A COMPARATIVE STUDY ON EFFECT OF CENTCHROMAN ON MASTALGIAS AND FIBROADENOMAS

A DISSERTATION SUBMITTED TO THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY CHENNAI

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M.S. DEGREE EXAMINATION BRANCH

I – GENERAL SURGERY

DEPARTMENT OF GENERAL SURGERY

MADURAI MEDICAL COLLEGE - MADURAI

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CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled "**A COMPARATIVE STUDY ON EFFECT OF CENTCHROMAN ON MASTALGIAS AND FIBROADENOMAS**" submitted by **DR.M.SENTHIL** to Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfilment of the requirement of the award of MS Degree Branch - I (General Surgery) is a bonafide research work carried out by him under direct supervision and guidance from August 2018 to August 2019 in the Department of General Surgery, Madurai Medical College.

Place: Madurai
Date:

DR.J.AMUDHAN, M.S.,DLO,
Professor and Unit Chief,
Department of General Surgery
Madurai Medical College,
Govt. Rajaji Hospital,
Madurai-625020.

CERTIFICATE BY THE HEAD OF THE DEPARTMENT

This is to certify that the dissertation entitled "**A COMPARATIVE STUDY ON EFFECT OF CENTCHROMAN ON MASTALGIAS AND FIBROADENOMAS**" submitted by **DR.M.SENTHIL** to Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfilment of the requirement of the award of MS Degree Branch - I (General Surgery) is a bonafide research work carried out by him under direct supervision and guidance from August 2018 to August 2019 in the Department of General Surgery, Madurai Medical College.

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Place: Madurai

Date:

DR.A.M.SYED IBRAHIM ,M.S.,
Professor and Head of the Department
Department of General Surgery
Madurai Medical College,
Govt. Rajaji Hospital,
Madurai-625020

CERTIFICATE BY THE DEAN

This is to certify that the dissertation entitled "**A COMPARATIVE STUDY ON EFFECT OF CENTCHROMAN ON MASTALGIAS AND FIBROADENOMAS**" is a bonafide research work done by **DR.M.SENTHIL,** Post Graduate Student, Department of General Surgery, Madurai Medical College and Government Rajaji Hospital, Madurai under the guidance and supervision of **DR.J.AMUTHAN,M.S.,DLO,** professor, Department of General Surgery, Madurai Medical College, Madurai.

Place: Madurai

Date :

DR.K.VANITHA,M.D.,DCH,

The DEAN,

Madurai Medical College,

Govt Rajaji Hospital,

Madurai-625020

DECLARATION BY THE CANDIDATE

I, **DR.M.SENTHIL,** hereby declare that this dissertation entitled "**A COMPARATIVE STUDY ON EFFECT OF CENTCHROMAN ON MASTALGIAS AND FIBROADENOMAS**" is a bonafide and genuine research work carried out by me in the Department of General Surgery, Madurai Medical College during the period of AUGUST 2018 TO AUGUST 2019. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any other University, Board either in India or abroad. This is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of regulations for the award of M.S. degree (Branch I) General Surgery course.

Place: Madurai

Date:

DR.M.SENTHIL,

Post graduate,

MS General Surgery,

Madurai Medical College,

Madurai-625020.

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LIST OF ABBREVIATIONS

FA- Fibroadenoma

USG-Ultrasonogram

FNAC- Fine Needle Aspiration Cytology

ANDI-Aberration In Normal Development And Involution

ER-Estrogen Receptor

ERE-Estrogen Receptor Elements

SERM-Selective Estrogen Receptor Modulator

FSH-Follicle Stimulating Hormone

LH-Luteinizing Hormone

CONTENTS

INTRODUCTION

INTRODUCTION

Fibroadenoma (FA) is the most common tumour of breast in young females (<35 yrs) and second most common breast tumour in females. It is a benign condition. FA is responsible for 15% palpable breast lump. It is clinically presents as painless breast lump in reproductive age groups. FA is very rare as new lump over the age of 40 -45 yrs.

Most of the FA cases are self diagnosed and consult surgeon in fear of breast cancer. For the patients with small FA (<3cm) ,below the 35 yrs of age without suspicious cytology, FA is very slow growing hence simple observation with reassurance is enough because 15 to 30 % FA regress completely by simple observation over 1 to 6 yrs follow-up.

Breast pain among women, with or without lump is common complaint and a cause of significant anxiety and fear of breast cancer . Annually 200,000 breast disorders are identified and it is noted that most of the palpable lesions are benign . Approximately half of the women in reproductive age group suffer from Benign Breast Diseases (BBD). Among the BBD, mastalgia, fibrocystic disease and fibroadenoma are the most common. Mastalgia (Greek masto-breast and algia-pain) signifies breast pain. It can be classified into two types:

1) Cyclic mastalgia: Characterized by more pain during the menstrual cycle and it is frequently related with fibrocystic breast changes or duct ectasia. Minimal tenderness during menstrual cycle is thought to be typical, and is normally associated with menstrual cycle and/or premenstrual syndrome (PMS)

2) Non-cyclic mastalgia: Characterized by the pain, which is unaltered during the menstrual cycle. This type is not common. It has different causes and difficult to diagnose. Non- cyclical pain is not usually related with the menstrual cycle. Some level of non-cyclic breast tenderness is present because of hormonal changes in adolescence, pregnancy and menopause.

Breastfeeding is additionally one of the reasons for non-cyclic pain. Fibrocystic breast disease is otherwise called Fibroadenosis. It is a non-carcinogenic breast condition, which presents as a diffuse lump and is connected with hormonal changes (menstrual cycle). Many women experience the ill effects of fibrocystic disease particularly in their conceptive age. Fibrocystic diseases are uncommon among menopausal women. Fibrocystic changes can happen in one or both breasts. A post mortem study conducted in 2005 by Courtillot C et al., concluded that 50% women had some form of fibrocystic disease and 20% had fibroadenoma .

Most of the drugs used for fibroadenosis and mastalgia are expensive and have side effects. Till date, only four articles are available in medical literature on Centchroman for regression of fibroadenosis and ours is fifth one. Multicentre randomised double blind controlled studies with larger sample size in comparison with other drugs are needed for global acceptance. This study was conducted to find out the efficacy of centchroman, a Selective Estrogens Receptor Modulator (SERM) on regression of fibroadenosis and mastalgia.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

The purpose of this study is to study the effectiveness of centchroman on mastalgias and fibroadenomas

PRIMARY OBJECTIVES

- Centchroman (also known as Ormeloxifene) is one of the selective estrogen receptor modulators, or SERMs, a class of medication which acts selectively on the estrogen receptor.
- Because of its selective antiestrogen action, centchroman has been used for treatment of mastalgia and fibroadenoma

SECONDARY OBJECTIVES

- Centchroman (also known as Ormeloxifene) is one of the selective estrogen receptor modulators, or SERMs, a class of medication which acts selectively on the estrogen receptor.
- Because of its selective antiestrogen action, centchroman has been used for treatment of mastalgia and fibroadenoma

Study design: Randomized control trial

Material: 60 Patients

Study and follow-up period : 1 Year

INCLUSION CRITERIA:

1. Females of age less than 35 who had mastalgia with or without nodularity.
2. Patients with fibroadenomas of size 1.5 to 3 cm.
3. Patients consented for inclusion in the study according to designated proforma
4. Patient not willing for excision (fear of scar)

Exclusion criteria:

1. Patients more than 35 years of age
2. Patients who are pregnant, lactating and planning for pregnancy in near future.
3. Patients with polycystic ovarian disease
4. Patients who have history of breast carcinoma or family history of breast carcinoma

5. Patients diagnosed to have associated chest wall disorder and dermatological lesions
6 .Lactation
7 .Pregnant and who desire to pregnant
8 .Complexfibroadenoma

HISTORICAL ASPECTS

HISTORICAL ASPECTS

Galen	130- 200AD	A greek physician mentioned about breast and used the word oncos for tumours.
	6th centuary	Acoustics, the science of study started
john moir	1620	Explained the breast is composed of small glands
Jacques	1880	piezoelectric effect discovered
	1890	It was established that ovaries controls female reproductive system through a hormone.
Sir Francis galton	1893	constructed a whistle producing ultra Sound
Salomon	1913	noticed small block spots in xray film of amputated breast
Paul langevin	1917	The first technological application of ultrasound was an attempt to detect submarines

Allen and Doisy	1923	doisy found alcoholic extract of ovaries was capable of producing estrus.
	1929	active principle of estrogen obtained in pure form
Dr. Ludwig	1940	Used ultrasonic energy as medical tool on the human body
Leborgne	1951	Published his discovery that microcalcification are found in 30% of ca breast.
EGAN et al	1980	Expressed “ the radiographic signs are so non specific that all punctuate microcalcification require histologic evaluation”
Maimonides medical center	1981	The first FNAC biopsy in the united sates was done and Eliminated the needs for hospitalization for biopsy.

