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Original Research Article

Total Estrogen Blockade with Centchroman and Gonadotropin Releasing Hormone Analogues for Regression of Fibroadenomas in Comparison to Centchroman Alone

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Conflict of interest: Nil

Abstract

Background: Fibroadenoma is a benign breast lesion affecting adolescents and young women. Centchroman offers a non-surgical option, but incomplete regression is frequent. Adding ovarian estrogen suppression may improve response.

Objectives: To compare the efficacy and safety of Centchroman plus leuprolide with Centchroman monotherapy for fibroadenoma regression in women below 30 years.

Materials and Methods: This prospective, two-arm randomized controlled trial was conducted over 18 months at Chhatrapati Shivaji Subharti Hospital, Meerut. Thirty women with ultrasonographically confirmed fibroadenoma were randomized equally. Group 1 received Centchroman 30 mg orally once daily for three months, whereas Group 2 received the same regimen with leuprolide 3.75 mg intramuscularly once monthly. Fibroadenoma volume was assessed ultrasonographically at three and six months. Mild, moderate or marked regression was noted with adverse effects.

Results: Mean volume reduction in Group 1 increased from 27.6 ± 7.1% at three months to 58.5 ± 13.4% at six months, while Group 2 improved from 44.1 ± 21.6% to 77.0 ± 13.4%. Within-group improvement was highly significant in both groups ($p < 0.0001$). Combination therapy achieved greater reduction at three months ($p = 0.018$) and six months ($p = 0.001$). Marked regression at six months occurred in 1 of 15 and 11 of 15 participants, respectively. Amenorrhea occurred in 1 and 4 participants; no hot flashes were reported.

Conclusion: Total estrogen blockade produced greater and more sustained fibroadenoma regression than Centchroman alone, with acceptable short-term tolerability.

Keywords: Fibroadenoma; Centchroman; Leuprolide; Total Estrogen Blockade; Regression; Randomized Controlled Trial.

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Introduction

Fibroadenoma is a benign breast tumour that commonly affects adolescents and women in early reproductive life. The giant juvenile form may enlarge rapidly, producing breast asymmetry, cosmetic concern and psychological distress. In adolescents aged 11–19 years with lesions larger than 5 cm, combined ormeloxifene and leuprolide produced size reductions of 16–60%, while menstrual irregularity was the most frequent adverse effect. [1] In a placebo-controlled trial of 104 women, Centchroman achieved more than 50% volume reduction in 28.8% compared with 13.5% of controls and improved mastalgia, anxiety and depression scores. [2] Evidence for Centchroman monotherapy remains inconsistent. A double-blind trial involving 130 biopsy-confirmed cases found

complete regression at 12 weeks in 9% of the ormeloxifene group and 10.8% of the placebo group; adverse events occurred in 21 treated participants, and efficacy was not demonstrated. [3]

Conversely, a prospective study of 60 women with 2–5 cm fibroadenomas reported complete response in 30%, lesion-size reduction in 66.66%, and no response in 3.33% following Centchroman therapy. [4] Among patients with multiple fibroadenomas and mastalgia, six-month assessment showed complete dissolution in 34%, partial response in 46%, no change in 17%, and substantial early pain relief. [5] However, a meta-analysis of two randomized trials involving 234 participants found no significant efficacy advantage over control, while non-serious adverse effects were more frequent with Centchroman. [6] An Indian hospital-based comparison also demonstrated significantly more partial or complete fibroadenoma responses with Centchroman than with evening primrose oil. [7] Clinical guidance identifies fibroadenoma as the most common benign breast tumour, particularly among women aged 15–35 years. Clinical examination and ultrasonography are the principal diagnostic methods, while pathological examination remains the reference standard. [8] The supplied references do not provide reliable population-based estimates for India, Uttar Pradesh or Meerut.

GnRH agonists suppress ovarian estrogen production and provide reversible ovarian-function suppression in premenopausal women. [9] Estradiol is the preferred biomarker for assessing the adequacy of this suppression. [10] combining central ovarian suppression with peripheral estrogen-receptor blockade may therefore provide a biologically coherent breast-conserving approach. Direct comparison with Centchroman alone among young women attending a tertiary hospital in Meerut is needed to address the evidence gap and forms the rationale for the study.

