

Role of Ormeloxifene (SERM) in Treatment of Fibrocystic Breast Disease in patients aged 18-50 years in a tertiary care hospital in Chennai.

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ABSTRACT

BACKGROUND AND OBJECTIVE: The most prevailing clinical problem that drives women to the surgical outpatient department is mastalgia, or breast soreness. It's captious to fully grok the problem's epidemiological, pathological, and radiological aspects. The intention of this study, which took place at a tertiary care centre in Chennai, was to see how well ormeloxifene worked in female patients aged 18 to 50 who had breast pain from fibrocystic breast disease or not.

METHODOLOGY: 69 patients were selected consecutively based on inclusion and exclusion criteria. Mastalgia is diagnosed based on a history of breast discomfort lasting more than 10 days per cycle, followed by a USG B/L breast to confirm the existence of fibrocystic breast disease. Patients who used Tab Ormeloxifene 30mg every alternate day per week for three months were evaluated for follow-up at months one, two, three, and six. Breast nodularity was assessed using the Lucknow-Cardiff Scale.

RESULTS: Decrease in breast nodularity.

CONCLUSION: Fibrocystic breast disease has been proven to respond well to ormeloxifene.

KEY WORDS: Mastalgia, Ormeloxifene, Lucknow-Cardiff Scale.

AIMS AND OBJECTIVES

AIM: The present study aimed to investigate the role of ormeloxifene in the treatment of women diagnosed with fibrocystic breast disease in a tertiary care hospital in Chennai.

OBJECTIVE: To analyze the use of Ormeloxifene, a selective oestrogen receptor modulator, in the treatment of Fibrocystic Breast Disease in women aged 18 to 50.

MATERIALS AND METHOD:

This is a cross-sectional research project for which 69 patients were consecutively selected as and when they present, supported on by inclusion and exclusion criteria. Patients who were prescribed Tab. Centchroman 30mg OD every other day for three months were monitored. The patients were instructed to evidence their breast pain on the mastalgia chart (Visual Analogue Score) and the Lucknow-Cardiff nodularity Scale were used to measure breast nodularity. This is a 5-point ordinal scale that depicts increasing order of nodularity in the upper outer quadrants of a paired breast graphically. Grade 0 denotes a smooth textured breast with exceptional normality, whereas grade 4 denotes the most nodularity. Patients were reviewed for a period of

6 months at months 1,2,3 and 6 for clinical outcomes with respect to pain and nodularity and side effects were noted.

INCLUSION CRITERIA:

Patients with complaints of cyclical or non-cyclical mastalgia by history, diagnosed to have fibrocystic breast disease using USG of both breasts and FNAC in presence of breast lump belonging to the reproductive age group of 18 - 50 years

EXCLUSION CRITERIA:

Age <18 or >50 years

Post-Menopausal women

Women who are pregnant, nursing, or contemplating a pregnancy in the near future.

Patients who have had a previous breast cancer diagnosis or who have a family history of breast cancer. Patients who have been complaining about their menstrual periods being erratic.

Patients diagnosed with ovarian cysts/tumours/adenomyosis, endometriosis and cervical hyperplasia. Patients with liver/kidney disease.

MATERIALS AND METHODS

This cross-sectional non randomized observational prospective study was conducted on patients visiting the General Surgery OPD of Sree Balaji Medical College, Chennai diagnosed with fibrocystic breast disease, on T.Ormeloxifene 30mg every alternate day for 3 months.

SAMPLING METHODS - Convenient Sampling

SAMPLE-SIZE CALCULATION - Calculated using the formula, $N = 4PQ/LXL$.
Minimum sample size thus obtained is 69.

STUDY PERIOD - September 2020 - October 2021

INCLUSION CRITERIA:

Patients with complaints of cyclical or non cyclical mastalgia by history,

Diagnosed to have fibrocystic breast disease using USG of both breasts and FNAC in presence of breast lump belonging to the reproductive age group of 18 - 50 years

EXCLUSION CRITERIA :

Women under the age of 18 or over the age of 50.