LE Hughes	1987	Coined ANDI first time.
	1990	Centchroman (Ormeloxifene)marketed for OCPand DUB
by Dhar A ,Srivastava,aims,	2007	Role of centchroman in regression of mastalgia and fibroadenoma,Study Done

MATERIALS AND METHODS

MATERIALS AND METHODS

Patients attending general surgery op with complaints of breast lump less than35 yrs of age will be taken detailed clinical history, clinical examination, ultrasonagram (USG) of both breast and fine needle aspiration (FNAC)/ core needle biopsy

Patients who are all diagnosed as fibroadenoma (FA) and willing for simple observation with reassurance at least for 6 months will be included in this study after getting informed consent with sign in both tamil and English language.

Willing patients after randomization included in study group and control group. Patients in study group will get Centchroman 30mg orally on alternative days and for control group patients only observation with simple assurance.

Study group patients will be reviewed after 1week to check tolerance and later follow-up at 4, 8, 12, and 24 weeks.

USG will be done at 0 days, 4, 8, 12 and 24 weeks for both groups to assess regression

VOLUME OF FIBROADENOMA:

Size of FA was calculated by doing breast ultrasound using 7.5 –MHZ linear probe on “Siemens versa” ultra sound scanner. Volume in cubic centimetre is calculated by using following formula

SIZE – a × b × c × 0.52

a-largest dimension,

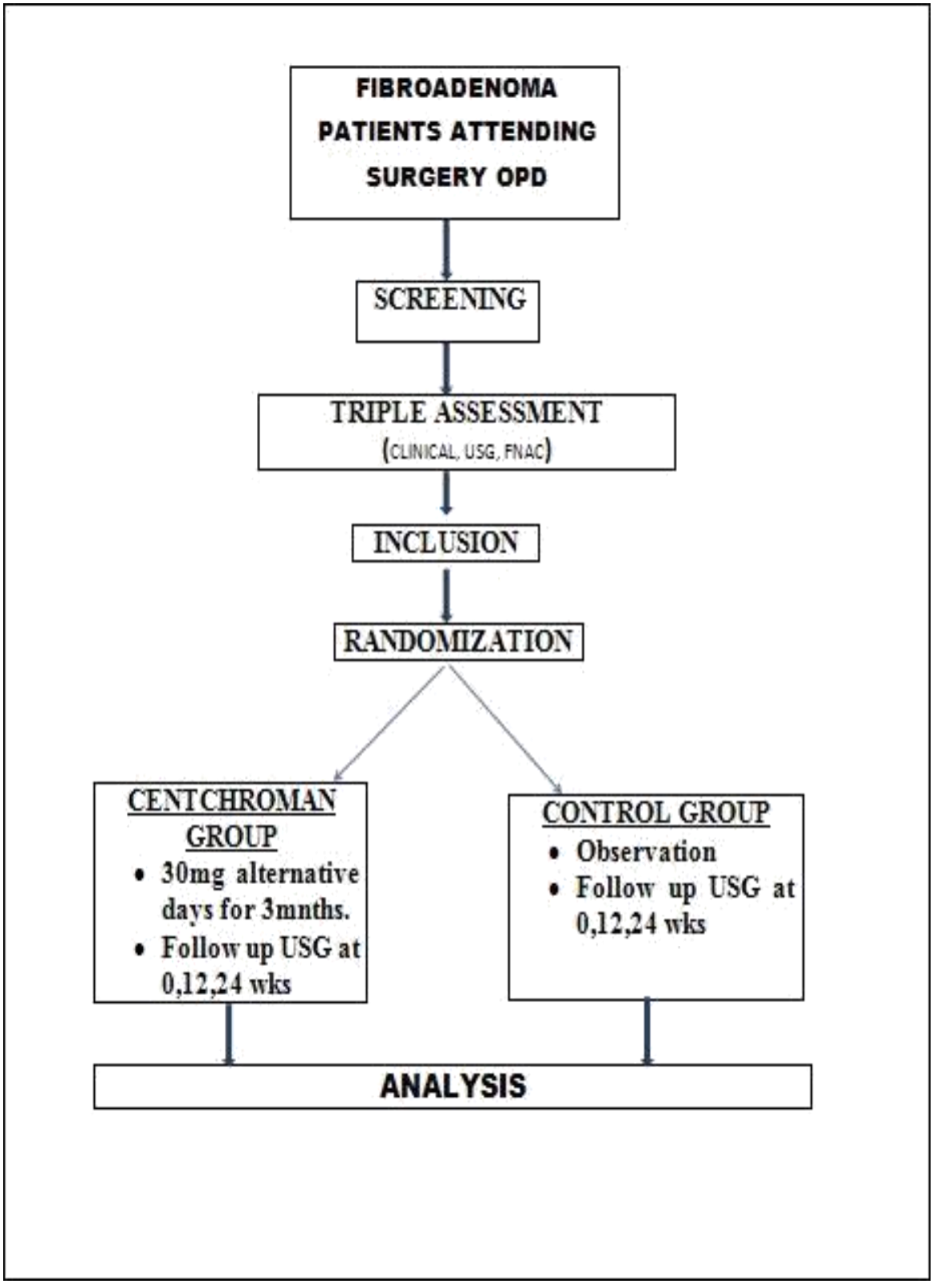
b- dimension at right angle to a.

c-a+b/2.

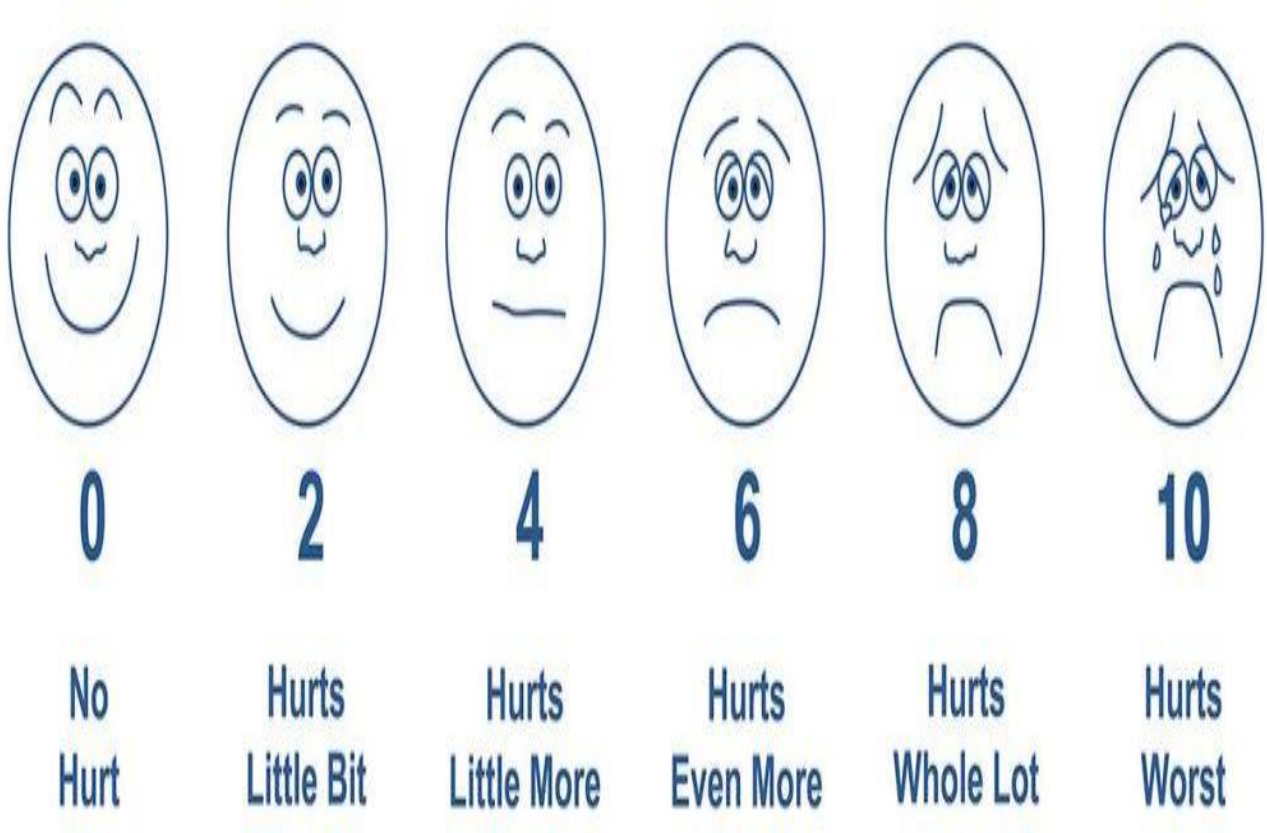
Diagnosis of fibroadenosis was made by ultrasound guided Fine Needle Aspiration Cytology (FNAC) and mastalgia by history. For all patients ultrasonography of abdomen was done to rule out ovarian diseases and uterine cervical hyperplasia. Patients fulfilling inclusion criteria were explained in detail about the study and were started on Tab. Centchroman 30 mg alternate days for a period of 3 months. Patients were taught how to mark mastalgia chart.

