

# Role of Ormeloxifene in Regression of Cyclical Mastalgia

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**Abstract:** Background: Benign breast diseases are common pathological entities with which women in their early reproductive age present to OPD with fear of malignancy and significant morbidity. Except for surgery and use of non-selective estrogen receptor blockers, there are no other treatment options, and these have lot of side effects. Ormeloxifene, a newer drug has shown promising results with minimal side effects and used as the first line of treatment reducing the morbidity of surgery and subjecting the patient to less hormonal side effects. Methods: Diagnosis of benign breast diseases was made by baseline investigation which included measurement of defectsize of fibroadenoma using Vernier calliper and USG; fibroadenosis, ie nodularity measured using Lucknow-Cardiff scale and VAS score was used for pain assessment of mastalgia after which patients were given the drug and placebo and the response for the drug and its side effects were noted. Results: 61.9% (44) were diagnosed with fibroadenoma, 16.9% (12) with fibroadenosis and 21.1% (15) with mastalgia. Lucknow Cardiff score for fibroadenosis exhibited 50% having smooth breasts with no nodularity at the end of six months, in fibroadenoma group 52% showed decrease in size and 31% showed complete disappearance of the lump and in the mastalgia group 40% had no pain (VAS score of 0). 16(22.5%) had menstrual abnormality as the major side effect. Conclusions: Ormeloxifene can be used as the first line of treatment in patients with fibroadenosis and mastalgia and used as an alternative to surgery for fibroadenoma.

**Keywords:** Benign breast diseases, Fibroadenoma, Fibroadenosis, Mastalgia, Ormeloxifene

## 1. Introduction

Benign breast diseases (BBD's) are commonly seen among the younger age group with incidence peaking in second and third decades. Most of the women experience a lump with or without pain which inflicts fear of malignancy and gets the patient to the breast clinic, out of which 2/3rd are benign. Yearly 200,000 patients visit a surgeon with palpable breast lump of which most of the palpable lesions are benign.<sup>1</sup> The most common fear about a benign breast condition is of it turning into a malignancy.<sup>2</sup> Hence the term "benign breast diseases" comprises of a heterogeneous group of lesions in the form of developmental abnormality, epithelial and stromal proliferation detected using microscopic findings.

The incidence of BBD's is less common after menopause.<sup>3,4</sup> Generally, it gets wider attention among women because of their high prevalence and it having a severe influence on women's life.<sup>5</sup> BBD's are a set of breast conditions which range from normality to disorder to disease and 50% women throughout their reproductive life will suffer from BBD's at some point of time.<sup>6</sup> The most common complaint in patients with BBD is breast lump or breast nodularity (42%) and breast pain (66%).

Histologically it encompasses entities like, non-proliferative, proliferative without atypia, and atypical hyperplasias, out of which atypical lesions carry a risk factor for cancer.<sup>7</sup> However, benign breast diseases differ from one person to another person. It encompasses a range of disorders from Hyperplasia, cysts, fibroadenomas, intraductal papilloma, sclerosing adenosis, fibro adenosis to benign phyllodes tumours, fat necrosis, mastitis, mastalgia. Of all the BBD's, most women face fibroadenoma, fibro adenosis and mastalgia.

Fibrocystic breast disease otherwise termed as fibro adenosis which comes under non-carcinogenic breast condition. exhibits as diffuse lump with or without pain which is highly associated with hormonal changes at the time of menstrual cycle.<sup>8</sup> Women face fibrodenosis particularly in their conceptive age which affects one or both breasts. According to the study of Courtillot et al, 50% of women are affected with fibrocystic disease.<sup>9</sup> Fibroadenoma (FA) is the most common benign lesion of the breast in young females (<30 yrs) and second most common breast tumour in females. Fibroadenoma is to be held responsible for a 15% palpable breast lumps. Most of the times it presents as painless breast lump in reproductive females. FA usually never occurs after the age of 40 yrs. Most of the FA cases are self-diagnosed and clinicians are consulted in fear of breast cancer.<sup>10</sup> However, breast pain otherwise termed as mastalgia significantly influences the women in their lifetime and nearly 70% of them are affected by pain. In Asian countries, women having mastalgia is high, and it is estimated to be around 5%.<sup>11</sup> Generally, mastalgia represents the pain arising especially in the breast tissue.<sup>12</sup> Having breast pain influences a woman negatively.<sup>13</sup> It may present as unilateral or bilateral condition the later being more common.<sup>14</sup> Consequently, whenever women has pain in breast, it is recommendable to contact health centres because many of them are misdiagnosed with breast cancer.<sup>15</sup> In mastalgia, two varied types occur in which one is cyclical, and the other is non-cyclical mastalgia. In general, most common type of mastalgia is cyclical mastalgia which starts in the luteal phase of the menstrual cycle. Patients present with the symptoms of breast pain followed by tenderness and heaviness.<sup>16</sup> However, noncyclic mastalgia is unilateral and is localised particularly within one quadrant of the breast and the pain is in the form of burning, aching or as soreness.<sup>13</sup> Cyclic mastalgia pain is primarily seen among

