast pain was the most common presenting complaint (67.16%), followed by breast lump (51.49%). Most patients were diagnosed as proliferative BBD (50%) followed by mastalgia (32.8%) and non-proliferative BBD (17.2%), 36.57% patients had fibroadenoma. The 73.88% of patients showed abnormal serum levels of at least one of the hormones. Most common abnormalities were significantly detectable levels of serum PSA (51.4%), and decreased levels of serum testosterone (20.8%). Among the rest, TSH was raised in 9.7%, estrogen was raised in 9.7%, FSH was raised in 8.9%, prolactin was raised in 8.9%, LH was raised in 6.7% and progesterone was raised in 2.9%.

Conclusions: Our study suggests that abnormality in various hormones (seen in 73.88% of our patients) could be responsible for development of BBD. The interplay of these hormones on aberrations in breast development and involution is unclear and warrants further studies on larger populations.

Keywords: Breast, BBD, Fibrocystic breast disease, Fibroadenoma, Mastitis, Steroid hormone

INTRODUCTION

Benign breast disorders (BBD) are one of the most common health problems seen in women, particularly in the reproductive age group.¹ Since development of breast is under influence of various hormones, aberrations in its development could be associated with aberrations in the circulating levels of these hormones.

Estrogen is responsible for development of ductal system and stroma, and progesterone and prolactin are responsible for glandular proliferation.² Testosterone has been shown to inhibit the development of breast tissue in males.³ Thyroid hormone, LH and FSH have a role in development of secondary sexual characteristics; however, their exact role in breast development is not known.

The current study was done to document the clinico-pathological profile of patients with benign breast diseases presenting to the surgery OPD, and to study the serum levels of estrogen, progesterone, LH, FSH, testosterone, TSH, PSA and prolactin in these patients with BBD.

METHODS

This was a cross sectional study of 134 consecutive female patients, attending the surgical OPD of Lady Hardinge Medical College, New Delhi, presenting with complaints of breast lump, nodularity, breast pain or nipple discharge. Included in the study were all patients diagnosed to have non-inflammatory benign breast disease after triple assessment, i.e., clinical examination, radiological evaluation (ultrasound $\pm$ mammography), and cytopathology. Patients diagnosed with malignancy, inflammatory BBD, who were pregnant or lactating at presentation, or those on drugs that either contained hormones or that modified hormone levels, were excluded from the study. This study was conducted from November 2014 to January 2016.

The study was approved by the institutional ethics committee.

After a written and informed consent, all the patients were evaluated with a detailed history and examination of the breast. Ultrasound examination / mammogram of the breast, followed by a pathological examination using FNAC/ core needle biopsy were done.

After the diagnosis of the non-inflammatory benign breast disorder was established by triple evaluation-clinical, radiological and pathological, the patient's blood sample was collected and serum levels of the following hormones were estimated-estrogen, progesterone, testosterone, prolactin, TSH, FSH, LH, and PSA.

Of these, TSH and PSA were measured using chemiluminescent immunoassay in Beckmann coulter access-2 analyser using system packs. Estrogen, progesterone, LH, FSH, testosterone as well as prolactin were measured by electro-chemiluminescent immunoassay in Roche Cobas e411 analyser using system packs.

The study group patients were offered treatment as per the accepted norms for each benign breast condition.

The data collected was analysed using the SPSS version 12.

RESULTS

A total of 134 consecutive patients with non-inflammatory benign breast diseases attending our surgery out-patient department, who met the inclusion criteria, were included the study.

The study patients ranged between 17-59 years of age, with an average age of 26.9 years (SD=8.77). These patients had a BMI ranging from 14.32 kg/m² to 36.49 kg/m², with an average BMI of 23.72 kg/m² (SD=3.40).

Among those included, 129 (96.26%) patients were in the reproductive phase, 2 were post-menopausal and 3 were post-hysterectomy. The age of menarche of these patients ranged from 12 to 17 years with an average of 14.4 years (SD=1.15). 112 (83.58%) patients had regular periods and 17 (12.69%) complained of irregular periods.