Patients were reviewed in General Surgery outpatient department every month with the marked mastalgia chart. Patients were followed up to 6 months

and the results were recorded as per clinical examination, Visual Analog Scale (VAS) for pain. Results were compared using chi-square and p-value was calculated.


FIBROADENOMA PATIENTS ATTENDING SURGERY OPD
SCREENING
TRIPLE ASSESSMENT (CLINICAL, USG, FNAC)
INCLUSION
RANDOMIZATION
CENTCHROMAN GROUP
• 30mg alternative days for 3mnths.
• Follow up USG at 0,12,24 wks
CONTROL GROUP
• Observation
• Follow up USG at 0,12,24 wks
ANALYSIS

Visual Analog Scale(VAS)



REVIEW OF LITERATURE

REVIEW OF LITERATURE

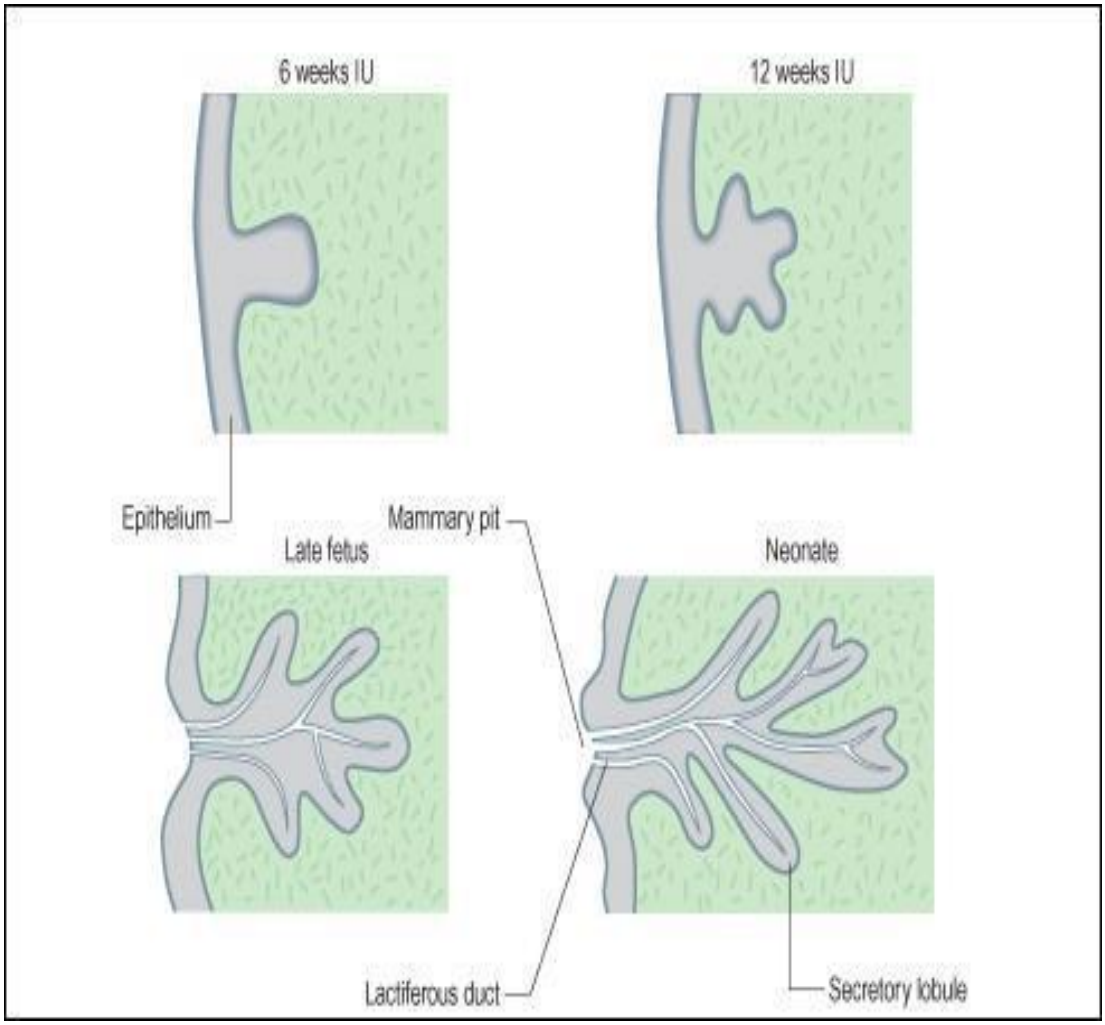
EPIDEMIOLOGY

Benign breast diseases particularly fibroadenoma because of its high prevalence, fear of cancer and its impacts on quality of women life. It is the most common benign tumour of the breast below 35 yrs old females. It comes under Aberration in normal development and involution (ANDI). Incidence of fibroadenoam is 15 % of all palpable breast lumps. FA is bilateral in 20 % and multiple in 20 % of cases.

Fibroadenoma is common in blacks and negroes.Endocrine factors are involved in the etiology of fibroadenoma but their precise roles remains to be elucidated. There is no modifiable risk factor for fibroadenoma. Benign breast disorders has an incidence of 1.5/1000 total hospital admissions, 6.4/1000 of surgical admissions and 8.1/1000 of adult female admissions in india.

EMBRYOLOGY

The epithelial/ mesenchymal interactions will give rise to the glandular tissue of the breast, can be seen at first on 5th or 6th weeks when two ventral bands of ectoderm, the mammary ridges/milklines, extend from axilla to inguinal region. Invagination of thoracic bud occurs on 49th day and the remaining mammary lines involutes.



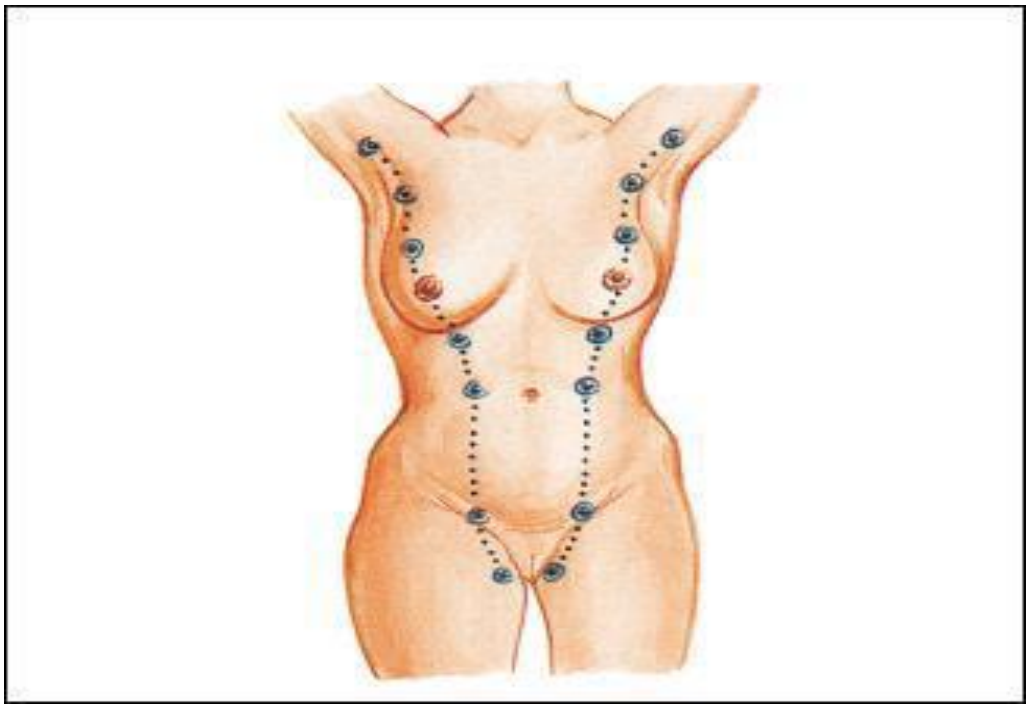
Thoracic ectodermal ingrowths branches into 15 to 20 solid buds which becomes the lactiferous ducts and their associated lobes of alveoli. They are surrounded by somatopleuric mesenchyme which forms the connective tissue, vasculature and fat which is invaded by the nerves. Proliferation, elongation and branching the alveoli are formed and the duct system becomes well defined.

Nipple formation occurs on 56^{th} day and primitive duct develops on 84^{th} days with canalization occurring on 150^{th} day. The ducts become canalized during the last 2 months of gestational period.

Small mammary pit developed by the epidermis at the point of original development of the mammary gland into which the lactiferous tubules open. Mesenchymal proliferation forms the nipple perinatally.

CONGENITAL INVERSION OF NIPPLE

It occurs in 3% of female population. Bilateral in 85% cases and unilateral in 15% cases. It may cause recurrent mastitis and difficulty in breast feeding and has psychological implications but it can be corrected surgically.



