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Surgery Section

Effects of Tamoxifen, Ormeloxifene and Evening Primrose Oil in the Management of Breast Fibroadenoma: A Prospective Observational Study

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ABSTRACT

Introduction: Breast fibroadenoma, a common benign tumour in young women, is often managed conservatively. Selective Oestrogen Receptor Modulators (SERMs), such as tamoxifen and ormeloxifene, have shown therapeutic potential, while Evening Primrose Oil (EPO) is used as an alternative remedy.

Aim: To compare the efficacy of tamoxifen, ormeloxifene, and EPO in the management of breast fibroadenoma.

Materials and Methods: A prospective observational study was conducted in the Department of Surgery, Moti Lal Nehru Medical College (tertiary care centre), in collaboration with the Departments of Pathology and Radiodiagnosis, Medical College, Prayagraj, Uttar Pradesh, India from September 2020 to September 2021. A total of 142 female patients (15–40 years) with fibroadenoma (2–10 cm), confirmed by clinical examination, ultrasound, and FNAC/Tru-Cut biopsy, were included. Participants were allocated into four groups: Ormeloxifene (n=39), Tamoxifen (n=40), Evening Primrose Oil (n=33), and Placebo (n=30). Tumour volume was assessed using ultrasound, as determined by the formula. V = axβxcx0.52 and diagnosis was confirmed by Tru-cut biopsy or Fine-needle Aspiration Cytology (FNAC). Patients were followed up at weeks 12 and 24 to assess adverse effects and therapeutic response. Clinical examinations and repeat ultrasound assessments were performed at 12 and 24 weeks to evaluate changes in tumour size and consistency.

Results: Among 142 women, fibroadenoma was most common in the 26-30-year age group. Ormeloxifene showed the greatest regression, with 76.9% achieving ≤1.9 cm lesions at 24 weeks, followed by tamoxifen (60.0%). EPO showed a limited effect, and the placebo showed none. The differences were statistically significant (p-value <0.001). Ormeloxifene proved to be the most effective therapy in reducing fibroadenoma size.

Conclusion: Ormeloxifene demonstrated the highest efficacy in fibroadenoma regression, followed by Tamoxifen. SERMs, particularly Ormeloxifene, should be considered for conservative fibroadenoma management.

Keywords: Benign tumour, Progesterone relexified, Selective oestrogen receptor modulators, Tumour regression

INTRODUCTION

Breast fibroadenoma is one of the most common benign breast tumours encountered in women of reproductive age, often presenting as a painless, firm, and mobile mass [1]. Although non cancerous, its occurrence causes considerable anxiety among patients due to its resemblance to malignant lesions, leading to frequent surgical interventions [1]. Traditionally, surgical excision has been the mainstay of treatment for fibroadenoma, particularly for symptomatic or enlarging lesions. However, surgery carries drawbacks such as scarring, psychological distress, and the possibility of recurrence [2]. In recent years, there has been a growing emphasis on conservative medical management to reduce the need for invasive procedures [3]. Among various pharmacological options, tamoxifen, ormeloxifene (Centchroman), and EPO have gained attention due to their modulatory effects on Oestrogen Receptors (ER) and hormonal balance, which are believed to influence the growth of fibroadenomas [4].

Tamoxifen, a SERM, has been widely used in the management of oestrogen-dependent breast disorders. Its mechanism involves competitive inhibition of oestrogen binding to its receptor, leading to suppression of oestrogenic stimulation in breast tissue [5]. Tamoxifen exerts an anti-oestrogenic effect on breast epithelium while preserving oestrogenic actions on bone and endometrium. In the context of fibroadenoma, the tumour's growth is believed to be hormonally regulated, particularly by oestrogen and progesterone [6]. Tamoxifen, through its modulatory effect on ER, may facilitate regression of fibroadenomas and relieve associated mastalgia. Short-term tamoxifen therapy has been shown to produce partial or complete regression of benign breast lesions [4]. However, its long-term use is limited due to potential adverse effects such as thromboembolism, hot flashes, and endometrial hyperplasia. Despite these concerns, its ability to reduce fibroadenoma size and pain makes it a promising candidate for conservative therapy in selected cases [7].