Postmenopausal women.

Women who are pregnant, nursing, or intend to become pregnant in the near future.

Women with a history of benign disease.

Women with irregular menstrual periods.

Ovarian cysts/tumours/adenomyosis, endometriosis, and cervical hyperplasia patients.

Patients with liver/kidney disease.

STUDY PLACE: Chrompet, Chennai.

STUDY SETTING: General Surgical Out-Patient Department of Sree Balaji Medical College and Hospital,

METHODOLOGY:

This is a cross sectional study

During the research period, 69 patients were selected consequetively as and when they present, based on inclusion and exclusion criteria.

Patients who were prescribed Tab.Centchroman 30mg OD every other day for three months were monitored.

Breast nodularity was assessed utilizing the Lucknow-Cardiff Nodularity Scale, a 5-point ordinal scale that outwardly shows the expanding stages of nodularity in the upper external quadrants of a combined breast. Grade 0 alludes to a smooth textured breast with remarkable normalcy, while grade 4 refers to the greatest nodularity.

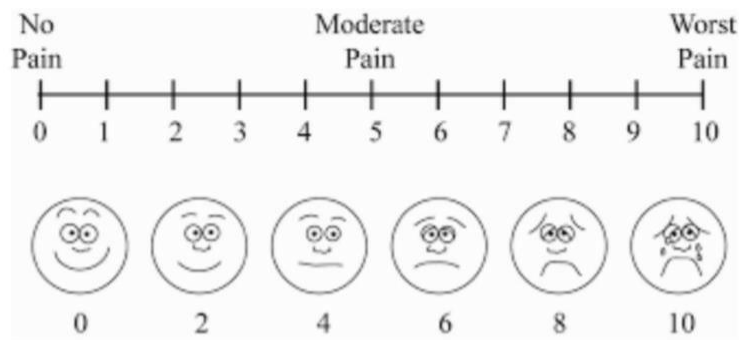
Patients were examined for 6 months at month 1, 2, 3, and 6 for clinical results related to pain and nodularity, as well as adverse reactions .

The pill count and self-reporting were used to determine compliance.

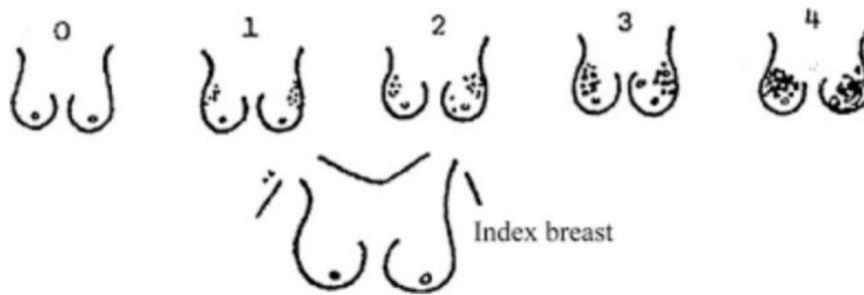
Patients who presented to Sree Balaji Medical College OPD with complaints of mastalgia and met the study's inclusion criteria were included after following informed and written consent. Mastalgia was diagnosed based on the patient's history (breast discomfort lasting more than 10 days each cycle), as well as bilateral breast ultrasound that confirmed the existence of fibrocystic illness.

Patients who were prescribed Tab Ormeloxifene 30mg/day every other day for three months were evaluated for follow-up at months one, two, three, and six. The Lucknow-Cardiff Scale was used to assess breast nodularity.

VISUAL ANALOGUE SCORE FOR PAIN AND LUCKNOW CARDIFF SCALE FOR BREAST NODULARITY



Visual Analogue Score for pain and Lucknow Cardiff nodularity Scale



STATISTICAL ANALYSIS:

Microsoft Excel was used to enter the data. SPSS version 23 was used for statistical analysis. Means, standard deviations, and graphs were used to present descriptive statistics. Because the data was longitudinal with follow-up from 0 to 6 months of pain score and nodule score, repeated measures anova was used for inferential statistics. Throughout the trial, a P-Value of 0.05 was deemed significant.

