International Surgery Journal
Singla NK et al. Int Surg J. 2021 Nov;8(11):3327-3334
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: https://dx.doi.org/10.18203/2349-2902.isj20214365

Original Research Article

A prospective study on the role of centchroman in regression of fibroadenoma

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Received: 10 June 2021
Revised: 02 October 2021
Accepted: 04 October 2021

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ABSTRACT

Background: Fibroadenoma commonly present as painless breast lump in young girls. Nearly 10-15% regress spontaneously over the period of 6-60 months, rest are managed surgically. Centchroman (Saheli), a novel non-steroidal, selective anti-estrogen has been used for the treatment of mastalgia and its effectiveness in the treatment of fibroadenoma is being tested in the ongoing trials.

Methods: A total of 60 patients between 15-35 years of age with painless lump breast of size 2 to 5 centimeters confirmed as fibroadenoma by fine needle aspiration cytology (FNAC) were included in the study. Detailed patient's characteristics, clinical history, physical examination (for size in 2 dimensions), ultrasound findings (for size in 3 dimensions) were assessed. All participants included in the study were given tablet Centchroman (Saheli) 30 mg thrice weekly orally for 3 months. Size of Fibroadenoma was reassessed clinically for size in two dimensions and ultrasonologically for size in three dimensions at 4 weeks and 3 months of starting of therapy.

Results: Out of 60 patients, 18 patients (30%) had complete response, 40 patients (66.66%) showed a decrease in the size of fibroadenoma and only 2 patients (3.33%) had no response to this therapy. None showed an increase in size.

Conclusions: It may prove to be the most effective modality for the treatment of small sized fibroadenoma breast especially in unmarried girls with minimal side effects. Ultrasonology may be relied upon for follow up measurements since it is more accurate in measuring the dimensions.

Keywords: Fibroadenoma, Centchroman, Saheli, Non-steroidal, Anti-estrogen, Ultrasonology

INTRODUCTION

Fibroadenomas are the most common cause of breast lump presenting in age group 15-25 years, although occasionally they occur in much older women.[1-3] The World Health Organization (WHO) has described fibroadenoma as "a discrete benign tumor showing evidence of connective tissue and epithelial proliferation".[4] It presents as a painless, smooth, firm, non-tender, well localized lump which moves freely within the breast tissue resembling a "breast mouse".[5,6] Although they can be located anywhere in the breast, majority are situated in the upper outer quadrant.[1,7]

Diagnosis of fibroadenomas is based on the "Triple test" which consists of the combination of clinical examination, imaging and non-surgical tissue biopsy (fine needle aspiration cytology/core biopsy).[8]

Estrogens seem to be linked to fibroadenoma genesis.[9] Several treatment options are available like observation, hormonal therapy, surgical excision and several other newer approaches which are less invasive than surgical excision.[10] Spontaneous regression is seen in nearly 10-15% of fibroadenomas; over period of 6-60 months.

Hormonal management with anti-estrogenic drugs like tamoxifene has been attempted but was not widely accepted due to its side effects.

Centchroman is a novel non-steroidal, a multifunctional selective estrogen receptor modulator (SERM) synthesized by the Central Drug Research Institute, Lucknow, India in the 1980s, is an oral contraceptive with no side effects except that it may prolong the menstrual period duration in about 10% of the cycles and in few cases of polycystic ovarian disease.[11,12]

Centchroman is economic and easily available (Sold at Rs 2 per 30 mg tablet by Hindustan Latex Ltd. by Trade name SAHELI).

Centchroman elicits weak estrogen agonist and potent antagonistic activities but is devoid of progestational, androgenic, and anti-androgenic activities.[13] There is an early return of fertility after stopping this drug; therefore, it is safe in the treatment of unmarried women and those who wish to conceive after treatment. It maintains normal ovulatory cycles since the low dose prescribed minimizes any effect on hypothalamic pituitary ovarian axis.[14] No teratogenic effect has been observed. Women who conceived while on treatment gave birth to healthy children in the phase 3 multicentric contraceptive trials during research.[15]

The use of this drug for fibroadenoma has already been permitted by the Drug Controller of India.[1]

The role of Centchroman in mastalgia and fibrocystic disease has been documented in several studies but its role in fibroadenoma is still an evolving issue of interest in order to find a definitive, non-surgical management thus avoiding a scar on young breasts with minimal or no side effects. Ours is one of them.