Ormeloxifene (Centchroman) is another SERM developed in India, introduced initially as a non steroidal oral contraceptive. It has gained recognition for its unique tissue-selective oestrogenic and anti-estrogenic actions [8]. In fibroadenoma management, ormeloxifene inhibits epithelial proliferation and stromal overgrowth, thereby inducing regression of fibroadenomatous nodules [8].

Evening Primrose Oil, derived from the seeds of *Oenothera biennis*, is a natural source of Gamma Linolenic Acid (GLA), an omega-6 essential fatty acid. It plays a role in the synthesis of prostaglandins that regulate inflammatory and hormonal responses [9]. EPO supplementation has been found beneficial in cyclic mastalgia and benign breast disease due to its ability to restore prostaglandin balance and reduce tissue sensitivity to oestrogen and prolactin [10]. The study aimed to compare the efficacy of tamoxifen, ormeloxifene, and EPO in the management of breast fibroadenoma.

MATERIALS AND METHODS

A prospective observational study was conducted in the Department of Surgery, Moti Lal Nehru Medical College (tertiary

care centre), in collaboration with the Departments of Pathology and Radiodiagnosis, Medical College, Prayagraj, Uttar Pradesh, India from September 2020 to September 2021. The study received Ethical approval from the Institutional Ethics Committee (IEC No.: ECR/922/Inst/UP/2017), and written informed consent was obtained from all participants or their legal guardians.

Inclusion criteria:

- Female patients aged 15-40 years with clinically and radiologically diagnosed fibroadenoma (size 2-10 cm);
- Triple assessment confirmation (clinical evaluation, ultrasound scan, histopathology by Tru-cut biopsy or FNAC);
- Patients willing to participate after informed consent.

Exclusion criteria:

- Malignant breast diseases;
- Simple breast cysts;
- Phyllodes tumours;
- Pregnant women;
- Patients planning pregnancy within the next six months;
- Patients with Polycystic Ovarian Disease (PCOD), cervical hyperplasia, chronic liver disease, or renal disease;
- Unwilling participants.

Participants were allocated into four treatment groups based on treatment received and patient preference: Group A – Ormeloxifene (n=39), Group B – Tamoxifen (n=40), Group C – Evening Primrose Oil (n=33), and Group D – Placebo (n=30). All analyses were performed on the final available sample.

- **Group A** (Ormeloxifene Group)- Participants received ormeloxifene 30 mg oral tablet, administered once every alternate day for three months, followed by a three-month post-treatment follow-up period to assess therapeutic response and regression stability.
- **Group B** (Tamoxifen Group)- Participants received tamoxifen 10 mg oral tablet, taken twice daily for three menstrual cycles (three months), followed by a further three-month observation period without treatment.
- **Group C** (EPO Group)- orally in soft gelatin capsule form, each capsule containing 1000 mg of EPO (liquid formulation). Participants were instructed to take one capsule twice daily for three months, followed by a three-month follow-up period to monitor therapeutic response and tolerance.
- **Group D** (Placebo Group)- Vitamin B-complex capsule once daily (each capsule containing Vitamin B1 - 10 mg, Vitamin B2 - 10 mg, Vitamin B6 - 3 mg, Niacinamide - 50 mg, Calcium Pantothenate - 50 mg, and Vitamin B12 - 15 µg) for three months, followed by a three-month follow-up.

Study Procedure

Clinical and radiological assessment: Fibroadenoma size was first assessed clinically by the palpation method, a standard subjective clinical technique performed by the same experienced investigator to minimise inter-observer variation. The patient was positioned supine with the arm raised above the head, and the lesion was examined using finger pads in a circular motion to record its size in two perpendicular dimensions using a flexible scale or calliper.