Material and Methods

Study Design: A prospective, two-arm, parallel-group randomized controlled trial with a superiority hypothesis and 1:1 allocation ratio was conducted over 18 months, from April 2024 to September 2025.

Study Setting: The study was undertaken in the General Surgery and Gynaecology outpatient and inpatient departments of Chhatrapati Shivaji Subharti Hospital, Meerut, Uttar Pradesh, a tertiary-care teaching hospital serving urban and rural populations.

Study Population: Female patients aged 14–30 years presenting with a clinically detectable breast lump and subsequently diagnosed with fibroadenoma on ultrasonography were screened for eligibility.

Sample Size and Allocation: Thirty eligible women were recruited and randomly allocated into two groups of 15 each by a random-number sequence. Allocation concealment was maintained using sealed, opaque envelopes. Group 1 received oral Centchroman 30 mg once daily for three months. Group 2 received oral Centchroman 30 mg once daily along with intramuscular leuprolide 3.75 mg once monthly for three months.

Inclusion Criteria: Female patients aged below 30 years, ultrasonographically confirmed fibroadenoma measuring less than 5 cm, and provision of written informed consent by the participant or guardian were included.

Exclusion Criteria: Patients aged above 30 years, those with a personal or family history of breast cancer, complex fibroadenoma or atypia, liver disease, renal failure, lactation, pregnancy, or planned pregnancy were excluded.

Data Collection and Investigations: Detailed clinical history, including family history of breast or ovarian malignancy, clinical breast examination, bilateral breast ultrasonography and baseline laboratory investigations were performed. Fibroadenoma volume was calculated using the ellipsoid formula.

Ultrasonographic reassessment was undertaken at three and six months. Regression was categorized as marked, moderate, mild or no response. Treatment-related adverse effects, particularly menstrual disturbances were also noted.

Ethical Considerations: Written informed consent was obtained from all the participants or their guardians. The Institutional Ethics Committee approval number should be added to the final manuscript.

Statistical Analysis: Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies and percentages. Paired and unpaired t-tests and Chi-square tests were applied as appropriate. A p-value <0.05 was considered statistically significant.

Results

Table 1: Mean age and Standard deviation by Group

	Mean	SD
Group 1	21.87 years	+/- 5.13 years
Group 2	21.53 years	+/- 4.86 years

p-value = 0.83, p-value > 0.05, is not statistically significant, and hence comparable.

The mean age of patients was 21.87 ± 5.13 years in the Centchroman monotherapy group and 21.53 ± 4.86 years in the combination therapy group (Table 1). There was no significant difference (p = 0.83) indicating both treatment groups were similar in regards to baseline age.

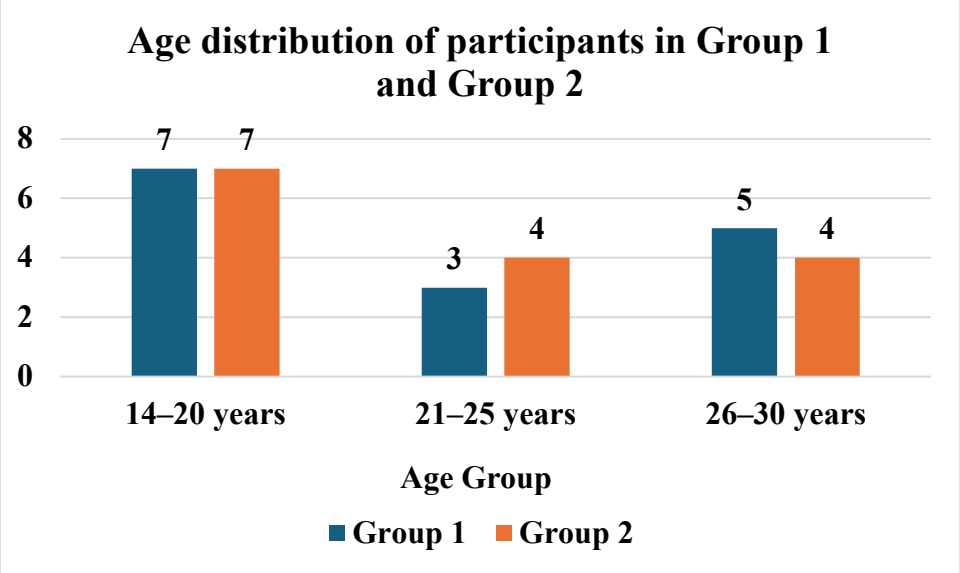

Figure 1: Age distribution of participants in Group 1 and Group 2

Table 2: Mean Outcome and Standard deviation Group 1

Reduction	Mean	SD
3-Month (%)	27.6%	+/- 7.1
6-Month (%)	58.5%	+/- 13.4

Within-group improvement (3 months vs 6 months) Mean difference = 30.9%. Paired t-test: t = 8.92, p < 0.0001 (Highly significant)