The 46 (34.33%) of the patients in the study were nulliparous. The age at first child birth for the 88 parous (65.67%) females ranged from 16- 28 years, average being 21.27 years (SD= 2.34) (Table 1).

The patients most commonly presented with breast pain followed by breast lump. These symptoms have been summarised in Table 1.

After clinical, radiological and histopathological examination, most patients were diagnosed as proliferative BBD (50%; 67/134), followed by mastalgia (32.8%; 44/134), and the least number were diagnosed as non-proliferative BBD (17.2%; 23/134). Fibroadenoma was found in 36.57% (49/134) of the patients.

The results of the hormonal assay in our patients are shown in Table 2.

A total of 99 (73.88%) patients showed abnormal serum levels of at least one of the hormones. The maximum number of these patients showed a significantly detectable level of serum PSA (69/134; 51.4%) and decreased levels of serum testosterone (28/134; 20.8%). Among the rest estrogen was raised in 9.7% (13/134), progesterone was raised in 2.9% (4/134), LH was raised in 6.7% (9/134) and reduced in 0.7% (1/134), FSH was raised in 8.9% (12/134), prolactin was raised in 8.9% (12/134) and reduced in 1.5% (2/134), TSH was raised in 9.7% (13/134) and reduced in 0.7% (1/134).

Elevated estrogen levels were seen in 13 (9.7%) patients. Among these, 8 patients were diagnosed with proliferative BBD, 4 of whom had bilateral fibroadenomas, and 1 had ductal hyperplasia. 2 patients had non-proliferative BBD and 3 were diagnosed with mastalgia.

Increased progesterone was found in 4 (2.98%) patients. Out of these 4 patients, 1 of them was diagnosed with non-proliferative BBD, and 3 were diagnosed with proliferative BBD of which 2 had fibroadenoma and 1 had hyperplasia.

Nine (6.7%) patients had raised LH levels, while 1 patient had decreased LH levels. Among those with raised LH levels, 1 was diagnosed as non-proliferative BBD, 6 as proliferative BBD, and 2 with mastalgia.

Among the proliferative BBD, 4 were fibroadenomas, 1 patient having bilateral fibroadenoma. A single 22-year-old was diagnosed with non-proliferative BBD and showed decrease in LH levels.

The 12 (8.95%) patients showed an increase in FSH levels. Among these, 3 diagnosed as non-proliferative BBD, 6 as proliferative BBD (5 had fibroadenoma, 1 patient having bilateral fibroadenoma) and 3 as mastalgia.

The 12 (8.95%) patients had an increase in prolactin levels and 2 had decreased prolactin levels. Those with increased prolactin levels were diagnosed as: 2 patients with non-proliferative BBD, 7 with proliferative BBD, 3 patients with mastalgia. Of the patients with proliferative BBD, 6 were fibroadenomas, 2 being bilateral.

The 28 (20.89%) patients showed less than normal testosterone levels. 10 patients were diagnosed with the

mastalgia, of which 5 had associated nodularity. The 13 patients were diagnosed with proliferative BBD, amongst which 11 were fibroadenoma (2 patients had bilateral fibroadenoma). 6 patients were diagnosed with non-proliferative BBD.

The 13 (9.7%) patients were found to have raised TSH levels. Out of these, 8 patients had proliferative BBD, 7 of which had fibroadenomas (1 had bilateral fibroadenomas). Non-proliferative BBD was seen in 1 patient and mastalgia in 4. A single patient diagnosed with fibroadenoma had decreased TSH levels.

The 69 (51.49%) patients had significantly detectable PSA levels, 15 had non-proliferative BBD, 37 patients had proliferative BBD and 17 had mastalgia. Of proliferative BBD, 26 fibroadenomas, 8 being bilateral. The 8 of the patients with mastalgia had underlying nodularity.