Baseline ultrasound examination was performed using a 7.5 MHz linear probe on a Siemens Versa ultrasound scanner to evaluate tumour morphology and volume, which was calculated using the formula: V = axbxcx0.52 Where *a* represents the largest dimension, *b* is the dimension at a right angle to *a*, and *c* is calculated as (a+b)/2.

For histopathological confirmation, a Tru-cut biopsy was performed in consenting patients to determine ER and Progesterone Receptor (PR) status. Fine-Needle Aspiration Cytology (FNAC) was also conducted to exclude malignancy. Patients were followed up at weeks 12 and 24 to assess adverse effects and therapeutic response. Clinical examinations and repeat ultrasound assessments were performed at 12 and 24 weeks to evaluate changes in tumour size and consistency.

STATISTICAL ANALYSIS

Data were analysed using SPSS software (version 15.0 Inc., Chicago, IL, USA). Continuous variables, such as fibroadenoma size, were summarised as the mean±Standard Deviation (SD), while categorical variables, including marital status and treatment response, were expressed as frequencies and percentages. The statistical tests have now been explicitly mentioned: Chi-square test for categorical variables and One-way Analysis of Variance (ANOVA) for continuous variables.

RESULTS

Most patients were aged 26-30 years, indicating a predominance of women of reproductive age. A higher proportion belonged to rural areas (55.6%) and was literate (80.3%) [Table/Fig-1]. At the start of the study, none of the patients had fibroadenoma ≤1.9 cm. The majority of lesions were in the 3.0-3.9 cm and 4.0-4.9 cm ranges, indicating moderate-sized fibroadenomas as the predominant presentation [Table/Fig-2]. The ormeloxifene group showed the most substantial reduction, followed by the tamoxifen group. The EPO group showed moderate improvement, whereas the placebo group demonstrated no regression [Table/Fig-3]. Statistical analysis revealed highly significant differences (p-value <0.01) among the four groups, confirming that ormeloxifene was the most effective therapeutic agent in reducing fibroadenoma size over 24 weeks [Table/Fig-4]. As per the imaging method, the highest number of cases fell within the 3.0-3.9 cm and 4.0-4.9 cm size categories [Table/Fig-5].

Parameters	Category	Ormeloxifene n (%)	Tamoxifen n (%)	Evening Primrose Oil (EPO) n (%)	Placebo n (%)	Total (N=142)
Drug used	-	39 (27.46)	40 (28.17)	33 (23.24)	30 (21.13)	142 (100)
Age group (years)	≤20	13 (33.33)	8 (20.00)	11 (33.33)	2 (06.67)	34 (23.94)
	21-25	13 (33.33)	12 (30.00)	8 (24.24)	10 (33.33)	43 (30.28)
	26-30	11 (28.20)	15 (37.50)	12 (36.36)	12 (40)	50 (35.21)
	31-35	2 (05.14)	5 (12.50)	2 (06.06)	6 (20.00)	15 (10.56)
	36-40	0	0	0	0	0
Habitat	Urban	15 (38.46)	17 (42.50)	14 (42.42)	17 (56.66)	63 (44.36)
	Rural	24 (61.54)	23 (57.50)	19 (57.58)	13 (43.34)	79 (55.64)
Educational status	Literate	32 (82.05)	31 (77.50)	25 (75.75)	26 (86.66)	114 (80.28)
	Illiterate	7 (17.95)	9 (22.50)	8 (24.25)	4 (13.34)	28 (19.72)
Marital status	Married	24 (61.53)	19 (47.50)	20 (60.60)	11 (36.66)	74 (52.11)
	Unmarried	15 (38.47)	21 (52.50)	13 (39.40)	19 (63.34)	68 (47.89)

[Table/Fig-1]: Socio-demographic characteristics of subjects.