METHODS

It is an observational cohort study. 60 consecutive patients between age of 15-35 years presenting with breast lump of size 2 to 5 centimeters confirmed as fibroadenoma by triple test attending Surgery out-patient Department (OPD) of Government Medical College and Rajindra Hospital, Patiala (Punjab, India) from December 2015 to May 2018 were included in the study.

Exclusion criteria

The patients with age above 35 years, Size of Fibroadenoma less than 2 cms and those more than 5 cms, those with hypersensitivity to Centchroman and those not willing for or averse to the use of contraceptives, those with any contraindications for the use of oral contraceptives like smokers, patients with hypercholesterolemia, tuberculosis, renal disease or hepatic disease and those with high risk for deep vein thrombosis, pulmonary embolism or myocardial infarction, those presenting with endocrine disorders, pregnancy or in puerperium or patients with polycystic ovarian syndrome, cervicitis and cervical hyperplasia or suspected carcinoma and patients with denial to give a written informed consent were excluded from the study.

Initial work-up

Subsequently, in all confirmed cases, ultrasonological scan of bilateral breasts was done to assess initial size of fibroadenoma three dimensionally before starting Centchroman therapy.

All eligible patients underwent a complete general physical examination to rule out the comorbidities, a detailed gynecological examination to rule out cervicitis and cervical hyperplasia, Urinary Pregnancy Test and Ultrasound of pelvis to rule out polycystic ovarian disease or pregnancy.

All participants included in the study were prescribed tablet Centchroman (Saheli) 30 mg thrice weekly orally for 3 months which they bought from the market. Size of Fibroadenoma was reassessed clinically and sonologically at 4 weeks and 3 months of starting of therapy.

During the study all the demographic details of the patients was also recorded and in the end of the study, data was analysed statistically in terms of range; mean, Standard Deviation (SD), frequencies (number of cases). And relative frequencies (percentages) as appropriate. Comparison of quantitative variable was done with Student t-test and for comparing categorial data Chi-Square test was performed. A probability value (P value) was also calculated to find out whether the comparison was statistically significant or not. All statistical calculations will be done using Statistical package for the social science (SPSS) 21version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

RESULTS

Out of 60 patients studied for the effect of Centchroman, 56 patients (93.33%) had solitary fibroadenoma in either of the breasts and 4 patients (6.66%) had multiple fibroadenomas in same or both breasts. In these patients, the fibroadenoma with larger dimensions was opted for study.

Patient characteristics

Age

Age of the patients vary between 15 years to 35 years. There were 14 patients (23.3%) in the age group of 15-20, 26 patients (43.3%) in the age group of 21-25, 16 patients (26.6%) in the age group of 26-30, and 4 patients (6.66%) in the age group 31-35 (Figure 1). Thus, majority of the patients (66.6%) belonged to the age of 15-25

years justifying the age range of presentation of fibroadenomas.

Duration of symptom of lump

The duration of symptom of lump in the breasts varied from 7 days to 300 days with a mean of 82.433 days and median of 60 days.

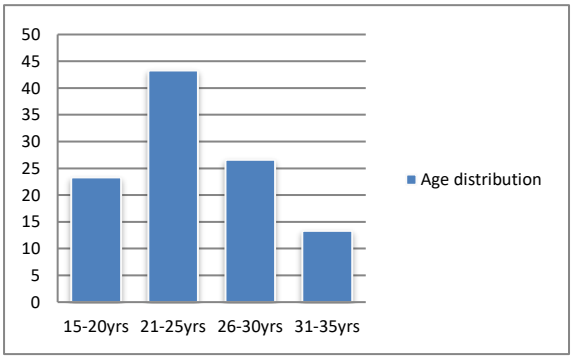

Figure 1: Age distribution among patients.

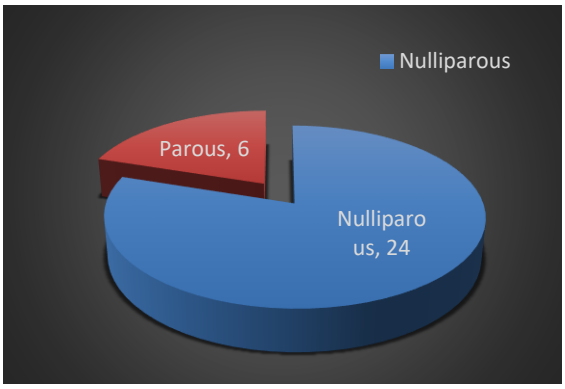

Figure 2: Response to therapy in relation to obstetric index.