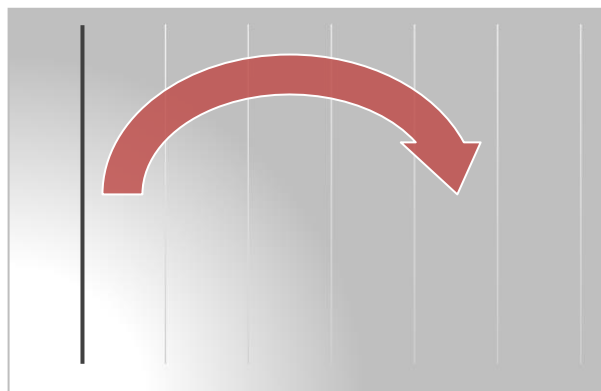
OBSERVATION AND RESULTS

This is a prospective study involving 70 participants. Because one patient did not finish the entire

appointment, they were removed from the research. As a result, we only looked at 69 cases in our research. All 69 patients were successfully treated. The study was done after receiving ethical clearance from Sree Balaji Medical College and Hospital's ethics council in Chennai. Those who satisfied the eligibility requirements were acknowledged to participate in the study.

Patients aged 18 to 50 years were included in the current investigation, with a mean age of 31.67 ± 8.42 . 44 % of the patients were between the ages of 31 and 40, Only 6 % were between the ages of 18 and 20, and 25% were beyond the age of 40. [figure: 1]

Figure: 1 Distribution of patients with respect to age group.



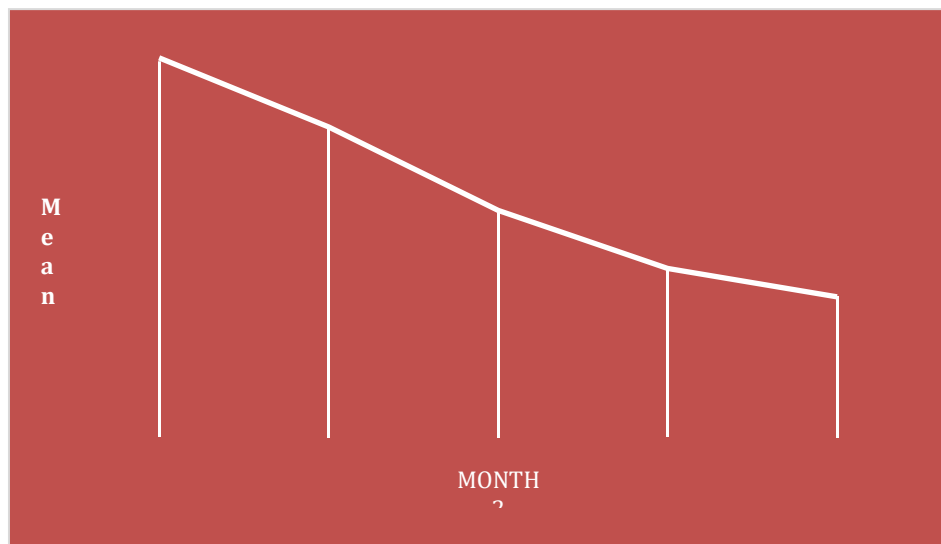
Frequency of nodule score (percentage) among patients receiving treatment and their subsequent follow up

period were enlisted in table:1 and reduction in mean value were shown in figure: 2

Table: 1 Nodular score frequency

	Mean	Std. Deviation	N
MONTH 0	3.33	.980	69
MONTH 1	2.72	.765	69
MONTH 2	1.99	.653	69
MONTH 3	1.48	.503	69
MONTH 6	1.23	.425	69