Fibroadenoma size range (cm)	Ormeloxifene n (%)	Tamoxifen n (%)	Evening Primrose Oil (EPO) n (%)	Placebo n (%)	Total
≤1.9	0	0	0	0	00
2.0-2.9	0	03 (07.50)	0	05 (16.67)	08
3.0-3.9	15 (38.46)	10 (25.00)	08 (24.24)	09 (30.00)	42
4.0-4.9	09 (23.08)	12 (30.00)	11 (33.33)	06 (20.00)	38
5.0-5.9	06 (15.38)	09 (22.50)	09 (27.27)	05 (16.67)	29
6.0-6.9	04 (10.25)	05 (12.50)	04 (12.12)	04 (13.33)	17
≥7.0	05 (12.83)	01 (02.50)	01 (03.04)	01 (03.33)	08
Total	39 (100.00)	40 (100.00)	33 (100.00)	30 (100.00)	142
Mean±SD	4.25±1.12	4.10±1.24	4.35±1.30	4.40±1.28	-

[Table/Fig-2]: Size of breast fibroadenoma by palpation method (pre-treatment) (N=142).

Palpation size range (cm)	Ormeloxifene n (%)	Tamoxifen n (%)	Evening Primrose Oil (EPO) n (%)	Placebo n (%)	Total cases n (%)
≤1.9	26 (18.31)	23 (16.20)	12 (8.45)	0	61 (42.96)
2.0-2.9	06 (4.23)	01 (0.70)	01 (0.70)	02 (1.41)	10 (7.04)
3.0-3.9	01 (0.70)	02 (1.41)	0	11 (7.75)	14 (9.86)
4.0-4.9	0	02 (1.41)	06 (4.23)	06 (4.23)	14 (9.86)
5.0-5.9	01 (0.70)	7 (4.93%)	09 (6.34)	06 (4.23)	23 (16.20)
6.0-6.9	03 (2.11)	4 (2.82%)	04 (2.82)	04 (2.82)	15 (10.56)
≥7.0 cm	02 (1.41)	1 (0.70%)	01 (0.70)	01 (0.70)	05 (3.52)

[Table/Fig-3]: Size of breast fibroadenoma by palpation at 12 weeks.

Palpation range (cm)	Ormeloxifenen n (%)	Tamoxifenn n (%)	Evening Primrose Oil (EPO)n (%)	Placebon (%)	Total	p-value
≤1.9	30 (76.9)	24 (60.0)	13 (39.4)	0	67	
2.0-2.9	03 (7.7)	01 (2.5)	0	2 (6.7)	6	
3.0-3.9	0	01 (2.5)	0	9 (30.0)	10	
4.0-4.9	02 (5.1)	02 (5.0)	6 (18.2)	8 (26.7)	18	
5.0-5.9	0	07 (17.5)	9 (27.3)	6 (20.0)	22	0.001
6.0-6.9	02 (5.1)	04 (10.0)	4 (12.1)	4 (13.3)	14	
≥7.0	02 (5.1)	01 (2.5)	1 (3.0)	1 (3.3)	5	
Total	39 (100)	40 (100)	33 (100)	30 (100)	142	
Mean±SD	2.45±0.98	2.80±1.02	3.30±1.10	4.20±1.25	-	

[Table/Fig-4]: Size of breast fibroadenoma by palpation at 24 weeks.
ANOVA was used; The palpation findings correspond with the ultrasound findings

Fibroadenoma size range (cm)	Ormeloxifene n (%)	Tamoxifen n (%)	Evening Primrose Oil (EPO) n (%)	Placebo n (%)	Total
≤1.9	0	0	0	0	0
2.0-2.9	0	03 (7.5)	0	05 (16.7)	8
3.0-3.9	15 (38.5)	10 (25.0)	12 (36.4)	09 (30.0)	46
4.0-4.9	09 (23.1)	12 (30.0)	07 (21.2)	07 (23.3)	35
5.0-5.9	06 (15.4)	09 (22.5)	09 (27.3)	04 (13.3)	28
6.0-6.9	05 (12.8)	05 (12.5)	04 (12.1)	04 (13.3)	18
≥7.0	04 (10.3)	01 (2.5)	01 (3.0)	01 (3.3)	7
Total	39 (100)	40 (100)	33 (100)	30 (100)	142
Mean±SD	4.30±1.25	4.15±1.20	4.35±1.22	4.45±1.15	-