Table 2 shows that in Group 1 the mean reduction in fibroadenoma volume increased from 27.6 ± 7.1% at 3 months to 58.5 ± 13.4% at 6 months. Mean improvement was 30.9 percentage points and highly statistically significant (t=8.92, p<0.0001) demonstrating progressive regression with centchroman monotherapy.

Table 3: Mean Outcome and Standard deviation Group 2

Reduction	Mean	SD
3-Month (%)	44.1%	+/- 21.6
6-Month (%)	77.0%	+/- 13.4

Within-group improvement (3 months vs 6 months) Mean difference = 32.9%. Paired t-test: t = 6.41, p < 0.0001 (Highly significant)

The mean volume reduction of fibroadenoma in Group 2 was 44.1±21.6% at 3 months, and it increased to 77.0±13.4% at 6 months (Table 3). The mean improvement of 32.9 percentage points was highly significant (t = 6.41, p < 0.0001), indicating progressive and sustained regression with combination therapy.

Table 4: Group comparison of response to treatment at 3 months:

Response category	Group 1 – Monotherapy Centchroman	%	Group 2 - Combination therapy	%
Marked regression	0	0%	2	13.3%
Moderate regression	0	0%	3	20%
Mild regression	15	100%	10	66.7%
No response	0	0%	0	0%
Total	15		15	

Table 4 shows that, at 3 months, all participants in the Centchroman monotherapy group had mild regression. In the combination therapy group, 66.7% had mild, 20.0% moderate and 13.3% marked regression. No participant showed absence of response, indicating a better early therapeutic response with combination therapy.

Table 5: Group comparison of response to treatment at 6 months:

Response category	Group 1- Monotherapy	%	Group 2 - Combination therapy	
Marked regression	1	6.67%	11	
Moderate regression	11	73.3%	3	
Mild regression	3	20%	1	6.67%
No response	0	0%	0	0%
Total	15		15	

Table 5 shows that, at 6 months, marked regression was achieved by 73.3% of participants receiving combination therapy compared with 6.7% receiving Centchroman monotherapy. Moderate regression predominated in the monotherapy group (73.3%), whereas mild regression occurred in 20.0% and 6.7%, respectively. No participant showed absence of response.

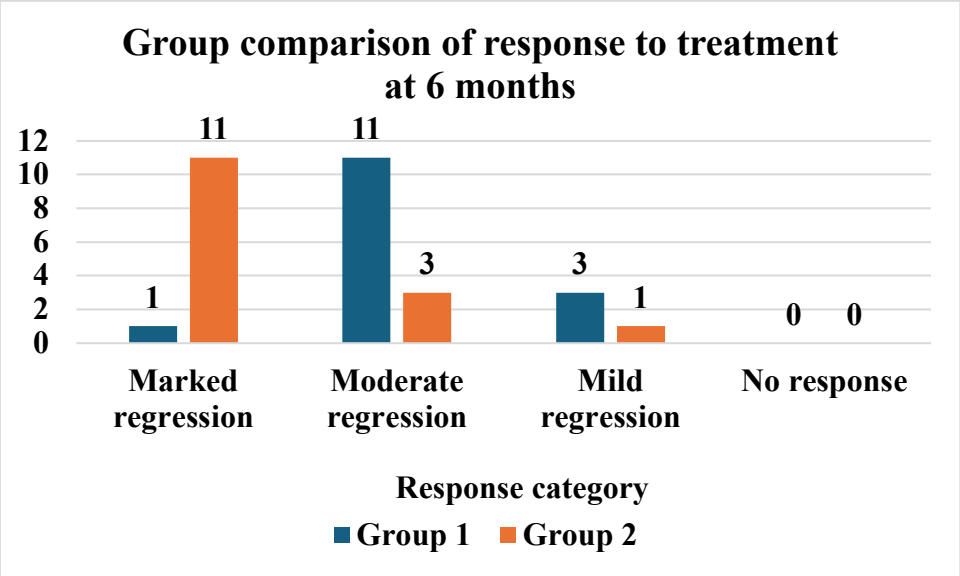

Figure 2: Response comparison at 6 months

Table 6: Secondary Outcomes: Adverse Effects from both therapies

Adverse effect	Monotherapy group (Centchroman only)	Combination therapy group
Amenorrhea	1/15	4/15
Hot flashes	None	None
Headache	1/15	2/15