Table 1: Demographic and clinical data of the study patients, (n=134).

Variables	Mean, n (%)	Range
Age (In years)	26.9	17-59 (SD=8.77)
BMI (kg/m ²)	23.72	14.32-36.49 (SD=3.40)
Menopausal status		
Premenopausal	129	
Menopausal	2	
Post-hysterectomy	3	
Age at menarche (In years)	14.4	12-17 (SD=1.15)
Periods (n=129, premenopausal)		
Regular	112 (83.58)	
Irregular	17 (12.68)	
Parity:		
Nulliparous	46 (39.33)	
Age at first child (n=88, parous) (in years)	21.27	16-28 (SD=2.34)
Symptoms (n=134) (%)		
Lump	69	51.49
Pain	90	67.16
Nodularity	39	29.10
Nipple discharge	06	04.48

Table 2: Hormonal profile of study patients with non-inflammatory BBD.

Variables	Estrogen (pg/ml)	Progesterone (ng/ml)	LH (IU/L)	FSH (IU/L)	Prolactin (ng/ml)	Testosterone (ng/dl)	TSH (μIU/ml)	PSA (ng/ml)
Normal range	20-150	0-2.7	1.68-15	1-10	3.34-26.72	15-70	0.34-5.6	0
Study patients								
Range	21.04-856	0.105-24.32	1.57-42.71	1.86-66.45	1.86-59.29	2.5-67.71	0.09-26.94	0-0.11
Mean	107.9	1.05	9.05	8.51	18.23	25.44	3.57	0.008
STD deviation	92.33	2.24	6.17	6.35	8.76	12.95	3.13	0.013
<Normal (%)	0	0	1 (0.7)	0	2 (1.5)	28 (20.8)	1 (0.7)	0
>Normal (%)	13 (9.7)	4 (2.9)	9 (6.7)	12 (8.9)	12 (8.9)	0	13 (9.7)	69 (51.4)

DISCUSSION

The patients presenting with BBD in our study were in the age group of 17-59 years (average 26.9 years), of which 129 (96.3%) were in the reproductive age group. The average age of presentation in our study was similar to study done in Pondicherry by Maychet et al where the average age of presentation was 28.6 years and 85% of the females were in the reproductive age group.⁴ This was higher than what was found in another study in an Indian population by Navneet Kaur et al where 80.5% were in the reproductive age group, but having the same age distribution as in our study (12-75 years, average-28 years).⁵

In our study, breast pain was the most common presenting complaint found in 67.16% (90/134) of the patients followed by breast lump which was 51.49% (69/134) of the patients. This was different from a study on similar population done by Kaur et al where in breast lump was the most common presenting complaint, found in 42% followed by breast pain which was found in 39% of the patients, and also from the study done in Pondicherry where also breast lumps (87/100; 87%) were the most common presenting complaint followed by breast pain (33/100; 33%).^{4,5}

In our study 29.10% (39/134) of the patients had nodularity in the breast and only 4.48% (6/134) of the patients complained of nipple discharge. This was almost similar to that found by Kaur et al where nodularity accounted for 26.3% (69/262) of the presenting complaints and nipple discharge was found in 5.7% (15/262) patients.⁵

A study from Greece showed that among 578 women with BBD and no previous exogenous hormone use, 254 had non-proliferative disease, 324 had proliferative disease, which was similar to what was found in our study.⁶ However, this data was at variance with a study on Sub-Saharan females where non-proliferative BBD (82%; 160/195) was more common as compared to proliferative BBD (18%; 35/195).⁷

Mastalgia with or without nodularity was found in 102 out of 262 patients (39 %) by Kaur et al of which 26 patients had associated nodularity.⁵ This was similar to our study where 44/134 patients had mastalgia (32.8%) of which 18 had associated nodularity.