Figure 2: Line graph of Mean nodule score



There is significant mean difference between nodule grade from month 0 to month 6 when patients are followed up with p-value<0.05 i.e 0.04. The mean

nodule grade shows significant reduction when followed up from baseline to 6th month. [Table: 3]

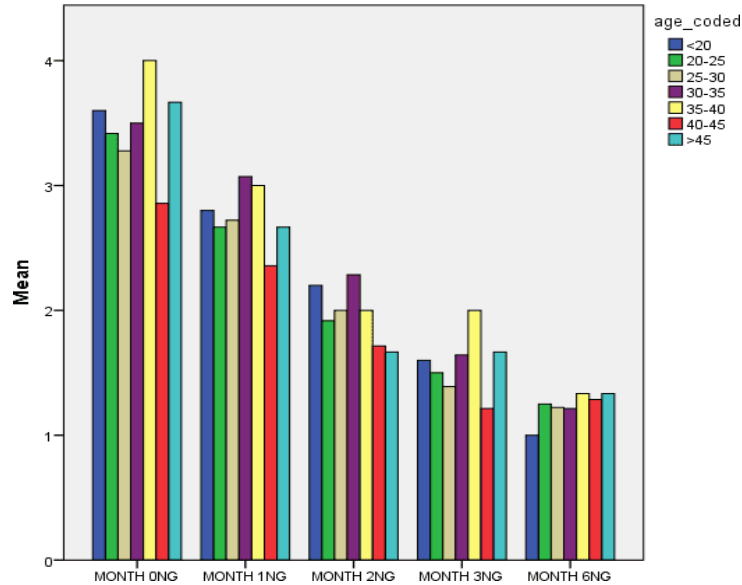
Table: 3 Pairwise comparison

		Mean Difference (Months)	Std. Error	Sig.	% Confidence Interval for Mean Difference	
					Lower Bound	Upper Bound
Month 0	Month 1	.609*	.059	.000	.437	.780
	Month 2	1.348*	.071	.000	1.142	1.554
	Month 3	1.855*	.088	.000	1.599	2.111
	Month 6	2.101*	.134	.000	1.713	2.490

The pairwise comparison between each age group shown in figure:6, interpret the nodule score is drastically reduced or increased for better clinical

results. Figure 3 states that when compared to baseline nodularity grade decreases by 2 units at the end of 6th month.

Figure 3: Pairwise comparison between different age groups



Nodularity changes

There are no patients with a grade 0 nodular score at the start of therapy. 22 percent received a grade 1, 38 percent had a grade 2, 26 percent had a grade 3, and the remaining 15% earned a grade of 4.

42 percent had grades 1 and 39 percent had grade 2 at

the conclusion of the first month of therapy. Only 17 percent of patients exhibited grade 3 nodularity at the end of first month, while 1% had grade 0.

The grade of nodularity improved significantly between the third and sixth months (Table 4).

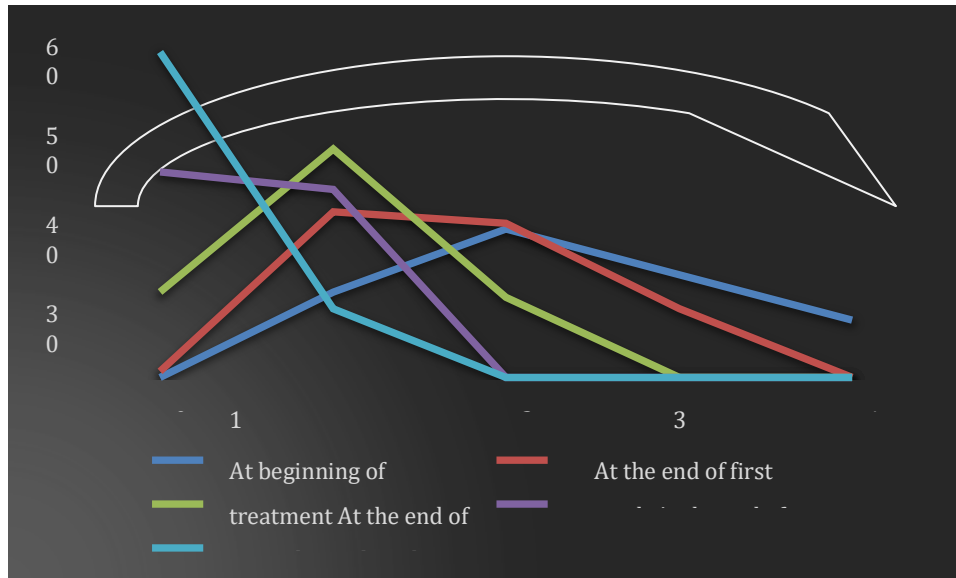
Table 4 : Grades of Nodularity following each visit