Table 6 shows that amenorrhea was reported in 1 of 15 participants receiving Centchroman monotherapy and 4 of 15 receiving combination therapy. Headache occurred in 1 and 2 participants, respectively, while no hot flashes were observed in either group. Adverse effects were more frequent with combination therapy, but still limited.

Discussion

The mean age at baseline was not statistically significantly different in the two groups (Group 1, 21.87±5.13 years; Group 2, 21.53±4.86 years; p=0.83). This age group is comparable with the age group in Singh and Kurre (2024) [1] who recruited participants in the age group of 11 to 19 years and Singla et al. (2021) [4] who recruited patients in the age group of 15 to 35 years. In addition, the study by Yuan et al. (2021)[8] showed that the highest prevalence of fibroadenoma was women of 15-35 years. Rai et al. (2025)[2] have studied a wider age range of 18–45 year olds and thus a wider age representation than the narrow young cohort studied herein. In general, recruitment was appropriate to the peak reproductive age group.

Group 1 included 15 patients. The mean percentage reduction in fibroadenoma volume was 27.6 ± 7.1% at 3 months and 58.5 ± 13.4% at 6 months (mean

improvement 30.9 percentage points, t = 8.92, p < 0.0001). Singla et al. 2021 [4] reported size reduction of 66.66% with complete regression in 30% which was comparable with progressive response. and Brahmachari et al (2021) [5] reported partial and complete regression in 46% and 34% respectively. Rai et al. 2025 [2] 28.8% 50% reduction Sinha et al. (2024)7 Major regression (p=0.007) Kumar et al. (2025) [6] Agrawal et al. (2024) [3] No significant benefit

The mean reduction of fibroadenoma volume in group 2 was 44.1 ± 21.6% at 3 months and 77.0 ± 13.4% at 6 months with an improvement of 32.9 percentage points (t = 6.41, p < 0.0001). The result is in agreement with Singh and Kurre (2024) [1] who reported 16%–60% size reduction and significant reduction in 42% after ormeloxifene and leuprolide. The response was better than that reported in the studies of centchroman alone by Rai et al. (2025) [2], Singla et al. (2021) [4] and Brahmachari et al. (2021) [5], though the definitions of outcomes varied LeVasseur et al. (2024) [9] McCann et al. (2024) [10]. Supportive ovarian suppression with GnRH agonist. However, monotherapy showed poor efficacy in the studies of Kumar et al (2025) [6] and Agrawal et al (2024) [3].

3 months all the patients treated with Centchroman monotherapy showed mild regression and in the combination group regression was mild, moderate and marked in 66.7%, 20.0% and 13.3% respectively.