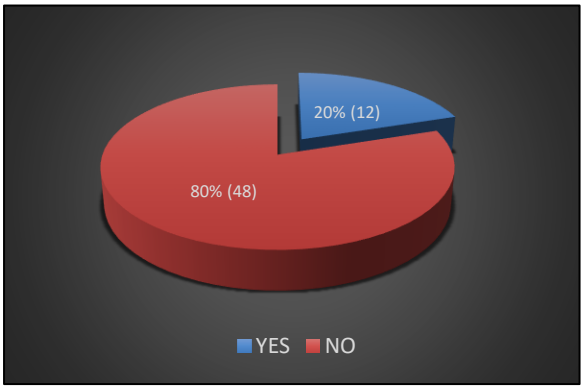

Figure 3: History of previous OCP intake.

Majority of the patients 42 (70%) presented to the hospital early i.e., between 0-90 days. But a significant number 18 patients (30%) presented late- between 91-365 days (Table 1), the reason being the fear of undergoing surgery, the unawareness of the medical management, the failed conservative approach and the quacks providing treatments.

Menstrual history

Age at Menarche

The age at menarche of the patients varied between 12 to 18 years with a mean of 14.6 years (±1.673 SD) and a median of 14.5 years. All 60 patients had regular and normal menstrual cycles. None had an early or late menarche age to establish a possible relation with the breast symptoms.

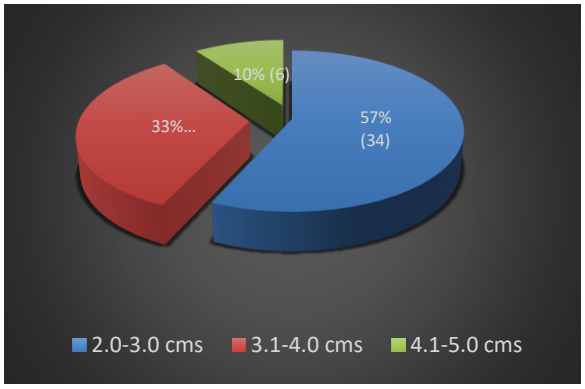

Figure 4: Distribution of the size of fibroadenoma in the patients.

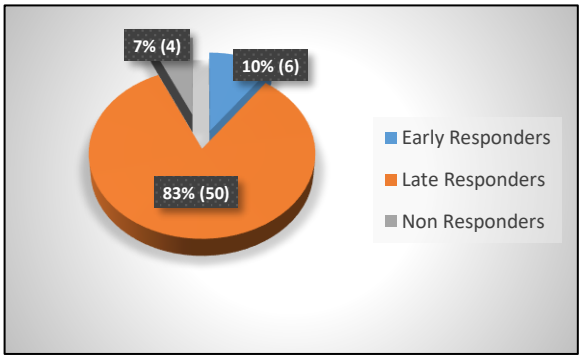

Figure 5: Classification of patients based on clinical response.

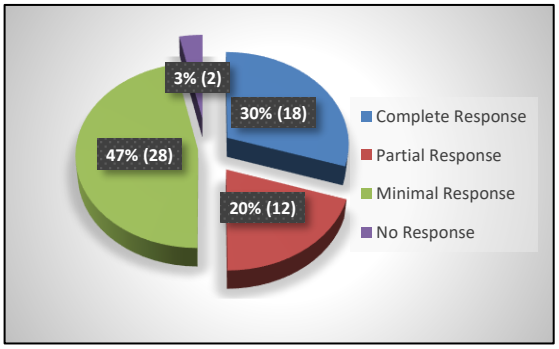

Figure 6: Classification of the response to therapy based on USG.

Obstetric history

Out of the 60 patients, 24 (40%) were married of which 12 were parous. 48 out of 60 patients (80%) were nulliparous (Gravida 0-G0) of which 40 patients were late responders (LR), 6 patients were early responders (ER) and 2 patients did not respond to the treatment and 12 patients (20%) were Parous (of which 10 were late responders and 2 patient did not respond to the treatment). ER, LR and NR were on the basis of clinical examination till 3 months (Table 2, Figure 2). Among the nulliparous, there were a significant number of ER whereas, none of the parous women responded early to the therapy. This data also exhibits the relationship between parity and decreased incidence of fibroadenoma.