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younger women whereas noncyclic mastalgia mostly prevails among the women who are between the age category of 40-50 years.<sup>17</sup> Women experience mastalgia primarily because of attributes like menstrual irregularity, oral contraceptives, hormone therapy, psychotropic drugs, psychosocial attributes and emotional stress leading to breast pain.<sup>18</sup> It influences the woman's personal and sexual life and is notorious in posing significant constraints to treat it due to its diverse etiology, fewer treatment options and even fewer successful trials.<sup>19,20</sup>

To treat benign breast diseases agents like bromocriptine, tamoxifen, evening primrose oil (EPO) and danazol are used and were found to have lot of side effects due to their non selective estrogen blockade action and led to patient incompatibility.<sup>21</sup> Surgery is the first line of treatment for patients suffering from fibroadenoma but poses the risk of anaesthesia, injury to lactiferous ducts, cosmetically leaves a scar and subjects the patient to hospital stay. Other agents like vitamins B6, E, diuretics, gamolenic acid, caffeine withdrawal have been used in the past but not found to be effective. Likewise, creams, tablets, injectables were discarded from the study due to poor response. Hence, a new agent named ormeloxifene was taken into account. Ormeloxifene is a selective estrogen receptor modulator and a class of medication which is otherwise known as centchroman.<sup>20</sup> During the early period of the 1990s, India permitted ormeloxifene only for birth control, but now it is marketed under the trade name of Saheli. Besides, other companies also licensed for trading ormeloxifene in the names of NovexDS, Centron and Sevista. In the previous study with ormeloxifene, it showed 90% improvement at a dose of 30 mg taken on an alternate day in 42 patients. It also showed complete disappearance of fibroadenoma in 40% women after three months of treatment.<sup>22</sup> Hence, the researcher makes an effort to investigate the extent to which ormeloxifene diminishes the pain, reduces the size of the lump and decreases nodularity in patients suffering from three most common etiological benign breast diseases, fibroadenoma, fibroadenosis and mastalgia in women who visit breast clinic at SMIMER Hospital, Surat.

## 2. Methods

The study on benign breast diseases was conducted in the General surgery department of SMIMER Hospital, Surat, from 2016 to 2017 after getting prior approval from the ethical committee. A prospective clinical study was conducted for 24 weeks considering the total number of patients to be 152 in which 142 were taken into account. The study had patients who came with complaints of a Breast lump or pain, who were below the age group of 30 years. Patients were then segregated into three arms fibroadenoma, fibroadenosis and mastalgia based on triple assessment. The study excluded the patients whose FNAC report showed any evidence concerning malignancy, galactocoele and phyllodes tumour, and patients with a lump of size less than or equal to 5cm taken into account to rule out the possibility of giant fibroadenoma. Patients in their lactation period or pregnancy for the first six months and the patients on other oral contraceptive pills were also excluded. Besides, patients having the previous history of breast carcinoma or a family

history of breast malignancy and patients with h/o polycystic ovarian disease, cervical hyperplasia and liver disease.

For assessing the patients with benign breast disease, the researcher applied a triple assessment. One is clinical evaluation and the second is an ultrasound scan, and the third is USG guided FNAC. The clinical assessment was made by using Vernier calliper to measure the size of fibroadenoma, Lucknow-Cardiff scale (LCS) to know the grade of nodularity in a non-discrete lumpy breast, VAS score for mastalgia, after which patients who signed up by giving a consent were given centchroman 30 mg alternative days for 24 weeks and the other half was given a placebo.

### Follow up

Lump size was assessed using a Vernier calliper and a breast USG to determine the size of the fibroadenoma for patients with a diagnosis of fibroadenoma. Other attributes like pain based on visual analogue and nodularity using LCS. Each time the increment, decrement and disappearance in lump, nodularity and pain was documented and the percentage recorded. The outcomes were assessed based on patients' condition symptomatically and the side effect.