In our study, 9.7% patients showed raised estrogen level, among which 2 had non-proliferative BBD, 8 had proliferative BBD (4 had fibroadenoma) and 3 had mastalgia. This is in concordance with studies done by Sasaki et al who have shown an increased concentration of estrogen in patients with BBD, especially in patients with fibroadenomas.⁸ Similar results were obtained by Samoli et al in Greece, where serum estradiol and estrone levels were found to be significantly higher in patients with BBD as compared to healthy females, this contrast

being more in the peri/postmenopausal age group.⁶ They also observed that estrogen levels were higher in patients with proliferative BBD. This is in agreement with our study where the association of serum estrogen levels was more with proliferative BBD (11.9%) than with the non-proliferative BBD (8.7%). The WHI (Women's health initiative) trial where conjugated equine estrogen was randomly given to women, also shows similar findings of an increased incidence of proliferative BBD that was seen over a follow up of 6.9 years.⁹ Another case-control study among 184 women with BBD and 50 apparently healthy women, have suggested that estrogens may be increased in BBD.¹⁰ However, other studies indicate no increase in estradiol and estrone in BBD.¹¹

In our study serum progesterone levels were raised in 2.9% (4/134) patients. 50% of these patients (2/4) had an associated increased estrogen level, which is in concordance with various studies reporting an increase in progesterone levels along with estrogen and increase in progesterone receptors in response to estrogen. Women's health initiative (WHI) randomized controlled trial showed that in 16608 postmenopausal women who were randomly assigned either to 0.625 mg/d of conjugated equine estrogen plus 2.5 mg/d of medroxyprogesterone acetate or to placebo, there was a 74% increased risk of development of proliferative BBD.¹²

These findings were supportive of findings of raised levels of these hormones found in benign breast lesions, particularly fibroadenomas, by various authors.

In our study, 6.7% (9/134) patients had raised LH, most of whom had proliferative BBD. Four of the patients with raised LH levels had raised FSH levels too. In our study, 8.95% (12/134) patients showed an increase in FSH levels. Most of these patients had proliferative BBD (6/12), 5 being fibroadenoma. Patients also had associated raised LH (4), TSH (4) and PSA (6) levels and decreased testosterone (4) levels.

Similar to the findings in our study, Garde SV showed presence of higher levels of FSH in benign mammary lesions.¹³ Macini et al studied 131 premenopausal females and exhibited an elevated FSH/LH ratio.¹⁴

In our study, 8.95% (12/134) patients showed an increase in prolactin levels and 2 had decreased prolactin levels. Most patients with raised prolactin (7/12) were diagnosed with proliferative BBD.

Variable data exists regarding relation of prolactin levels and benign breast diseases.

Peters et al studied basal serum prolactin concentrations in 193 patients with fibrocystic disease and compared it to serum prolactin levels in 193 healthy women and showed serum prolactin levels were above normal in 45.6% of the patients and in 21.2% of the control subjects.¹⁵ Watt-Boolsen et al showed the basal prolactin

level was significantly elevated in patients with cyclical mastalgia.¹⁶

Supporting the role of prolactin in cyclical mastalgia, a double-blind crossover trial was done by Mansel et al where 29 women with cyclical mastalgia and 11 with non-cyclical pain were treated with bromocriptine and significant improvement in breast symptoms and a significant fall in prolactin levels were seen in the patients with cyclical pain.¹⁷ Another similar randomised, double-blind study by Nazli et al on 50 pre-menopausal women with severe and persistent cyclical mastalgia showed that bromocriptine, effectively controlled the symptoms of cyclical mastalgia.¹⁸ In contrast to the above studies, a study in France on 95 premenopausal females failed to establish any such relation.¹⁹ Similar findings were seen by Nicol et al, who evaluated 153 consecutive patients with operable benign and malignant breast lesions for preoperative serum prolactin levels.²⁰ Most patients (93%) had serum prolactin levels within the normal limits.