ATHELIA -Congenital absence of nipple but this occurs commonly in accessory breast tissue

Polymastia- supernumerary breast

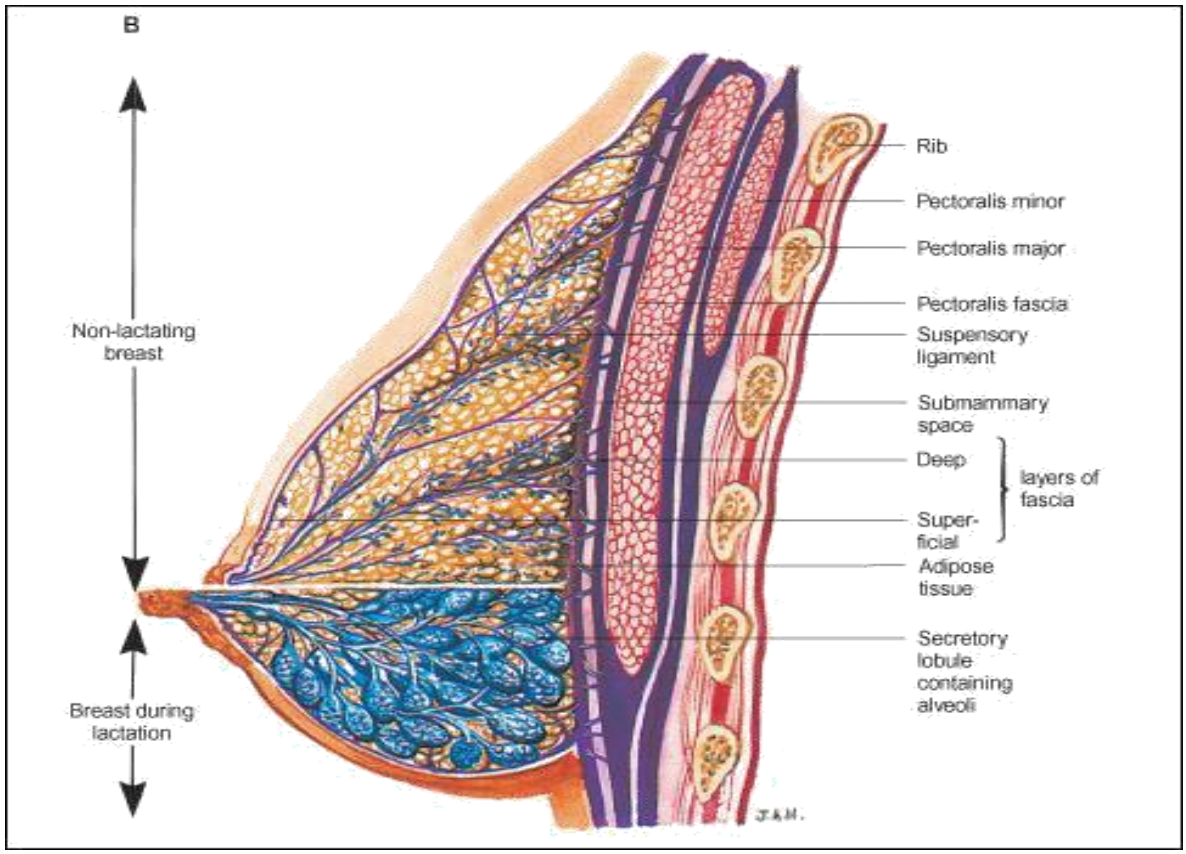
Polythelia- Supernumerary nipples which is more common in males.

Amastia –Congenital absence of breast Amazia-nipple development without breast tissue

BREAST ANATOMY

Breast is a modified sweat gland which vertically extends from 2nd to 6th rib in the MCL and horizontally from the side of sternum to mid axillary lineand lies over pectoralis major, serratus anterior and external oblique muscles.

It forms secondary sexual character of females and it is the eource of nutrition for neonates. It also present males but in rudimentary form. Shape and size of the breast depends on the of the racial, genetic,dietary factors and the age, parity and menopausal status of the individual.



SKIN

Female breast is covered by modified thin skin of the anterior thoracic wall and bears fine hairs. Skin over the nipple and areola lacks hair and contains sweat and sebaceous glands which open directly .

Oily secretion from this sebaceous gland form protective lubricant during lactation. Melanocytes are numerous in nipple and areola complex.

Vascular supply of skin

Skin of the breast supplied by branches from the

1.anterior intercostals arteries

2.lateral thoracic artery, a branch of axillary artery

3.posterior intercostals arteries.

Venous drainage

Venous drainage of nipple and areola forms circular venous plexus which drains into the veins accompanying corresponding arteries.

Lymphatic drainage

Lymphatics from the lateral side of breast skin drains into pectoral nodes lymphatics from skin near drains into parasternal nodes and there is anastomosis

across the sternum and few from upper pectoral region drains into inferior deep cervical nodes.

SOFT TISSUE

Breast is composed of 15-20 lobes each of which consist of branching ducts and terminal lobules in a stroma. Stroma around the lobules is dense and fibrocollaagenous but intralobular connective tissue has a loose texture which enables rapid expansion during pregnanacy. Adipose tissue in the interloba stroma is responsible for increase in breast size during pregnanacy.

AXILLARY TAIL OF SPENCE:

It is a prolongation of the outer part of the mammary gland and reach upto the level of the 3rd rib in axilla through foramen of langer in the deep fascia which is in direct contact with the axillary lymphnodes.

Retromammary bursa is located between the deep layer of superficial fascia and pectoral fascia.

Suspensory ligament of cooper

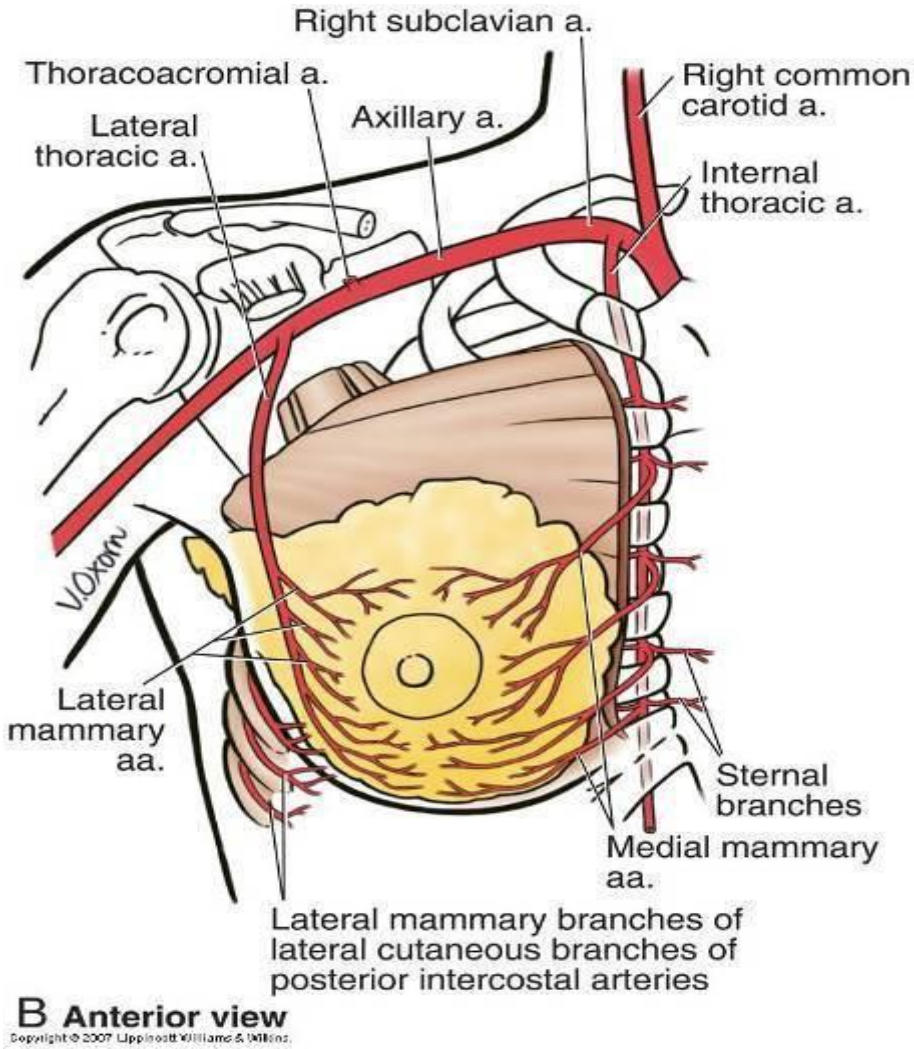
It is a band of connective tissue which connects skin and deep fascia and anchor the breast.

ARTERY

1.Axillary artery through thoraco acromial artery, lateral thoracic artery and subscapular branches

2.Internal thoracic artery through perforating branches

3. 2nd to 4th intercostals arteries



VEINS

There is circular venous plexus around the areola. Blood from this circular venous plexus and gland drains via veins accompanying correspond arteries.