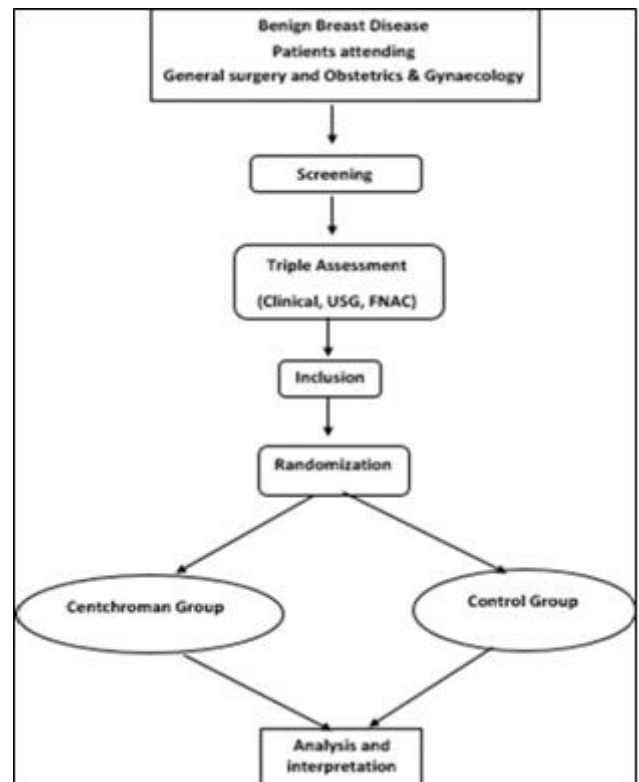


Figure 1: Algorithm for patient work up

## 3. Results

The researcher included 152 patients in the study in which ten patients showed a lack of participation and hence these ten patients were excluded from the study. Therefore, the study considers only 142 patients who visited breast clinic monthly. The patients were diagnosed with fibroadenoma, fibroadenosis and mastalgia. Besides, the study further assessed the patients into two groups in which one group belonged to the drug and the other diagnosed with placebo.

Figure 2 shows that the majority of the women in drug arm, ie, 45% (32) were between the age category of 18-22 years whereas in placebo, 59% (42) were above 26 years of age.

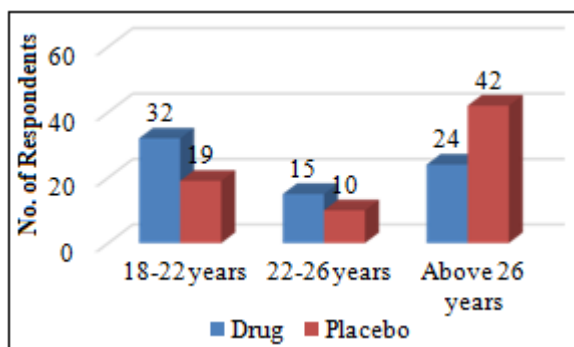


Figure 2: Age of respondents in years.

Figure 3 states that out of all women respondents, Drug arm have 61.9% (44) diagnosed with fibroadenoma, 16.9% (12) with fibro adenosis and 21.1% (15) with mastalgia. Concerning placebo, 45% (32) had fibroadenoma, 23.9% (17) with fibro adenosis and 30.9% (22) with mastalgia.

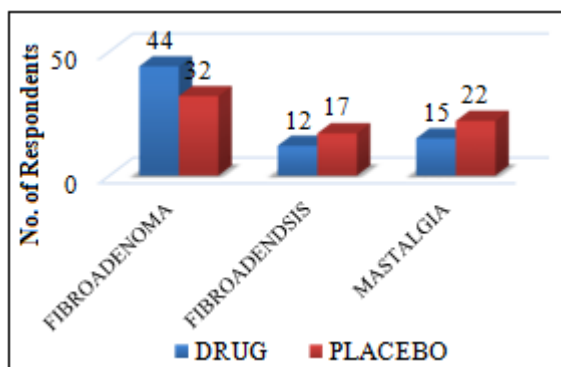


Figure 3: Types of benign breast diseases

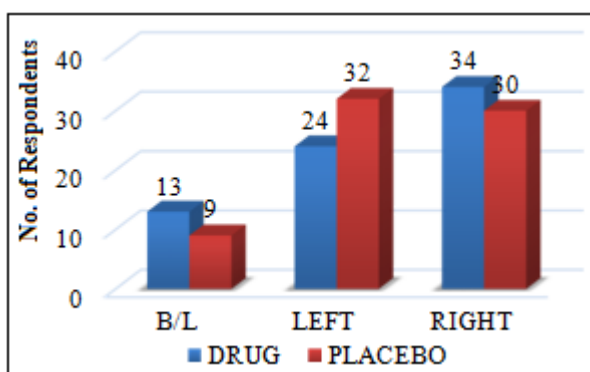


Figure 4: Focality and centrality of symptoms

Figure 4 shows the focality and centrality of symptoms of the affected side of the conditions. Considering both drugs and Placebo, the affected side is unilateral in which right breast was severely affected.

The researcher monitored the size of fibroadenoma using clinically and sonological modalities. Based on threemonth observation, in 19 (43.1%) patients, lump size decreased in ormeloxifene group whereas in 4 (12.5%), decrement was noticed in the placebo arm. In 9 (20.4%) patients the lump disappeared in drug arm as compared to 3 (9.3%) in placebo arm. In 4 (9%) patients the size of the lump increased

compared to 12 (37.5%) patients in the placebo arm. Size of the lump remained the same in 12 (27.2%) in drug arm and in 13 (40%) patients of placebo arm. However, after six months, 23 (52.2%) patients had a decrease in the size of the lump whereas only 7 (21.8%) patients in the placebo arm showed a reduction in size. 14 (31.8%) patients had complete disappearance of the lump and only 5 (15.6%) patients on placebo did not have lump. Size of the lump increased in 3(6.8%) patients in drug arm and in 15 (46.8%) patients in the placebo arm whereas the patients who had the same size of the lump were 4(9%) in drug arm and 5 (15.6%) in placebo arm (Figure 5).