In the present study conducted by us, 20.89% (28/134) patients showed less than normal testosterone levels. Most of these patients (13/28) were diagnosed with proliferative BBD, of which 11 patients had fibroadenoma.

Our results may be explained by findings that, in premenopausal women, circulating testosterone and estradiol levels peak at midcycle, but in transition to the luteal phase (during breast epithelial proliferation), testosterone levels go down and estradiol levels increase further.

A study done with 578 females with benign breast diseases in Europe, found evidence that levels of estradiol, estrone and testosterone tend to be higher among women with BBD compared with women with no breast pathology.⁶ Rose et al examined a variety of breast lesions and showed that fibroadenomas showed a high degree of testosterone metabolism forming both 14C-androstenedione and 14C-5alpha-dihydrotestosterone.²¹

However, a study done in 2000, with 40 BBD cases and unspecified number of control women indicated no increase in estradiol, estrone or testosterone in BBD.²²

In our study 9.7% (13/134) patients were found to have raised TSH levels. Most of these patients (8/13) had proliferative BBD (7 being fibroadenomas). There have been various studies that showed an increased prevalence of thyroid disorders in women with BBD; and various thyroid disorders, such as autoimmunity, goiter, hypothyroidism, and hyperthyroidism, have been linked with BBD and its outcome.

A prospective study on 201 women with BBD with no previous features of hypothyroidism who were followed up for 13 months showed 23% prevalence of

hypothyroidism in patients with benign breast diseases with maximum incidence seen in cases of nipple discharge and mastalgia.²³ Another study by Estes where nineteen patients were evaluated for breast pain and nodularity associated with fibrocystic disease and treated with levothyroxine showed rapid pain relief occurred in 73% of patients, with total relief in 47%, after daily treatment with 0.1 mg of levothyroxine.²⁴

Considering serum PSA, a hormone initially believed to be secreted by the prostate gland and hence, found only in males. Our study showed that significant detectable levels of PSA were found in 51.49% (69/134) patients with BBD. The 15 of these patients had non-proliferative BBD, 37 patients had proliferative BBD and 17 had mastalgia. In agreement with our study, various studies have shown raised serum PSA levels in patients with BBD as compared to normal population as well as in patients with breast carcinoma. Narita et al studied 24 breast tumours in 2005 and detected PSA in 7% of normal breast tissues and in 54.5% of benign tumors.²⁵ Another study by Yu et al examined quantitatively the PSA levels in 199 breast tumors, 48 tissues with benign breast disease (BBD, 34 fibroadenomas), and 36 normal breast tissues. Significant amounts of PSA were found in 28% of breast tumors, 65% of BBD tissues, and 33% of normal breast tissues.²⁶

In our study, raised serum levels of all the 7 hormones (estrogen, progesterone, LH, FSH, prolactin, thyroid, PSA), most prominent with PSA, estrogen, prolactin and FSH, and a decrease in testosterone was associated with BBD. This association was more with proliferative BBD than the non-proliferative ones.

Limitation

The predominant effect of a single hormone, the interplay of multiple hormones and their clinical significance is unclear and warrants further studies on larger populations.

CONCLUSION

Our study shows that 73.88% females with BBD have an abnormal level of at least one of the hormones which has been shown to effect normal breast development. The largest number of these patients show decreased testosterone levels and raised estrogen levels as compared to the normal levels.

Another interesting finding in our study was the significantly detectable levels of serum PSA, which has been postulated to be produced by the ductal cells of the breast in very small amounts, usually not detectable by regular testing. Since 51.4% of the females with BBD showed significant levels of PSA (detectable in our regular testing), which is way more than the percentage detected in normal population of females in earlier studies, it is possible that serum PSA might play a role in

the pathogenesis of these disorders. Breast is a target organ of various hormones, whose interplay on its development has been established.

Recommendations

Our study suggests that abnormalities in the hormones that affect breast development may be responsible for development of BBD. These patients might benefit from a hormonal profile to identify a cause for these BBD.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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