Table 1: Duration of clinical symptoms of lump.

	0-90 days	91-365 days	>365 days	Total
Frequency	42	18	0	30
Percent	70	30	0	100

Table 2: Response to therapy in relation to obstetric index.

Parity	Frequency	%	ER	LR	NR
Nulliparous (G0)	48	80.00	6	40	2
Parous (others)	12	20.00	0	10	2
Total	60	100.0	6	50	4

*ER: Early Responder, LR: Late Responder, NR: No Response

Table 3: History of previous surgeries.

H/o previous surgery	Frequency	Percent
No	56	93.33
Yes	4	6.66
Total	60	100.0

Usage of hormonal pills

Out of the 60 patient, 48 patients (80%) had no previous history of oral contraceptive pill (OCP) intake and 12 patients (20%) who were also parous had history of OCPs intake as a part of family planning (Figure 3); establishing another relationship of history of OCP intake and parity with incidence of fibroadenoma and late response to Centchroman (Table 2, Figure 3).

History of previous surgeries for fibroadenoma

Out of the 60 patients, 56 patients (93.33%) had no previous history of surgery for fibroadenoma, and 4 patients (6.66%) had history of the same (Table 3). History of surgery was in the same breast but different site in 3 patients and in the opposite breast in the another, signifying that fibroadenomas do recur following surgery and that surgical excision is not a definitive treatment.

Lump characteristics

Clinical size of the fibroadenoma at the beginning of the study

34 patients (56.66%) had a lump of the size of the maximum dimension of 2.0-3.0 cms; 20 patients (33.3%) had the size of 3.1-4.0 cms and 6 patients (10.0%) had a size of 4.1-5.0 cms at the beginning of the study (Figure 4). 90% of patients presented early with a small sized lump (2-4 cm), reason being awareness of malignancy, and knowledge of breast self-examination whereas, reason for 10% of patients who presented late was lack of awareness and previous history of treatment from quacks.

Estimation of the 'clinical response' to centchroman therapy

Based on clinical examination done at 3 months of starting therapy, it was noticed that the patients were (Figure 5):

Early responders (ER)

Complete regression of fibroadenoma was found in 6 patients (10%) out of which none was parous.

Late responders (LR)

Partial regression of fibroadenoma was found in 50 patients (83.33%) out of which 10 were parous. This late response can be attributed to the fact that a minimum of 3 months dose of the drug is needed to attain adequate bleed levels.

Non-responders (NR)

No regression of fibroadenoma was found in 4 patients (6.66%) out of which 2 was parous.

The maximum dimension of the largest fibroadenoma before starting Centchroman therapy measured clinically, varied from 2 cms to 5 cms with a mean of 3.251 cms (SD of 0.828) and a median of 3 cms. The maximum dimension of the largest fibroadenoma after 3 months of starting Centchroman therapy measured clinically, varied from 0 cms (no lump) to 3.5 cms with a mean of 1.833 cms (SD of 1.061 SD) and a median of 2 cms (Table 4); explaining the partial and complete regression of fibroadenoma as early as 4 weeks after starting Centchroman. 2 out of 30 patients showed complete regression at the end of 4 weeks of therapy while 4 others showed complete regression at the end of 3 months, measured clinically.

Table 4: Comparison of size of fibroadenoma from the beginning till 3 months measured clinically.

Period	Minimum size (cm)	Maximum size (cm)	Mean	Std. Deviation	Median
Size of the lump measured clinically at beginning of treatment	2.0	5.0	3.251	0.828	3
Size of the lump measured clinically at 4 weeks of treatment	0	4.5	2.583	0.891	3
Size of the lump measured clinically at 3 months of treatment	0	3.5	1.833	1.061	2

Table 6: Comparison of size (mm) of fibroadenoma measured by USG from the beginning to the end.

Period	Minimum (mm)	Maximum (mm)	Mean	Std. Deviation	Median
Size of the lump measured by USG at beginning of study	9	39	25.73	7.2868	24
Size of the lump measured by USG at 4 weeks of treatment	0	38	20	8.3169	21
Size of the lump measured by USG at 3 months of treatment	0	32	12.53	10.9410	12

Table 7: Percentage change of fibroadenoma from 0-3 months.