LYMPHATIC DRAINAGE

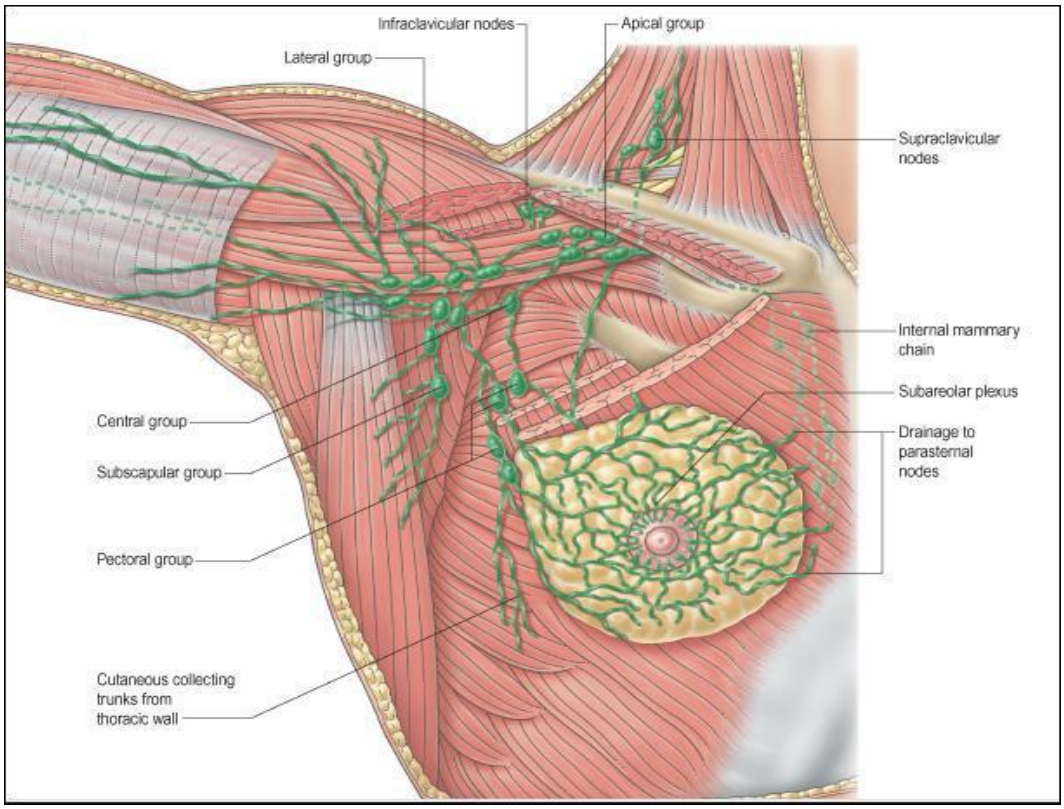
There are 20 to 40 axillary nodes receive more than 75% of the lymph from the mammary gland which is grouped into pectoral, subscapular, central and apical groups and surgically these nodes described in relation to pectoralis minor.

Lymphatic drainage from the the subareolar plexus of sapppey and outer quadrant of the breast takes place first to the pectoral, central and lostly to the apical nodes.

The other two groups of axillary nodes viz the subscapular and lateral group may be involved in a retrograde manner. From the apical group supraclavicular group may be involved.

The upper quadrant of the breast drains partly to deltopectoral nodes but mainly to the apical group. From the inner quadrant of the breast the lymph spread occurs to the internal mammary group and to the other breast.

From the lower and inner quadrant of the breast the lymph vessels form a plexus over the rectus over the rectus sheath and pierce the costal margin to communicate with subperitoneal lymph plexus known as transcoelomic implantation .

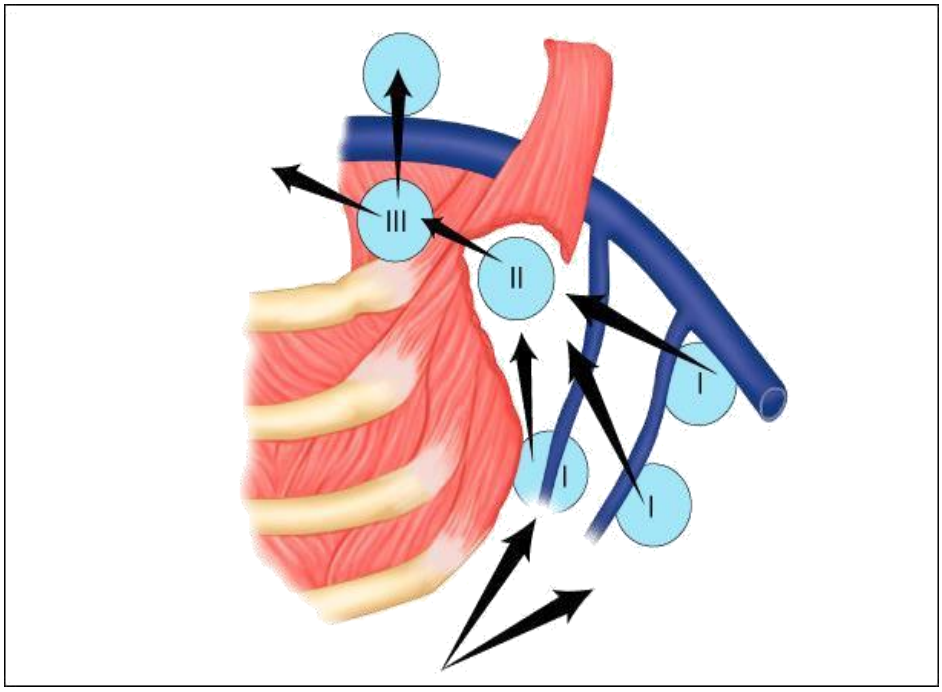


Level 1-nodes lying below pectoralis minor

Level 2-nodes behind the muscle

Level 3-nodes between pectoralis minor and lower border of clavicle.

Remainder drains into parasternal nodes.



Microstructure:

Depends on the age, time of the menstruation period, pregnancy and lactation the microstructure of breast tissues varies. Almost entire length of theducts are lined by columnar epithelium. In the larger ducts it is arranged in two cells thick but smaller duct shows single layer of columnar or cuboidal cells.

The bases of these cells in contact with numerous myoepithelial cells like other glandular epithelia. These numerous myoepithelial surrounds the ducts and alveoli and give the epithelium a bilayered appearance.

Lactiferous ducts draining each lobe of the breast enters the nipple and open as 15 to 25 orifices. Near the opening, each of these ducts is slightly expanded as a lactiferous sinus which is further dilated in lactating mothers.

Each lactiferous duct is connected to a system of ducts and lobules which is surrounded by connective tissue stroma, ultimately forms the lobe of the mammary gland. Lobules made up of portions of the glands that has the secretory potential. Depending upon the hormonal status these structure are variable.

In the mature resting mammary gland each lobules consists of a cluster of blind- ended, branched ductules whose ends lack terminal alveoli, which are the source of milk secretion in the lactating breast. Keratinized stratified squamous epithelium replacing stratified cuboidal epithelium near the opening of lactiferous ducts in the nipple.

Nipple is internally composed of collagenous dense connective tissue and contains numerous elastic fibres. Smooth muscle cells are arranged in circular fashion are lie deep to the nipple.

ABERRATIONS OF NORMAL DEVELOPMENT AND INVOLUTION (ANDI) OF THE BREAST

It is described by the Cardiff breast clinic. Pathogenesis involves disturbance in the normal breast physiology extending from slight deviation of the normality to well defined disease process.

It includes variety of benign breast disorders happening at different periods of the reproductive periods of the females. Early, matured and involution stage of reproductive period.

All disorders under ANDI should be carefully examined clinically and often USG, mammography and FNAC/core cut biopsy done to rule out malignant conditions

It is based on three phases of normal physiology of breast.

1.lobular development

2.cyclical hormonal modifications

3.Involutions

Pathology:

This disease consists of four features essentially

1.Cyst formation-it is almost inevitable and variable in size

2.fibrosi –elastic and fat tissues are replaced by dense white fibrous trabeculae. The interstitial tissue is infiltrated with chonic inflammatory cell

3.hyperplasia -hyperplasia of the epithelium in the lining of the ducts and acini may occur with or without atypia

4.Papillomatosis-The epithelial hyperplasia may be so extensive thatit results.

in papillomatous overgrowth within the ducts

MANIFESTATION OF ANDI:

The commonest manifestation of ANDI are cyclical pain and nodularity.when when pain is a prominent symptom. This should be assessed apart from nodularity. Such pain is classified unto cyclical or premenstrual mastagia and non cyclical mastagia. Cyclical mastalgia is related to ANDI and noncyclical mastalgia is not related to ANDI. It is usually due to musculoskeletal origin of the chest wall or it may be associated with inflammatory episodes caused by duct ectasia or periductal mastitis.