VISIT	GRADES [Lucknow Cardiff scale]				
	0	1	2	3	4
beginning of treatment	0	15 (21.7)	26 (37.7)	18 (26.1)	10 (14.5)
end of first month	1 (1.4)	29 (42.0)	27 (39.1)	12 (17.4)	0
At the end of second month	15 (21.7)	40 (58)	14 (20.3)	0	0
end of third month	36 (52.2)	33 (48)	0	0	0
end of sixth month	57 (82.6)	12 (17.4)	0	0	0

At the start of the sixth month, the majority of patients (83%) had a grade 0 score, indicating a significant reduction in nodularity. Only 17% of individuals with grade 1 have this condition. This demonstrated that the

medicine has a function in the therapy. Furthermore, the decline in nodular grades month after month indicates the Lucknow Cardiff scale's great reliability and validity in detecting nodules.

Figure 4: Frequency distribution of different Breast nodularity Grades



After six months of therapy, we associate the treatment with the nodularity score to determine the predicted outcome. As a result, table 5 demonstrates the

relationship between ormeloxifene and Lucknow Cardiff scaling score in mastalgia and fibrocystic breast disease patients.

Table 5: Correlation between Ormeloxifene and Nodularity

Tab. Ormeloxifene	
Given	69

X ² Tests			
	Value	Degree of freedom	Asymp.Sig (2- sided)
Pearson Chi Square	31.114*	3	.000
Probability Ratio	33.689	3	.000
Linear correlation	27.001	1	.000
No of worth cases	69		
33.3 percent [3 cells] of the cells have an anticipated count of fewer than 5. The anticipated minimum count is 4.00.			

DISCUSSION

Benign breast disease are of many types. Some of the main complications includes mastalgia, hyperplasia, fibrocystic disease, mastitis, sclerosing adenosis, and breast abscess. The most prevalent symptoms of benign breast disease are pain and swelling described as nodularity. They typically present with complaints of uncomfortable and nodular swelling to the clinic. Many benign breast disorders are managed with drugs, with surgery being used only in extreme cases. This non-cancerous illness has no effective therapy. [1]

As a result, we conducted a prospective observational study with a sample size of 69 patients who visited Sree Balaji Medical College and Hospital in Chrompet, Chennai, with symptoms of breast soreness and lumpiness.

Menstruation and Mastalgia

It is widely thought that when women happening breast discomfort as a result of hormonal imbalances caused by engorgement and ductal dilatation, the regularity of menstrual cycles are also affected, resulting in irregular menstrual periods. [3] However, this is not supported by research, given majority of the individuals in our study have normal menstrual periods. Similar findings were found in a research done at AIIMS by Srivastav et al. [2]

Patients who are now presenting with mastalgia have a history of benign breast complaints. In our study, we elicited a past history of breast disorders for which the patient got therapeutic or surgical treatment, which conforms to this reality.