Percentage change	Minimum	Maximum	Mean	Std. Deviation	Median
Percentage change in Max. Size of the lump measured clinically from baseline to 3 months	00.00	100.0	44.676	29.094	36.7
Percentage change in Max. Size of the lump measured by ultrasound from baseline to 3 months	0.00	100.0	53.095	38.292	44.655

Estimation of the response to centchroman therapy as detected by ultrasonography

Measured by ultrasound at beginning to 3 months of treatment

Out of 60 patients, 58 patients (96.66%) showed response to Centchroman, 18 patients (30%) had complete response, 40 patients (66.66%) showed a decrease in the size of fibroadenoma out of which 28 patients (46.67%) had minimal response, 12 patients (20%) had partial response and 2 patients (3.33%) had no response to this therapy (Figure 6).

Responses of Fibroadenoma to Centchroman therapy as detected by ultrasonography measured at the end of 3 months were observed as:

Complete response (CR)

Patients who had total regression of largest fibroadenoma (100%) to Centchroman therapy.

Partial response (PR)

The response to Centchroman therapy in these patients was between 51 to 99% regressions in the maximum dimension of the largest fibroadenoma.

Minimal response (MR)

The response to Centchroman therapy in these patients was between 1 to 50% regressions in the maximum dimension of the largest fibroadenoma.

No response (NR)

There was no change in the size after Centchroman therapy in these patients - 0%. (Maximum dimension of the largest fibroadenoma measured being considered).

The maximum dimension of the largest fibroadenoma measured by ultrasound before starting Centchroman therapy varied from 9 mm to 39 mm with a mean of 25.73 mm (SD of 7.2868) and a median of 24 mm. After starting Centchroman, at the end of 3rd months, the maximum dimension of the largest fibroadenoma

measured by ultrasound varied from 0 mms (no lump) to 32 mm with a mean of 12.53 mm (SD of 10.9410) and a median of 12 mm (Table 5).

Thus, on clinical basis, the percentage change in the size (maximum dimension) of largest of the fibroadenoma with Centchroman therapy measured clinically varies from 0 to 100% with a mean decrease in size by 44.676% (SD of 29.094) and a median of 36.7% decrease (Table 6).

Side-effects of centchroman therapy observed at the end of 3 months

Out of 60 patients those were started on Centchroman, 24 (40%) had scanty menses, 16 (27%) out of 60 patients complained of delayed menses, 4 (6%) patients did not have their menses while on therapy and none of them were married, whereas in the remaining 26.67%, no menstrual abnormality was noticed. All the 60 patients had regular normal menstrual cycles before starting them on therapy and other main causes of delayed or absent menses were ruled out before beginning the treatment. None of these patients experienced any other side effects.

All the patients with menstrual abnormalities were furthered followed up in Gynecology Department. Endometrium was thin lined (<5 mm on USG) in 3 patients with amenorrhea while the USG of another patient with amenorrhea showed follicular cyst of 3.5×3c ms in left ovary.

DISCUSSION

Fibroadenomas are the common disorders found in surgery OPD presenting in young women. 60 cases of diagnosed fibroadenoma patients attending the Surgery OPD of Government Medical College and Rajindra Hospital, Patiala from 2015-2018 were planned for therapy with Centchroman and were studied.

On studying the patient characteristics, the age at presentation in our study varied between 15 to 35 years with a mean of 23.73 years. 43.3% of these patients were in the age group between 21 to 25 years. According to Dhawan et al, Dent et al, Giri et al and Coriaty et al, Fibroadenomas commonly occurs in patients younger than 35 years, with a peak incidence at around 20 years of age.[1,16-18]

The age of menarche in our study varied between 12 to 18 years with a mean of 14.6 years. All 60 patients had regular and normal menstrual cycles. It was found that there is no relation with the age of onset of menarche and regularity of the menstrual cycles with the response to the therapy and with the occurrence of fibroadenoma with the age of menarche.

In our study majority (80%) of the patients (48) with fibroadenomas were nulliparous; this can be related to the fact that risk of fibroadenomas decreases with increasing no. of live births as observed by Coriaty et al The response to therapy was early (in 6 patients) and comparatively more significant in nulliparous women as compared to the parous subjects (none responded to the treatment early).[18] Ours has been a pioneer observation to relate parity with the response of fibroadenoma to Centchroman therapy. However, based on clinical examination 50 patients (83.33%) were late responders who signify that the response to this therapy depends on the circulating blood levels of the drug which accumulate over a period. Centchroman is a contraceptive having selective estrogen receptor modulator activity. According to a study by Thomas et al, doses of 30 mg twice weekly given for 12 weeks is recommended to build up adequate blood levels.[19] This explains for the late response of most of the cases to this therapy in our study.