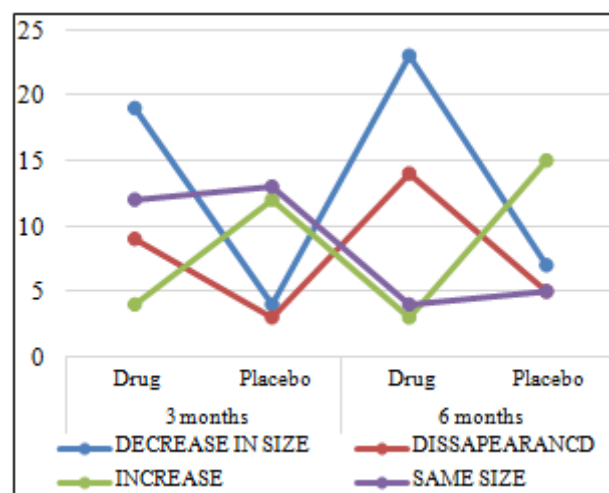


Figure 5: Fibroadenoma

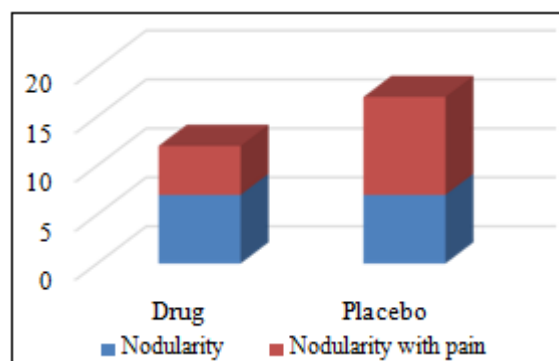


Figure 6: Fibroadenosis

Figure 6 states that amongst the 12 patients who had fibroadenosis in drug arm, 7 (58.3%) had only nodularity whereas 5 (41.6%) had nodularity with pain. With regards to placebo of 17 respondents, 7 (41.2%) had only nodularity and 10 (58.8%) had both nodularity and pain.

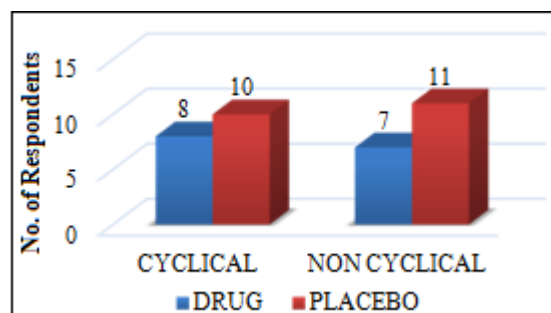


Figure 7: Mastalgia

Figure 7 states that out of 36 respondents of mastalgia, 8(53.8%) patients in the drug group had cyclical mastalgia whereas 7 (39%) had non-cyclical mastalgia. In Placebo group, 10 (45.4%) had cyclical and 11 (61%) had non-cyclical mastalgia. A line chart representation of the data given in the (Figure 8) shows that the study started off with no patients having grade 0 and grade 1 nodularity and 25% (3) each had grade 2 and 4 nodularity and 50% (6) had a grade 3 nodularity and over the study duration, a linear decrease in the nodularity over 3 months, showed that 25% (3) each had a grade 0 and 1 and 33.3% (4) had a grade 3 and 16% had a grade 4 nodularity. At the end of the study of six months, 50% (6) had absolutely smooth breasts with no nodularity and none of the patients had grade 4 nodularity, 16% (2) had a grade 2 and 8% (1) had a grade 3 nodularity. This was statistically significant ( $p < 0.05$ ).

With regard to placebo arm a linear increase in the LCS scale where 3 (17%) had grade 4 nodularity at the start and by 3rd and 6th month 23% (4) and 17% (3) respectively had grade 4 nodularity. 17% (3) of them had grade 3 nodularity at the start and 52% (9) of them ended with grade 3 nodularity at the end of the study. On the contrary none of the patients had smooth breasts in the placebo arm at the end of the study.

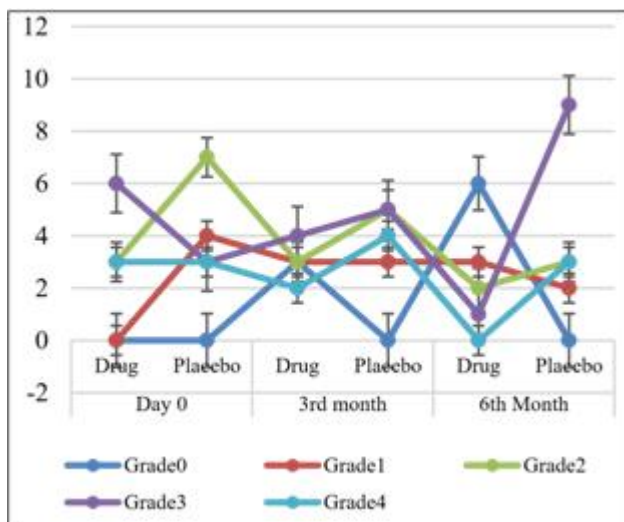


Figure 8: Fibroadenosis/nodularity -LCS for drug and placebo

A line chart representation of the data is given in the (Figure 9) shows a linear decrease in the pain scale where 60% (10) at the end of the study of 6 months had mild pain (0-3) out of which 40% (6) had absolutely no pain and only 6% (1) still persisted to have severe pain (7-10) as compared to 40% (6) who had severe pain at the start of the study. This was a statistically significant ( $p < 0.05$ ).