Investigation : In the present study, patients underwent ultrasound examinations in order to confirm for FCBD and look at incidental lesions. Similarly, An observational study by Samia PK et al., 2019, used ultrasounds for females with lump complaints at Medicare Hospital and Jinnah Medical and Dental College. He also stated that ultrasound was shown to be the most practical method for assessing various types of breast lesions and ruling out cancer. [4]

Age distribution:

The patients were chosen based on the criteria for inclusion and exclusion. Patients between the ages of 20 and 50 were included, with a mean and median age of 31.678.42.

Drugs used in therapy

Hormonal and non-hormonal therapies are the two most common types of medications. Danazol, progesterone, contraceptive pill and luteinizing hormone- releasing hormone (LHRH) analogue have all been used to modulate hormone levels. [5]

Non-hormonal therapy include analgesics,

phytochemicals, and gamma linolenic acid, among others (GLA). Ormeloxifene (centchroman) is an oestrogen receptor modulator and a medicine that targets oestrogen receptors (SERM). It's best known as a once-weekly nonhormonal, nonsteroidal oral contraceptive. Since the early 1990s, ormeloxifene has been available in India as a birth control pill. [6]

NovexDS, Centron, and Sevista are among the brand names for ormeloxifene. More oestrogenic drug like levormeloxifene has significantly stronger anti-ER action. It might be an effective treatment for postmenopausal osteoporosis. However, it was not commercialized because of greater risk of genital tract adverse effects. Even after long- term usage, no such negative effects have been observed for ormeloxifene. A meta- analysis of medicines routinely used to treat mastalgia was recently published. [7]

This meta-analysis comprised of several randomized, placebo-controlled studies. Bromocriptine was shown to be effective in seven studies, with a weighted mean difference in pain score of -16.31 (95 % CI -26.35 to -6.27), showing considerable alleviation from mastalgia. Danazol was shown to be helpful in alleviating breast pain in four studies, with a mean pain score difference of -20.23 (95 % CI -28.12 to -12.34). [8]

Changes in pain and nodularity:

Similar to the study conducted by Anjana Gandhi on a total of 406 patients where mean pain score at 3rd month and 6th month was 1.21 and 0.86, our study showed a mean pain score of 1.83 and 0.74 at the end of 3rd and 6th month. Using the Lucknow Cardiff scale to quantify nodularity, 83% had a score of 0, 17% had a score of 1. Therefore ormeloxifene was significantly effective in 80% of patients. In addition, the average recuperation duration is three months. As a result, ormeloxifene's computed p value is 0.0001, which is statistically significant. Patients who were given ormeloxifene had no side effects and were very compliant. The study's findings are based only on a six-month follow-up period. Ormeloxifene's long-term effects on recurrence and size reduction will require more research in the future.

Ormeloxifene is therefore a beneficial and effective medicine for the treatment of fibrocystic breast disease, as well as being reasonably priced. Patients are generally anxious when requested to take tamoxifen because it is also utilized as an anticancer medication. Bromocriptine causes headaches, nausea, vomiting, and dizziness in those who take it. In other experiments, this resulted in a 20% dropout rate. Danazol causes weight gain, acne, greasy hair and skin, headaches, nausea, hirsutism, breast reduction, and a change in voice (androgenic effect). About a quarter of people have these adverse effects. At greater doses, the risk of

amenorrhoea or irregular menstruation (owing to gonadal suppression) rises. [9,10]

There were no serious adverse effects in our trial, but Sandeep et al. Discovered 12 indivons are being conducted to determine the efficacy of tamoxifen, in the treatment of fibrocystic biduals with oligomenorrhoea but no indication of headache in any of them.

Many investigatireast disease. However, there have been some negative effects associated with this medicine. Only a few trials were done on ormeloxifene, and it was proven to be beneficial in treating fibrocystic breast disease with few adverse effects.

After six months, the mean chi square value for pain scale was 20.46 in our study. 92 percent of patients were

CONCLUSION

Patients with mastalgia and fibrocystic illness visit the clinic because they are afraid about cancer. After a comprehensive inquiry, reassurance is sufficient. However, discomfort has an impact on daily activities.