[Table/Fig-5]: Size of fibroadenoma by imaging method (pre treatment).
Baseline fibroadenoma size distribution showed minor differences between palpation and ultrasound assessments; These reflect the subjective nature of palpation versus the higher accuracy of ultrasound, leading to occasional reclassification into adjacent size categories

The ormeloxifene group showed the most substantial reduction, followed by the tamoxifen group [Table/Fig-6]. The differences between groups were highly significant (p-value <0.01), indicating that ormeloxifene and tamoxifen maintained their effectiveness in long-term follow-up. Complete disappearance of fibroadenoma was seen in 64.10% of patients treated with Ormeloxifene [Table/Fig-7].

Ormeloxifene group representative pre-treatment and post-treatment (12 and 24 weeks) ultrasound images showing fibrocystic breast changes [Table/Fig-8]. Tamoxifen Group Representative pre-treatment and post-treatment (12 and 24 weeks) ultrasound images demonstrating a reduction in cystic density [Table/Fig-9].

The EPO group representative pre-treatment and post-treatment (12 and 24 weeks) ultrasound images showing minimal cyst regression

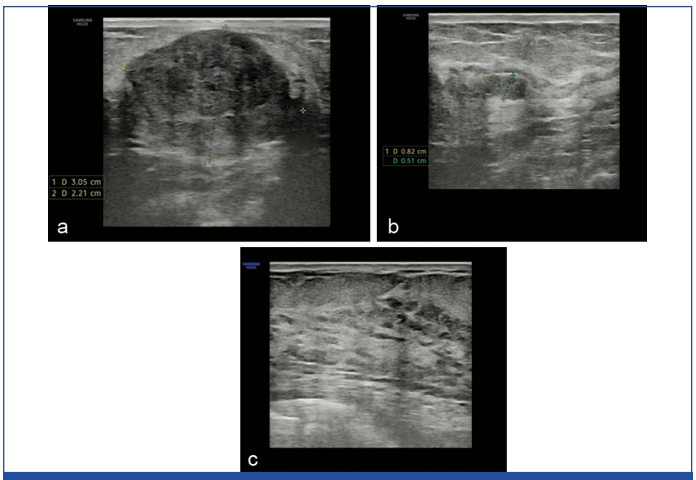
Fibroadenoma size range	Ormeloxifene n (%)	Tamoxifen n (%)	Evening Primrose Oil (EPO) n (%)	Placebo n (%)	Total
≤1.9	26 (66.7)	23 (57.5)	12 (36.4)	0	61
2.0-2.9	06 (15.4)	01 (2.5)	01 (3.0)	02 (6.7)	10
3.0-3.9	01 (2.6)	02 (5.0)	0	11 (36.7)	14

4.0-4.9	0	02 (5.0)	06 (18.2)	07 (23.3)	15
5.0-5.9	01 (2.6)	07 (17.5)	09 (27.3)	05 (16.7)	22
6.0-6.9	03 (7.7)	04 (10.0)	04 (12.1)	04 (13.3)	15
≥7.0	02 (5.1)	01 (2.5)	01 (3.0)	01 (3.3)	5
Total	39 (100)	40 (100)	33 (100)	30 (100)	142
Mean±SD	2.95±1.05	3.05±1.10	3.60±1.20	4.10±1.25	-