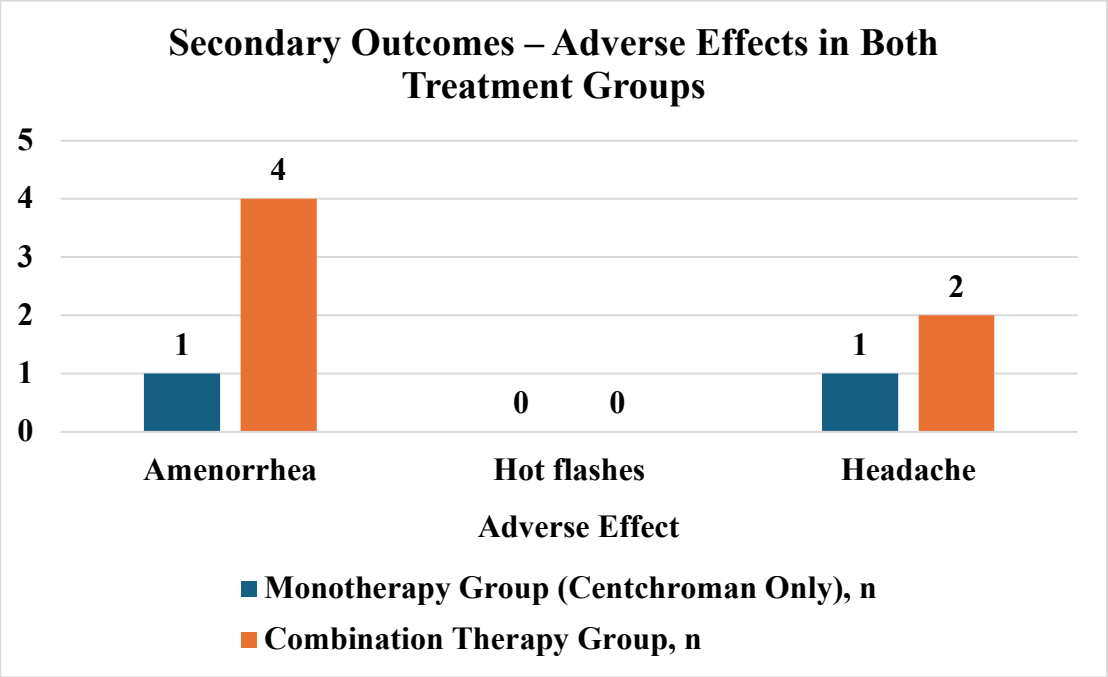

Figure 3: Adverse effects

No patient in any of the groups showed no response. This early benefit was consistent with the observations of Singh and Kurre (2024) [1] who reported size reduction of 16-60% with ormeloxifene + leuprolide and a significant reduction of 42%. Centchroman caused 50% volume reduction in 28.8% cases while complete regression was seen in 30% and 34% cases, respectively (Rai et al., 2025) [2] However, there was no significant benefit over placebo noted by Agrawal et al (2024)3 (p=0.49) and in the pooled analysis by Kumar et al (2025) [6] (RR 1.44, p=0.42).

At 6 months in the monotherapy group significant regression was noted in 1 of 15 patients and moderate regression in 11 of 15 patients. In the combination group, 11 of 15 patients had significant regression and 3 of 15 patients had moderate regression. Mild regression persisted in 20.0% of monotherapy group and 6.67% of combination group. There were no non-responders. This is consistent with positive response reported by Singh and Kurre (2024) [1] who reported 16%-60 % reduction and significant regression in 42% with combination hormonal therapy. Also, the magnitude of response was more than complete regression rates of Singla et al. (2021)[4] and Brahmachari et al. (2021) [5] (30% and 34%, respectively) and > 50% reduction rate of 28.8% of Rai et al. (2025) [2]. Conversely, Agrawal et al (2024) [3] reported complete regression in only 9% of patients treated with ormeloxifene.

Amenorrhea occurred in 1 of 15 women on Centchroman alone and 4 of 15 women on combination therapy, headache in 1 and 2 women respectively and hot flashes were not seen in either

group. This safety trend is similar to Singh and Kurre (2024)1 whereby 28.57% had menstrual irregularity after ormeloxifene plus leuprolide and 71.43% had no adverse effects. Singla et al. reported 40% scanty periods, 26.67% delayed periods and 6.67% absent periods. Adverse events in patients on Ormeloxifene. Agrawal et al, 2024 [3]. Rai et al. 2025 [2] 29% mild menstrual disturbances. Centchroman with significantly increased risk of adverse reaction (RR 13.08, p = 0.0001) Kumar et al. (2025) [6]

Conclusion

Total estrogen blockade with Centchroman and monthly leuprolide produced greater and more sustained regression of fibroadenoma than Centchroman monotherapy in women below 30 years. Mean volume reduction in the combination group increased from 44.1 ± 21.6% at 3 months to 77.0 ± 13.4% at 6 months, compared with 27.6 ± 7.1% and 58.5 ± 13.4%, respectively, in the monotherapy group. Improvement within both groups was highly significant, while the combination regimen showed superior reduction at 3 and 6 months. At 6 months 11 of 15 participants in the combination therapy group had significant regression compared with 1 of 15 in the Centchroman group indicating clinically meaningful benefit of dual estrogen suppression. The main adverse effects were transient amenorrhoea and occasional headache with no hot flushes or interruption of treatment. These findings lend support to combination hormonal therapy as a potentially effective, breast-conserving, non-surgical option, but larger trials with longer follow-up are required.

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