Patients treated with ormeloxifene 30 mg every alternate days of the week, which acts on estrogen receptor with antioestrogenic activity on the breast, showed excellent compliance and no adverse effects.

Ormeloxifene usage in fibrocystic disease patients showed statistically significant decreases in nodularity throughout the course of our research period.

Based on the outcomes of this study, we conclude that Ormeloxifene is a useful and economical medicine with substantial effectiveness in the treatment of fibrocystic illness in women of reproductive age.

LIMITATIONS OF THE STUDY

This is not a randomized study.

The sample size is limited.

Only a single therapeutic drug was studied with no comparison group.

Multicentric randomized double blind controlled studies with a larger sample size should be carried out for evidence of significant results.

Pain is subjective and multifaceted, the VAS Score are unable to represent the entire pain experience. However, because clinical judgments are based on current pain scales, it's critical to understand how much of a decrease in a VAS score is likely to be clinically relevant from the patient's perspective. The pain extremes on a VAS, such as 'no pain' and 'worst agony ever,' may not accurately reflect absolute boundaries of experience.

nodularity-free at the conclusion of the six-month therapy.

Sandeep Kumar et al. found comparable findings, with a mean chi-square score of 32.39 after three months and 20.98 after six months, and grades of nodularity grades of 93.3 percent with grades 1 and 2, and 6.7 percent with grades 3, 4, and 5.14 after six months. According to a clinical research done at the All India Institute of Medical Sciences in New Delhi, India, 90 percent of patients were pain-free after three months of therapy, with nodularity completely gone. [11]

Only 17% of patients have reported with grade 2 nodularity. Furthermore, the fact that nodular grades are decreasing month after month implies that the drug has an efficacy over pain and nodules.

BIBLIOGRAPHY

Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985; 312:146–151.

Srivastava A, Mansel RE, Arvind N, Prasad K, Dhar A, Chabra A. Evidence- based management of Mastalgia: a meta-analysis of randomised trials. *The Breast*. 2007 Oct 1;16(5):503-12.

Palli D, Rosselli Del Turco M, Simoncini R et al. Benign breast disease and breast cancer: a case-control study in a cohort in Italy. *Int J Cancer* 1991; 47:703–706.

Samia Perwaiz Khan and Arwa Iqbal Hussain. DIAGNOSIS OF FIBROCYSTIC DISEASE OF BREAST ON ULTRASOUND. *Int. J. of Adv. Res.* 7 (Feb), 2019; 557-56

Marshall LM, Hunter DJ, Connolly JL et al. Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. *Cancer Epidemiol Biomarkers Prev.* 1997; 6:297–301. O'Malley FP, Bane AL. The spectrum of apocrine lesions of the breast. *Adv Anat Pathol* 2004; 11:1–9.

Houssami N, Irwig L, Ung O. Review of complex breast cysts: implications for cancer detection and clinical practice. *ANZ J Surg* 2005; 75:1080– 1085.

Venta LA, Kim JP, Pelloski CE et al. Management of complex breast cysts.

AJR Am J Roentgenol 1999; 173:1331–1336.

Vargas HI, Vargas MP, Gonzalez KD et al. Outcomes of sonographybased management of breast cysts. *Am J Surg* 2004; 188:443–447.

Jensen RA, Page DL, Dupont WD et al. Invasive breast cancer risk in women with sclerosing adenosis. *Cancer*

1989; 64:1977–1983.

Gill HK, Ioffe OB, Berg WA. When is a diagnosis of sclerosing adenosis acceptable at core biopsy? Radiology. 2003; 228:50–57.

Sandeep Kumar, Rai R, Agarwal GG, Dwivedi V, Kumar S, Das V. A randomized, double-blind, placebo-controlled trial of ormeloxifene in breast pain and nodularity. Natl Med J India. 2013 Mar 1;26(2):69-74.