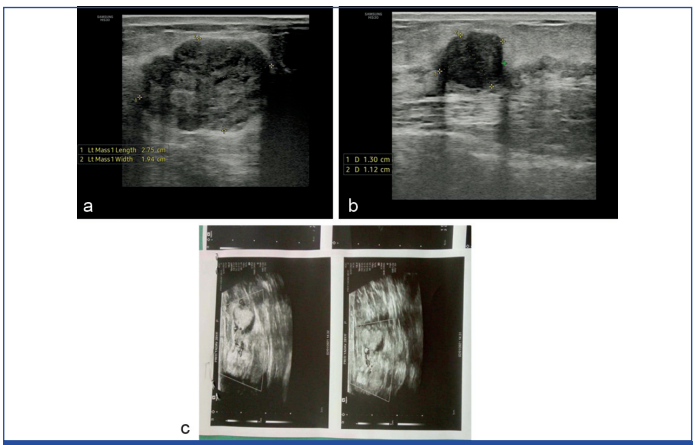
[Table/Fig-6]: Size of fibroadenoma by imaging at 12 weeks.

Effectiveness	Ormeloxifene n (%)	Tamoxifen n (%)	EPO n (%)	Placebo n (%)	Total	p-value
Complete disappearance	25 (64.10)	16 (40)	04 (12.12)	0	45	p-value <0.001
Partial disappearance	10 (25.64)	12 (30.00)	09 (27.27)	0	31	p-value <0.01
Non respondent	04 (10.26)	12 (30.00)	20 (60.61)	30 (100.00)	66	p-value <0.001
Total	39	40	33	30	142	

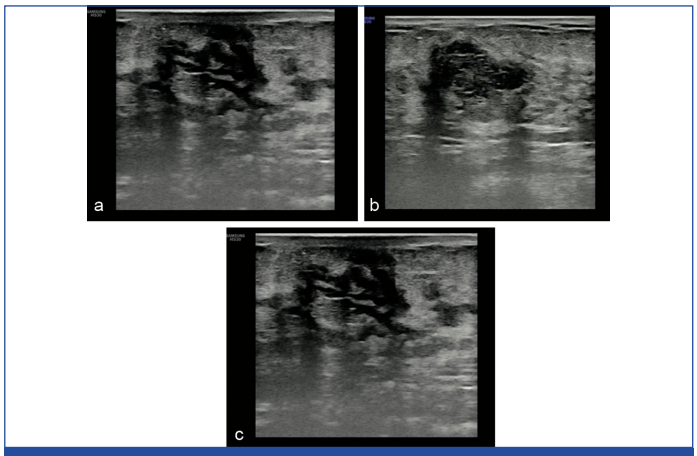
[Table/Fig-7]: Effectiveness of drugs at 24 weeks.
Chi-square test



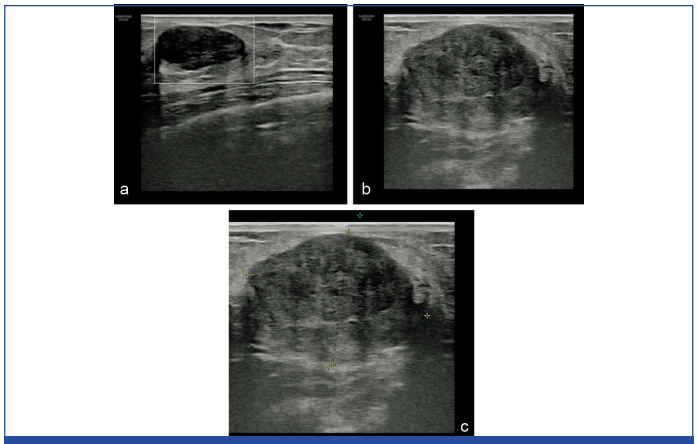
[Table/Fig-8]: a) Ormeloxifene group representative pre-treatment; b) Ormeloxifene group representative post-treatment 12 weeks; c) Ormeloxifene group representative post-treatment 24 weeks.