With regard to placebo arm a linear increase in the pain scale with initially 27% (6) patients having mild pain (03), 40% (9) having moderate pain (4-6) and 31.8% (7) having severe pain (7-10) at the start of the study and by the time the study was completed 45% (10) had severe pain (7-10) and 45% (10) had moderate pain and only 9% (2) patient had mild pain.

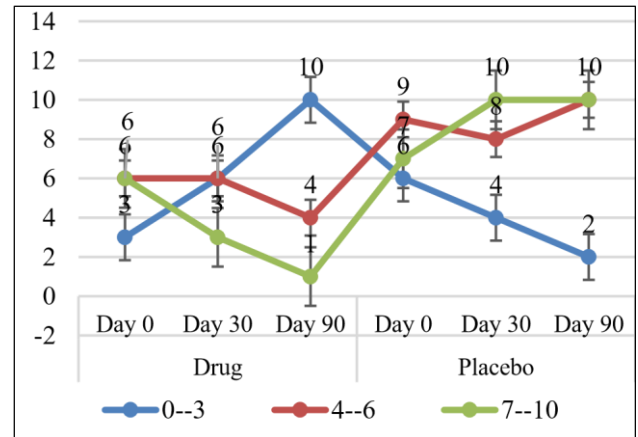


Figure 9: Mastalgia-VAS score for drug and placebo

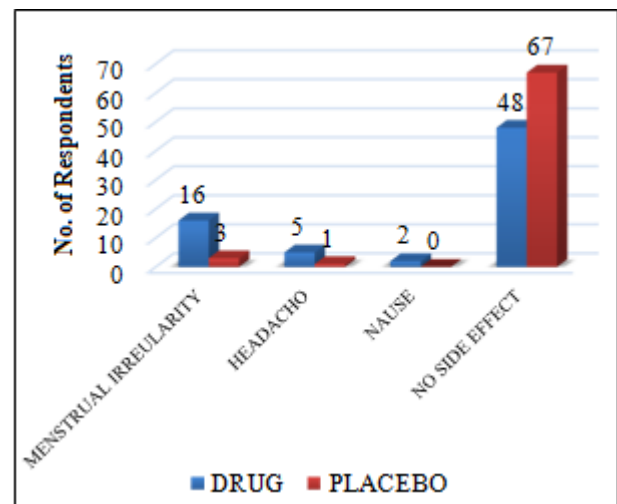


Figure 10: Side effects

Based on the study outcome, it identifies that 16 (22.5%) patients a menstrual abnormality, especially with delayed menstrual cycle whereas only 3 (4.2%) in placebo. The other side effects inclusion of headache to be 5 (7%) for drugs using patients whereas 1 (1.4%) of having a headache for Placebo. Besides, 2 (2.8%) of faced nausea in drugs whereas 0% for placebo. About drugs, 48 (67.6%) of patients had no side effects whereas 67 (94.3%) of having no side effects in placebo (Figure 10).

#### 4. Discussion

In the present study, 142 patients of breast specimen gathered from breast clinic at SMIMER hospital, Surat, in which all represented benign breast diseases. It was noted in the study that 78.52% of cases were registered under benign breast lesions.<sup>23</sup> 80.7% of cases considered for the study, whereas 71.6% of considered for Malik et al. Consequently Pudale et al depicted that 71.15% of cases noted as benign breast diseases followed by a study conducted at south Maharashtra which exhibited that 70% of cases registered as benign breast diseases and the same number of cases considered for Kumar et al.<sup>24-27</sup> Rasheed et al depicted that 77.7% of benign breast lesions considered for the study which conducted at North India 51 whereas Sarma et al stated that 70% of for East India.<sup>28,29</sup>



In India, benign breast diseases started its journey in the 2nd decades and got its accelerated state at 4th or 5th decades.<sup>30</sup> In this study, majority of the women in drug group, i.e., 45% (32) were between the age category of 18-22 years whereas in placebo 59 (42) were of above 26 years of age. Kumar et al stated that most of the benign breast diseases were faced by the respondents who are between the age category of 11-30 years whereas Bagale et al pointed out that most cases lie between the age category of 21-40 years.<sup>24,27</sup> Similarly, our study noticed that most of the respondents who had diseases lie between 18-22 years of age. Fibroadenoma was the most prevailing breast lesion in our study 57.7% of seen with benign breast lesion. Likewise, Amr et al, Kulkarni, Malik et al in their study, they found the most common benign breast lump was a fibroadenoma.<sup>24,25,31</sup> Amr et al reported 30.7%, Kulkarni et al 62.32%, Malik et al 41% of cases filed with fibroadenoma.<sup>25,26,31</sup>