Keep in mind that persistent , localized pain or discomfort may be a symptom of cancer.Nodularity or lump of the breast is the most common symptom. It may be associated with pain. Sometimes the pain only draw the patient attention to lump in breast. These lumps usually located in the upper and outer quadrant of the breast and lumps in these areas are noticed easily than the lumps located in the centre and inner quadrant of the breast.

These lumps become more larger and painful during premenstrually. Eventhough it is difficult for the patient to judge whether the swelling is gradually increase in size or not but if the patients tell that the lump fluctuate in size is particular to this condition and excludes carcinoma breast . lumps may be single or multiple and may be sudden in onset. Lumps are often cyst and changes in secretory activity of breast leads give to rise of such cyst. Cyst may be single, multiple and vary in size.

Cysts are usually smooth, round and variable in consistency . Fluctuation can be elicited if the cyst are located superficially and very tense cyst is not fluctuant and very hard. Diffuse nodularity is often bilateral and found mainly in the upper and outer quadrant. If the patient first came at menstrual period better to Reexamine the patient in first half of the menstrual period.

Focal nodularity must be examined properly to rule out the carcinoma breast.

EARLY REPRODUCTIVE AGE GROUP (15-25 YRS)

Normal lobule development may present as aberration as FA. If it is more than 5cm it is called giant fibroadenoma as a diseased status .Normal stroma may develop juvenile hypertrophy as aberration and multiple fibroadenoma

IN MATURE REPRODUCTIVE AGE GROUP (25 TO 40 YRS)

Exagerrated normal cyclical hormonal effect on stroma and on glands may present as aberration cause generalised enlargement of the mammary gland. Its diseased status is cyclical mastalgia with nodularity also known as fibrocystadenosis.

INVOLUTION AGE GROUP (40-55 YRS)

LOBULAR INVOLUTION

Lobular involution with adenosis, microcyst, fibrosis, apocrine metaplasia and eventual aberrations as macrocyst and cystic disease of the breast. Macrocyst is an ANI.sclerosing adenosis is also a type of aberration.

DUCTAL INVOLUTION

Ductal involution may cause ductal dilatation and nipple discharge as aberration. Later disease status develops with bacterial infection, periductal mastitis, mammary duct fistula and non lactational brest abscess. Partial nipple retraction may be caused by periductal fibrosis.

EPITHELIAL CHANGES

Epithelial changes leads into epithelial hyperplasia and atypia.

Table 17-3 ANDI Classification of Benign Breast Disorders			
	Normal	**Disorder**	**Disease**
Early reproductive years (age 15–25 y)	Lobular development	Fibroadenoma	Giant fibroadenoma
	Stromal development	Adolescent hypertrophy	Gigantomastia
	Nipple eversion	Nipple inversion	Subareolar abscess
			Mammary duct fistula
Later reproductive years (age 25–40 y)	Cyclical changes of menstruation	Cyclical mastalgia	Incapacitating mastalgia
		Nodularity	
	Epithelial hyperplasia of pregnancy	Bloody nipple discharge	
Involution (age 35–55 y)	Lobular involution	Macrocysts	–
		Sclerosing lesions	
	Duct involution		
	Dilatation	Duct ectasia	Periductal mastitis
	Sclerosis	Nipple retraction	–
	Epithelial turnover	Epithelial hyperplasia	Epithelial hyperplasia with atypia

FIBROADENOMA

Fibroadenoma (FA) or adenofibroma is a benign tumor composed of fibrous tissue and epithelial elements. It is a common cause of discrete, firm, and mobile lump in breast between 15 to 25 yrs old age group.

It is considered asan aberrations in 'development and involution of ductotubular tissue' in the breast and not a true neoplasm.

It begins as a hyperplasia of the lobules from the terminal ductal lobular units which progressively increase in size from 1 to 3 cm. The main symptom of fibroadenoma is painless lump in the breast.

FA is a slow growing tumour and remains more or less same size for a quite long time. It may occurs anywhere within the breast tissue but more oftenly seen in lower half of the breast than the upper half.

On examination , the sweeling is not tender and without any temperature any rise in temperature. It is very smooth,firm and contains well defined border. This tumour is not fixed to skin or deeper structure.

It is a highly mobile tumour without any tethering inside the breast substance. That is why it is often called a " breast mouse" or "a floating

tumor" . There is no enlargement of axillar lymph nodes. Some Most of the lesions single , discrete and static but sometimes multiple lesions can occur in the same breast or bilaterally. Near10 – 15 % lesions disappears spontaneously over a period of 6 to 60 months on observation itself.

Fibroadenoma is considered to arise from hyperresponsiveness of lobular tissue to estrogen. Presence of estrogen receptors on tissue obtained from fibroadenoma has been described. Hence antiestrogen ,Centchroman(Ormeloxifene)can be used to suppress the proliferation of ductolobular tissue of fibroadenoma.

Sometimes soft fibroadenomas may may undergoes cystic degeneration leading to cystadenoma which ultimately transform to cystosarcoma phylloides.

Cystosarcoma phylloides (Serocystic disease of brodie):

This is real giant fibroadenoma, seen in women over the age of 40 yrs. main complaint is large swelling , though occasionally may may present as nipple discharge from the nipple.

It is not malignant condition. It doesn't infiltrate the skin but the overlying skin becomes thin and tense and subcutaneous veins become prominent. This tumour is not fixed to deeper structure.

Sometimes axillary nodes become rarely enlarged but mostly it is because of secondary infection.

Grossly classified as,

1.soft-more cellular and often bilateral. Seen in more than 35 yrs old

2.hard –more fibrous , common below 35 yrs

3.giant- size more than 5 cm.

Microscopically classified as

1.Intracanalicular

It contains more glands which becomes stretched into elongated spidery shapes and become indented by fibrous tissue. This type of fibroadenoma are soft and larger in size. Which occurs in middle aged females between 35 to 50 yrs.

2.Pericanalicular

Pericanalicular FA which is made up of fibrous tissue surrounding small tubular glands. This type of FA is small and hard. Which occurs in young females between 15 to 35 yrs old.

Clinically presents as painless swelling in one of the breast quadrant which is smooth, nontender, firm, well localised and freely moves within the breast Juvenile fibroadenoma- seen in adolescent girls.

It shows rapid growth with stromal and epithelia hyperplasia but doesn't show alteration in the stromal epithelial balance/ cellular atypia/ periductal cellular concentration. Clinically it mimics phylloides but doesn't turn to phylloides or carcinoma.

Complex fibroadenoma-

It is a typical FA with fibrocystic changes like cyst formation, apocrine metaplasia, sclerosing adenosis. It occurs in old age groups. Occasionally turn into malignancy. Core biopsy needed to confirm the condition.

Investigations

1.Mammography

2.FNAC

3.USG

Indication for surgery

1.size > 3 cm

2.multiple

3.giant type

4.recurrence

5.cosmesis

6. Complex type

7. family history of ca breast.

Surgery:

Enucleation is done under general anaesthesia

Types of incision

1.webster `s incision- circumareolar incision

2. Gaillard Thomas incision-submammary incision.

Conservative management of FA:

Patient under 35 yrs old doesn't require excision unless associated with suspicious cytology, or if it is >3cm size, or patient desires the lump to be removed.

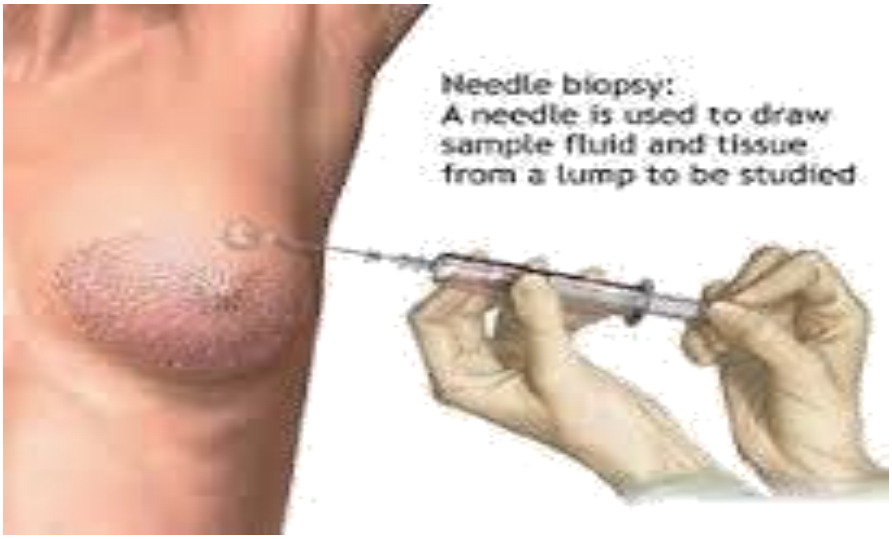
For these patients regular follow-up with usg at 6monthly interval with simple observation is enough.

FINE NEEDLE ASPIRATION CYTOLOGY (FNAC)

It is the least invasive method to obtain a cell diagnosis which is rapid and accure if both cytologist and operator are experienced but false negative may occur. This procedure involves aspiring cells and attendant fluid with a small core needle, followed by cytologic examination of the stained smear.