Out of the 60 patients, 48 patients (80%) had no previous history of Oral Contraceptive Pill intake and 12 patients (20%) had history of its intake. The intake OCPs have been linked to decreased incidence and regression of fibroadenoma by Coriaty et al and Esteveo et al respectively.[18,20] However, no other study justifies this finding. The response to Centchroman therapy in nowhere related to history of previous OCP intake.

In the studies similar to ours, a significance decrease has been observed in the size of fibroadenoma when Centchroman was given on daily or alternate regime.[21-26] Comparing the data of all these studies it is observed that daily dose schedule of Centchroman therapy was associated with better results as compared to when it was administered on alternate day regimen.

In a study conducted by Balamurugan et al, 55% showed decrease in size and 5% had an increase in the size of fibroadenoma when Centchroman was given on alternate day for 3 months.[26] Whereas in our study, none of the fibroadenoma did increase in size till 3 months.

The percentage of clinical change of size (maximum diameter) of largest of the fibroadenoma varied from 0 to 100% with a mean decrease in the size by 44.676%. There were 4 patients with no response to Centchroman therapy. Whereas the percentage of ultrasonologic change of the size (maximum diameter) of the largest of the fibroadenoma with Centchroman therapy varied from 0 to 100% with a mean decrease in the size by 53.095%.

The difference in percentage of clinical (44.676%) to that of ultrasonologic change (53.095%) was found to be of the order of 8.419% which signifies that the response to Centchroman treatment may be reliably measured both clinically and ultrasonologically. However, ultrasonographic response in more as compared to the clinical response since it is more accurate in measuring the dimensions. Hence ultrasonology may be relied upon for follow up measurements.

Ormeloxifene is one of SERM which binds with high affinity of estrogen receptors and mimics the effect of

estrogen in some tissue. It acts as estrogen antagonist in uterine endometrium, leading to endometrial atrophy hence decreases menstrual blood loss.[27] This may explain for the oligomenorrhea in the form of delayed or scanty menses and in certain cases amenorrhea as the side effect of this therapy which is mostly dose dependent and reversible once the drug is stopped. This has been evidenced by a great number of studies.[21-25]

In addition, Gupta et al observed allergic rash as a side effect of Centchroman.[23] According to another study, there are concerns about this drug causing urinary incontinence and uterine prolapse.[28] Other side effects observed are giddiness, abdominal pain, headache and development of ovarian cyst noticed when Centchroman was given at a higher dose as a treatment trial for dysfunctional uterine bleeding.[29,30] In our study, 24 (40%) complained of scanty menses, 16 (26.67%) had delayed menses and 4 (6.67%) patients had absence of menses during therapy as the only side effects which may be attributed to the low dose and alternate day regime.

The limitations of our study is the small sample size and short duration of follow up. Therefore, further studies with a larger sample size and a longer follow up is required in order to firmly establish Centchroman as preferred non-hormonal non-steroidal therapy for the treatment of fibroadenoma along with the detailed study of its side-effect profile.

CONCLUSIONS

In our study, 18 patients (30%) had complete response, 40 patients (66.66%) showed a decrease in the size of fibroadenoma out of which 28 patients (56.66%) had minimal response and 12 patients (20%) had partial response and only 2 patients (3.33%) had no response to this therapy. None showed an increase in size. The only side-effects noticed during therapy were scanty menses (40%), delayed (26.67%) and absent menses (6.67%). On completion of the study, we conclude that Centchroman is significantly effective in regression of fibroadenoma breast of size ranging between 2-5 cms. And Ultrasonology may be relied upon for follow up measurements since it is more accurate in measuring the dimensions. Also, Centchroman may prove to be the most effective modality for the treatment of small sized fibroadenoma breast with minimal side effects, thus avoiding unnecessary surgeries leading to scar formation and increased morbidity hampering the normal day to day life especially in young and unmarried females.

ACKNOWLEDGEMENTS

A special acknowledgement to Ms. RISHU VERMA for proving the help in typing and with the software knowledge.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Singla NK, Bhatia R, Verma R, Bhatia SK. A prospective study on the role of centchroman in regression of fibroadenoma. Int Surg J 2021;8:3327-34.