The second most crucial lesion is fibrocystic diseases which, otherwise termed as fibroadenosis, accounts for 21.12% with age limit of above 26 years of age. It is seen among young women especially under the age of 30.<sup>32</sup> Godwins et al stated in their study that the highest number of cases registered were at the age of above 30 years. Amr et al exhibited that maximum age limit for incurring fibroadenosis was between the age of 31-35 years.<sup>33</sup>

The third most crucial lesion is mastalgia which prevails among many young women. Generally, mastalgia is experienced by women under the age category of 55 years. Hence the present study considers a very meagre amount of respondents who were affected with mastalgia. However, respondents for our research is under the age category of below 30 years.

Benign breast diseases affected both focality and centrality of symptoms of diseases. Considering both drugs and Placebo, the affected side is unilateral in which right breast was severely affected. Similarly, Shashikala et al indicated that most of the cases were seen in right breast.<sup>34</sup> Sagar stated that 40% were seen in right breast.<sup>35</sup>

Amongst the 12 patients who had fibroadenosis in drug arm 7 (58.3%) had only nodularity whereas 5 (41.6%) had nodularity with pain. Ramesh et al stated that 24% had lumps associated with pain.<sup>36</sup> Chalya et al indicated that most of the patients (67.8%) had breast nodularity associated with pain.<sup>37</sup>

Mastalgias highly seen in third decades of women life.<sup>14</sup> In the present study, out of 142 respondents, 62 respondents in the drug group had only mastalgia (42), and the rest (20) had mastalgia with nodularity. Besides, 20 (27%) had cyclical and 54 (73%) having non-cyclical mastalgia. According to the study of Chowdhury et al severity was higher in noncyclic mastalgia than cyclical mastalgia. The primary reason for the emergence of noncyclic is fibroadenoma and fibroadenosis which create more pain compared to hormonal attributes.

In the present study, the researcher considered the patients who are attending surgery OPD with the complaints of

nodularity and lump in the breast or mastalgia assigned into drug and placebo group and the diagnosis recorded with clinical and then sonological and at last pathological examination. Patients in the drug arm given centchroman 30 mg alternate day for six months and that of the control group were given the placebo for the same duration of time. Each visit of the patients, size of the lump, nodularity, pain scale and then side effects monitored and tabulated.

#### ***Fibroadenoma, fibroadenosis and mastalgia***

The researcher monitored the size of fibroadenoma using clinically and sonologically. Each patient monitored using both drug and placebo. Based on six-month observation, lump size of fibroadenomas decreased in the ormeloxifene group to be 43.1% whereas decrement noticed to be 12.5% in the placebo arm. The patient whose lump disappeared in drug to be 20.4% whereas 9.3% of in placebo arm. The patient who faced increment in the lump especially in drug to be 9% whereas 37.5% in the placebo arm. Concerning the patients who had the same size of a lump to be 27.2% in drug whereas 40% of in placebo arm. However, in the six months, 52.2% of patients had a decrease in the size of the lump whereas in only 21.8% of patients in the placebo arm showed a decrease in size. 31.8% of patients had complete disappearance of the lump, and only 15.6% of patients on placebo had no lump. Patients breast to be increased to be 6.8% in drug whereas 46.8% in placebo and the patients who had the same size breast to be 9% in drug whereas in placebo it is 15.6%

In mastalgia group 40% of the patients out of the 60% patients who had mild pain (0-3) had no pain and only 6% experienced severe pain as compared to 40% at the start of the study. With regard to placebo arm shows an linear increase in the pain scale with initially 27% patients having mild pain (0-3), 40% having moderate pain (4-6) and 31.8% having severe pain (7-10) at the start of the study and by the time the study was completed 45% had severe pain (7-10) and 45% had moderate pain and only 9% patient had mild pain

In fibroadenosis group 50% of the patients had smooth breasts without nodularity and none of them had a grade 4 nodular breast, as compared to 25% who had grade 4 nodularity at the start of the study. In contrary in the placebo arm, 52% and 17% patients ended up with grade 3 and grade 4 nodularity as compared to 17% each with grade 3 and 4 nodularity at the start of the study and none of the patients had smooth breasts without nodularity in the placebo arm at the end of the study

From the observation, the researcher identified that 22.5% had a menstrual abnormality, especially delayed menstrual cycle, whereas only 4.2% in the placebo arm had this abnormality. The other side effects included headache to be 7% for drugs using patients and 1.4% of those having a placebo. Besides, 2.8% faced nausea in drugs whereas 0% for placebo. Among drug users, 67.6% of patients had no side effects whereas 94.3% of those having placebo had no side effects.