[Table/Fig-9]: a) Tamoxifen group representative pre-treatment; b) Tamoxifen group representative post-treatment 12 weeks; c) Tamoxifen group representative post-treatment 24 weeks.



[Table/Fig-10]: a) EPO group representative pre-treatment; b) Evening Primrose Oil (EPO) group representative post-treatment 12 weeks; c) Evening Primrose Oil (EPO) Group Representative post-treatment 24 weeks.



[Table/Fig-11]: a) Placebo group representative pre-treatment; b) Placebo group representative and post-treatment 12-week ultrasound images showing negligible change in cyst morphology; c) Placebo group representative and post-treatment 24-week.

[Table/Fig-10]. Placebo group representative pre-treatment and post-treatment (12 and 24 weeks) ultrasound images showing negligible change in cyst morphology [Table/Fig-11].

DISCUSSION

The present study supports the widely documented observation that fibroadenoma predominantly affects women in the reproductive age group. In the current findings, most participants were within the second and third decades of life, aligning with global epidemiological evidence. Ajmal M et al., reported that fibroadenoma is the most common benign breast tumour affecting women aged 15-35 years, strongly influenced by oestrogen-dependent growth patterns [11]. Similar observations were reported by Salih AM et al., who concluded that the lesion stabilises or regresses with advancing age due to hormonal decline [12].

The therapeutic analysis demonstrated that ormeloxifene produced the highest rate of regression among all treatment groups. This is consistent with the results published by Agrawal K et al., (2024), who found statistically significant regression in fibroadenoma volume following 12-24 weeks of ormeloxifene therapy [13]. A 2022 clinical evaluation by Kafle U et al., also reported comparable findings, identifying ormeloxifene as an effective, low-toxicity, non invasive treatment option for benign breast disease [14]. The therapeutic advantage is attributable to its function as a SERM, which inhibits oestrogen-dependent proliferative activity.

Tamoxifen demonstrated moderate response outcomes in the current study. This aligns with the findings of DeCensi A et al., who documented substantial symptom improvement and reduction in lump size among benign breast disease patients undergoing short-term tamoxifen therapy [15].

The EPO yielded minimal fibroadenoma regression, although patients demonstrated mild improvement in associated mastalgia. A randomised controlled trial by Alvandipour M et al., concluded that EPO is useful in mastalgia management but has no significant effect on fibroadenoma resolution [16]. These results reinforce its role as symptomatic rather than curative.

The placebo group demonstrated negligible or no tumour regression, underscoring that spontaneous reduction within short observation periods is unlikely. Sanders LM and Sara R. similarly reported that while fibroadenomas may involute over the years, meaningful reduction within six months is rare, especially in lesions larger than 2 cm [17].

Overall, the findings support ormeloxifene as the most effective non surgical intervention for fibroadenoma management, particularly in young women prioritising breast conservation. Future multicentric controlled trials with longer follow-up are warranted to assess recurrence, relapse, and cost-effectiveness relative to surgical excision.

Limitation(s)

The study presents follow-up data for only up to 24 weeks, highlighting the need for future research to evaluate the long-term effects of selected drugs on recurrence. The sample size was relatively small, and due to the pandemic, the limited patient flow to tertiary care centre restricted the feasibility of designing the study on a larger group. Furthermore, the results were derived from a single surgical unit within a tertiary care centre, which may limit their generalisability to broader clinical settings.

CONCLUSION(S)

The present study demonstrates that ormeloxifene and tamoxifen are significantly more effective in promoting fibroadenoma regression compared to EPO and placebo. Ormeloxifene exhibited the highest rate of complete fibroadenoma disappearance, followed by tamoxifen, while EPO showed limited efficacy. The placebo group exhibited no therapeutic benefit. These findings suggest that SERMs, particularly ormeloxifene, should be considered as a primary pharmacological option in the conservative management of breast fibroadenoma. Further studies with larger sample sizes and longer follow-up periods are warranted to validate these results and optimise treatment protocols for fibroadenoma management.

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