This method is mostly useful for readily palpable lesions in sites such as thyroid, lymphnode and breast. Although it has some difficulties, such as small sample size and sampling errors, in experienced hands it is extremely rapid, reliable and useful. Modern imaging techniques like usg permit extension of the method to lesions in deep seated structures like pelvic lymph node .

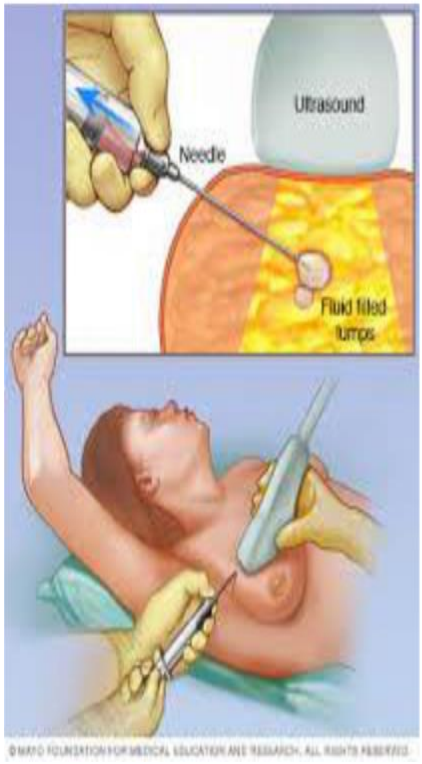
It can be done with 22 gauge needle. With the lump held properly, the needle is passed multiple times into the lump with negative pressure continuous aspiration till obtaining adequate material through the needle. Then needle witsyringe is removed without negative pressure.

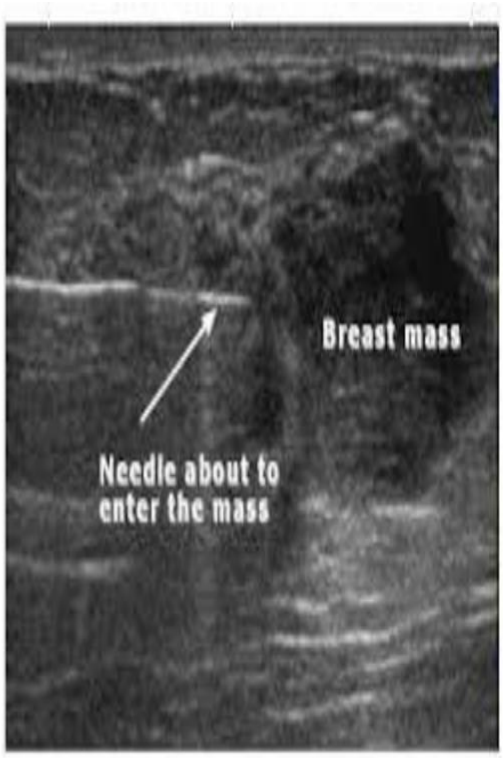


The aspirate is properly prepared over the slide for cytological examination using 100% alcohol.

Cytology is studied after staining it under microscopy

.Usg guided fnac: useful when the breast lump is not papable clinically, very deeply located and difficult to hold





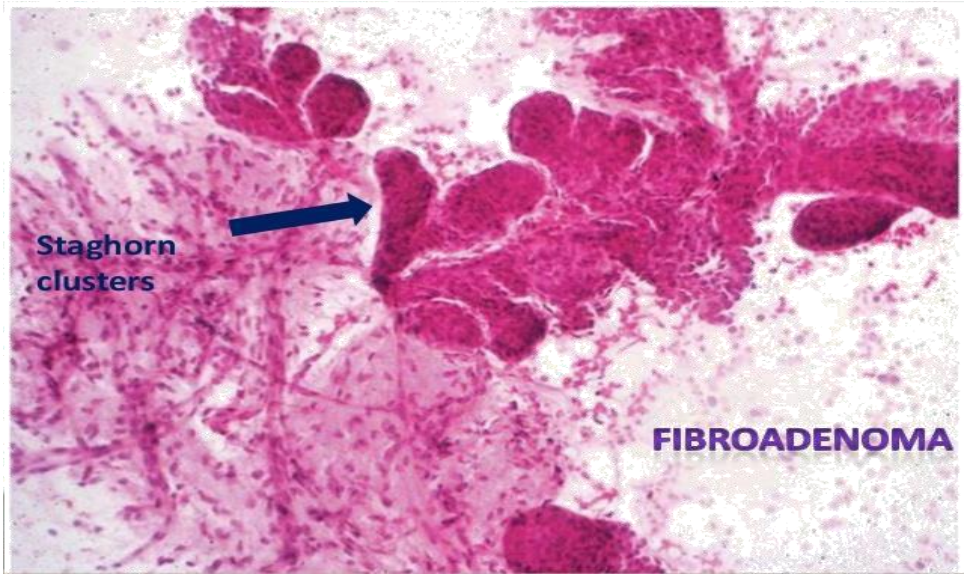
FNAC picture of fibroadenoma:

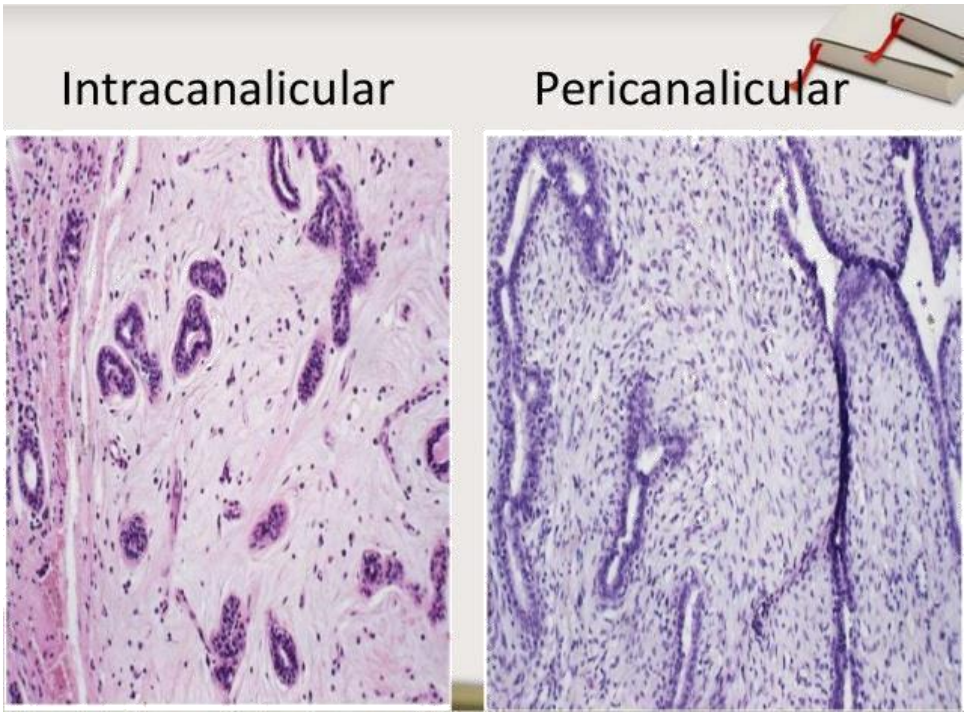
1.A high yield of cells, myxoid substance & some macroscopically visible tissue fragment

2.Large , branching sheets of bland epithelial cells(staghorn pattern of epithelial cells)

3.numerous single, bare bipolar nuclei

4.Fragments of fibromyxoid stroma.





Large needle biopsy -Sampling error decreases as the as per biopsy volume increases and using 8G or 11G needles allows more tissue to be taken.