## 5. Conclusion

In countries like India, treating benign breast diseases is a quite challenging task for the practitioner because of lack of education, poverty, lack of awareness, lack of accessibility in good health care and most importantly, superstitions among women. But, women in India, generally affected with benign breast diseases, especially at the reproductive age, present to the surgery OPD with lump and mastalgia with or without nodularity. Hence the study considers the most common conditions like fibroadenoma, fibroadenosis and mastalgia into account. Due to their etiological similarity, i.e. hyperresponsiveness of the breast parenchyma to estrogen, a novel SSRI ormeloxifene is the ideal drug for conservative treatment of BBD's causing significant reduction in the volume of the fibroadenoma, decrease in nodularity and pain with minimal side effects. Among the three common diseases, fibroadenoma was the collective entity followed by mastalgia and then fibroadenosis. Apart from the issues, patients profoundly suffered from right-sided symptoms. For fibroadenoma patients, the highest number of respondents showed a significant reduction in volume, and at the same time, they experienced complete disappearance of the lump. In patients with breast pain, there was a linear decrease in the pain scale and mean pain score at the end of the study.

With regard to nodularity, the maximum number of patients had a smooth breast. While, inhaling ormeloxifene as a hormone receptor modulator, showed minimal side effects with only menstrual irregularity. Finally, the study concludes that ormeloxifene can be a suitable alternative for enucleation surgery in the management of females in the reproductive age with fibroadenoma, reducing the risk of surgery, anaesthesia, cosmesis by scar contracture, damage to the lactiferous glands in a centrally located fibroadenoma and no hospital stay. In fibroadenosis and mastalgia, it can be used as the first line of treatment as there are no good alternatives other than evening primrose oil, vitamin E and anti-estrogen receptor blockers like tamoxifene, androgens like danazol which have low patient compliance and lot of side effects. Since there is no documented evidence of malignant predisposition of the above conditions, a more radical approach like surgery can be avoided and a cost-effective, compliant, safe drug with minimal side effects-ormeloxifene, can be used with significant results.

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**Conflict of interest:** None declared

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

## REFERENCES

- [1] Miltenburg DM, Speights VO. Benign breast disease. *Obstet Gynecol Clin North Am.* 2008;35:285-300.
- [2] Caleffi M, Duarte Filho D, Borghetti K, Graudenz M, Littrup PJ, Freeman-Gibb LA, et al. Cryoablation of benign breast tumors: evolution of technique and technology. *Breast.* 2004;13(5):397407.
- [3] Kelsey JL, Gammon MD. Epidemiology of breast cancer. *Epidemiol Rev.* 1990;12(1):228-40.
- [4] McDivitt RW, Stevensm JA, Lee NC, Wingo PA, Rubin GL, Gersell D. Histologic types of benign breast disease and the risk for breast cancer. *Cancer.* 1992;69(6):1408-14.
- [5] Prajapati SR, Patel KK, Nanavati M. Histopathological Study of Benign Epithelial Lesions of Breast. *Inter j scientific research.* 2015;7(4):2277-8179.
- [6] Dogliotti L, Faggiuolo R, Ferusso A, Orlandi F, Sandrucci S, Tibo A. Prolactin and thyrotropin response to thyrotropin-releasing hormone in premenopausal women with fibrocystic disease of the breast. *Horm Res.* 1985;21(3):137-44.
- [7] Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med.* 1985; 312:146-51.
- [8] Cheng J, Qiu S, Raju U, Wolman SR, Worsham MJ. Benign breast disease heterogeneity: association with histopathology, age, and ethnicity. *Breast Cancer Res Treat.* 2008; 111(2):289-96.
- [9] Courtilot C, Plu-Bureau G, Binart N, Balleyguier C, Sigal-Zafrani B, Goffin V, et al. Benign breast diseases. *J Mammary Gland Biol Neoplasia.* 2005;10(4):325-35.
- [10] Shabtai M, Saavedra-Malinger P, Shabtai EL, Rosin D, Kuriansky J, Ravid-Megido M, et al. Fibroadenoma of the breast: analysis of associated pathological entities-a different risk marker in different age groups for concurrent breast cancer. *IMAJ-RAMAT GAN.* 2001;3(11):813-7.
- [11] Goodwin PJ, Miller A, Del Giudice ME, Singer W, Connelly P, Ritchie JK. Elevated high-density lipoprotein cholesterol and dietary fat intake in women with cyclic mastopathy. *Am J Obstetr Gynecol.* 1998;179(2):430-7.
- [12] Preece PE, Baum M, Mansel RE, Webster DJ, Fortt RW, Gravelle IH, et al. Importance of mastalgia in operable breast cancer. *Br Med J (Clin Res Ed).* 1982; 284(6325):1299-300.
- [13] Smith RL, Pruthi S, Fitzpatrick LA. Evaluation and Management of Breast Pain. *Mayo Clin Proc.* 2004;79:353-72.
- [14] Kataria K, Dhar A, Srivastava A, Kumar S, Goyal A. A systematic review of current understanding and management of mastalgia. *Indian J Surgery.* 2014;76(3):217-22.
- [15] Barros AC, Mottola Jr J, Ruiz CA, Borges MN, Pinotti JA. Reassurance in the treatment of mastalgia. *Breast J.* 1999; 5(3):162-5.
- [16] Rosolowich V, Saettler E, Szuck B. Mastalgia. *J Obste tGynaecol Can.* 2006; 28:49-74.
- [17] Morrow M. The evaluation of common breast problems. *Am Fam Physician.* 2000; 61:2371-8.
- [18] Leung JW, Kornguth PJ, Gotway MB. Utility of targeted sonography in the evaluation of focal breast pain. *J Ultrasound Med.* 2002;21(5):521-6.
- [19] Makker A, Tandon I, Goel MM, Singh M, Singh MM. Effect of ormeloxifene, a selective estrogen receptor modulator, on biomarkers of endometrial receptivity and pinopode development and its relation to fertility and infertility in Indian subjects. *Fertil Steril.* 2009;91(6):2298-307.

- [20] Goyal A, Mansel RE. A randomized multicenter study of gamolenic acid (Efamast) with and without antioxidant vitamins and minerals in the management of mastalgia. *Breast J.* 2005;11(1):41-47.
- [21] Srivastava A, Mansel RE, Arvind N, Prasad K, Dhar A, Chabra A. Evidence-based management of Mastalgia: a meta-analysis of randomised trials. *Breast.* 2007;16(5):503-12.
- [22] Dhar A, Srivastava A. Role of centchroman in regression of mastalgia and fibroadenoma. *World J Surg.* 2007;31:1178-84.
- [23] Bagale P, Dravid NV, Bagale S, Ahire N. Clinicopathological study of benign breast diseases. *Int J Health Sci Res.* 2013;3(2):47-54.
- [24] Kulkarni S, Vora IM, Ghorpade KG, Shrivastava S. Histopathological spectrum of breast lesions with reference to uncommon cases. *Obste Gynecol India.* 2009;59(5):444-52.
- [25] Malik M, Salahuddin O, Azhar M, Dilawar O, Irshad H, Sadia SA. Breast diseases; spectrum in Wah cantt; POF hospital experience. *Professional Med J.* 2010;17(3):366-72.
- [26] Pudale S, Tonape SD. A histopathological study of non-malignant breast lesions. *Inter J Res Med Sci.* 2015;3(10):2672.
- [27] Kumar AD, Jayashankar E, Shailaja P, Ramamurti T. Expression of Estrogen, Progesterone and HER2/ neu Receptors in Breast Carcinoma- Study in a Tertiary Care Hospital. *J Evolut Med Dent Sci.* 2015;4(58):10170-7.
- [28] Rasheed A, Sharma S, Mohsin-ul-Rasool, Bashir S, Hafiz A, BashirSch N. A Three Year Study of Breast Lesions in Women aged 15-70 years in a Tertiary Care Hospital. *J App Med Sci.* 2014;2(1):166-8.
- [29] Sarma U, Deka R, Deuri S. ER & PR Status of Breast Cancer – A Single Center Study From Guwahati, North East India. *Ind J App Res.* 2015;5(7):283-4.
- [30] Sangma MBM, Panda K, Dasiah S. A ClinicoPathological Study on Benign Breast Diseases. *J Clin Diagn Res.* 2013;7(3):503-6.
- [31] Amr SS, Abdul Rahman, M Sadi, Fazallahi, SS Sheikh. The Spectrum of Breast Diseases in Saudi Arab Females: A 26 yr Pathological Survey at Dhahran Health Center. *Ann Saudi Med.* 1995;15(2):125-32.
- [32] Li P, Xiao-Yin T, Cui D, Chi JC, Wang Z. Evaluation of the safety and efficacy of percutaneous radiofrequency ablation for treating multiple breast fibroadenoma. *J Cancer Res Ther.* 2016;12:138-42.
- [33] Godwins E, David D, Akeem J. Histopathologic analysis of benign breast diseases in Makurdi, North Central Nigeria. *Inter J Med Med Sci.* 2011; 3(5):125-8.
- [34] Shashikala V, Sonia RP, Victor AJ. Clinicopathological study of benign breast diseases. *Int J Biomed Adv Res.* 2016;7(9):424-7.
- [35] Sagar R, Gaddikeri P, Ramakrishna MK. Analytical study of pattern and presentation of benign breast diseases in patients between age group 15 to 35 years. *Int J Biomed Res.* 2015;6(6):412-5.
- [36] Ramesh K, Bookya K. A study on clinical and pathological correlation of benign breast lesions. *Inter Surg J.* 2017;4(8):2700-5.
- [37] Chalya PL, Manyama M, Rambau PF, Kapesa A, Ngallaba SE, Masalu N, Mabula JB. Clinicopathological pattern of benign breast diseases among female patients at a tertiary health institution in Tanzania. *Tanz J Health Res.* 2016;18(1).