ULTRASONOGRAM (USG)

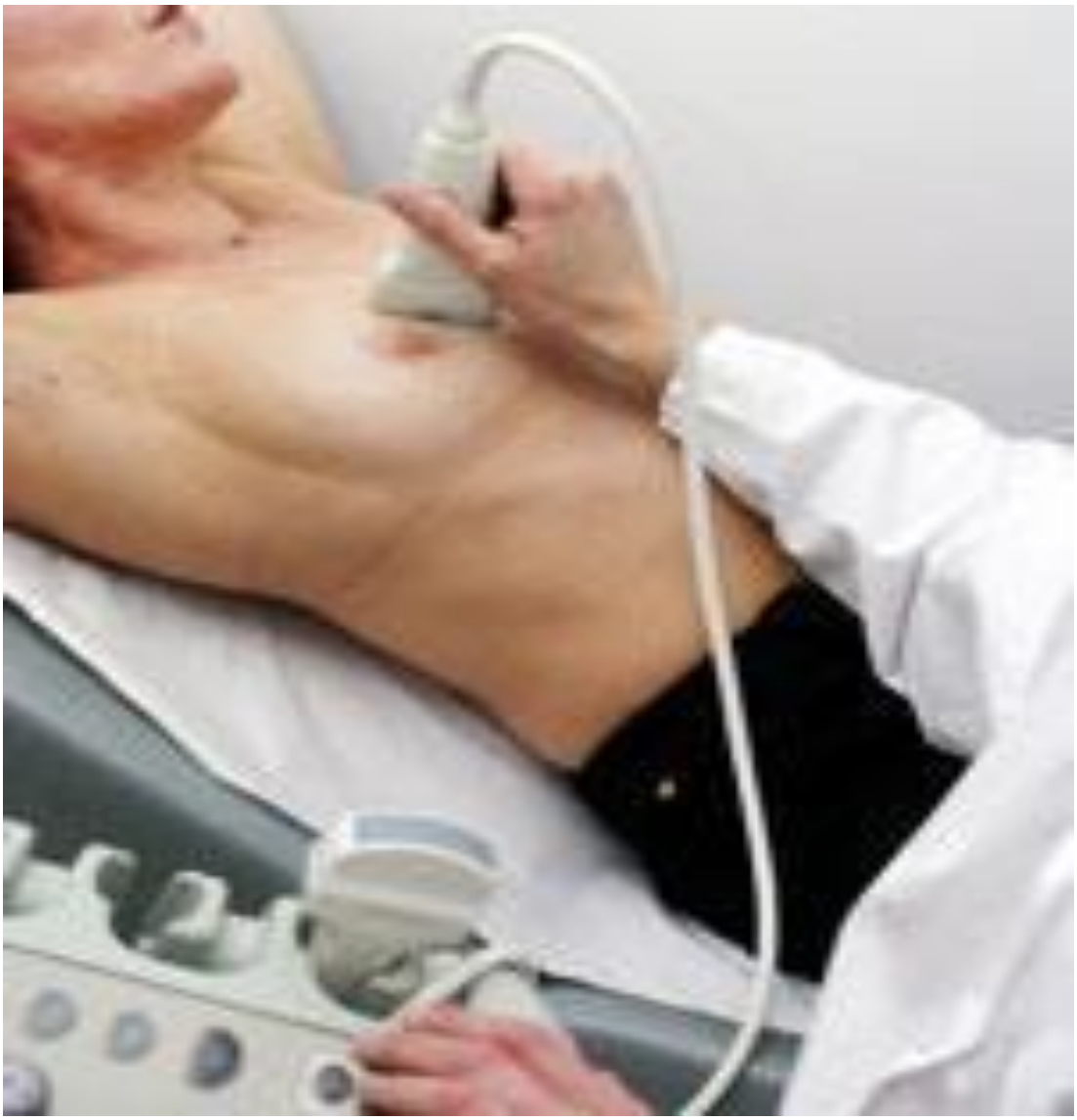
Ultrsound is inexpensive, quick, reliable and non invasive and it is the initial investigation of choice for wide range of clinical problems.usg is technically demanding and it need experienced operator to maximise the diagnostic reliability.

Inspite in the advancement in technology, there are still problem with gas because it reflects sound completely and in obese patients hence both are unsuitable for ultrasonagram.

Ultrasound is based on the generation of high frequency sound waves, usually between 3 to 7 MHz. Recent range of ultrasound includes probes measuring only millimetres and operating at 20 MHz.

It is useful to identify whether the lump is cystic or solid. Particularly useful in patients with dense breast. Usg is useful to localise impalpable areas of breast pathology. It is not useful as a screening tool.

FA appears oval on usg and their width is larger than anteroposterior diameter. Well circumscribed margins with gentle lobulations present .



Internal echogenicity may be homogenous but finding may range from isoechoic to hypoechoic. The through transmission of the tumour is variable. Thin echogenic capsule is typical of FA which denotes the lesion is benign.

This thin capsule is not true capsule ,it s a pseudocapsule which is formed by compression of adjacent structures

By using color –flow Doppler or power doppler imaging the distribution and vascularity of FA is highly variable hence vascularity of breast solid masses doesn’t help to distinguish a cancer from FA.

ESTROGENS

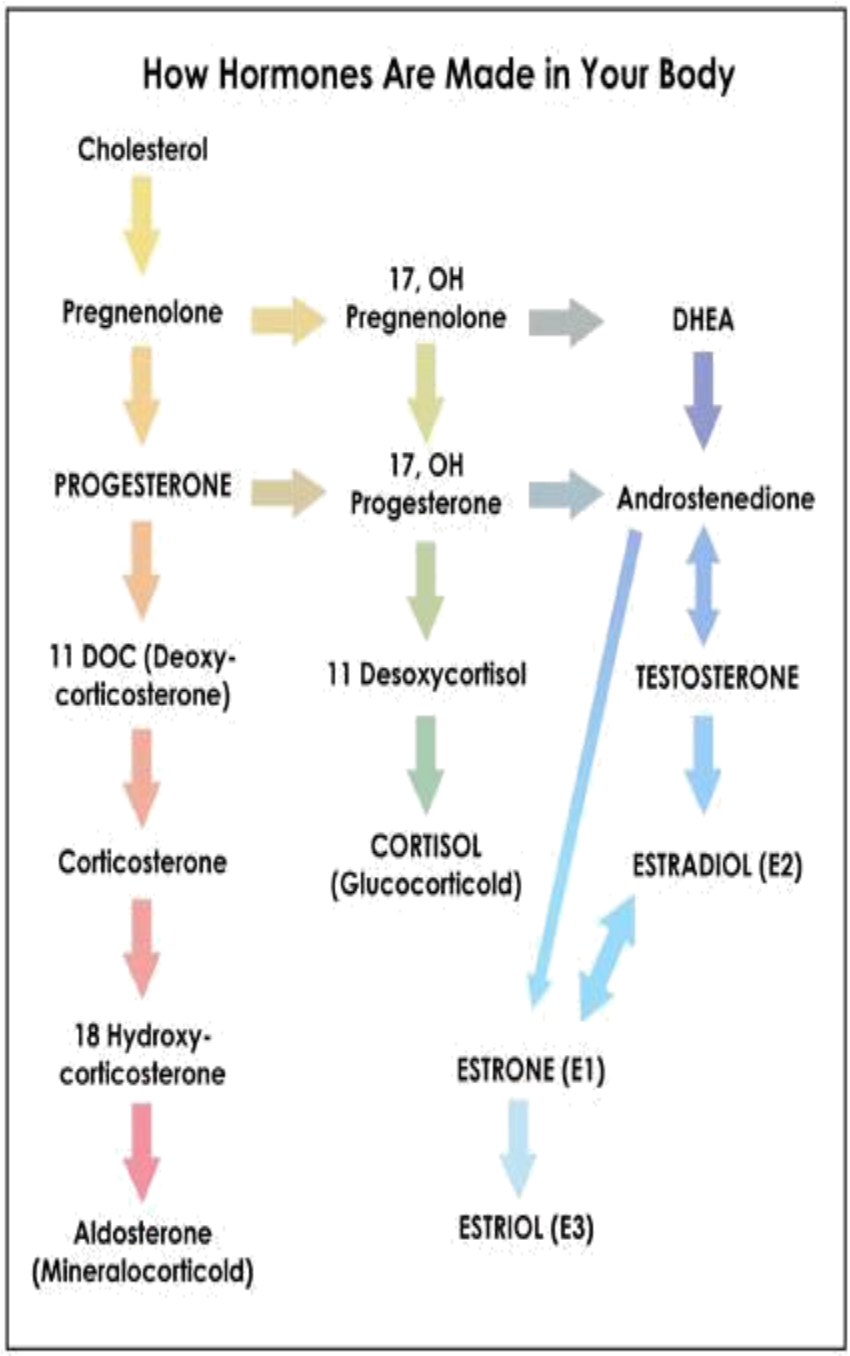
It is a female sex hormones. Mainly synthesized from the ovaries. The most potent natural estrogen for both estrogen recptors (ERα,ERβ) is 17β estradiol followed by estrone and estriol. Each molecule contains a phenolic A ring with a hydroxyl group at carbon 3 and a β-OH or ketone in position 17 of ring D.

The phenolic A ring is responsible for selective affinity for both receptors Ethinyl substitutions at C17 position imcreases oral potency by blocking first passs metabolism in liver.

NATURAL ESTROGEN

Estradiol is the major estrogen synthesized from the ovary. It is secreted from corpus luteum, graafian follicle and placenta which is produced from cholesterol.

Estradiol isimmediately oxidized to estrone in the liver . Estrone is hydroxylated to estriol..All the three hormones which mentioned above are found in the blood butamong these estrdiol is the high potent estrogen hormone.



In postmenopausal women, the principle source of circulating estrogen is adipose tissue stroma, where estrone is synthesized from dehydroepiandrosterone secreted by adrenals.

REGULATION OF SECRETION:

Menstruating women shows daily secretion of estrogen 10 to 100 µg depends on the phase of menstrual cycle. Graafian follicle secretes estrogen under the influence of FSH and its blood level increases during the follicular phase. Because of preovulatory FSH surge , estrogen rises transiently further. After ovulation corpus luteum secrets estrogen till 2 days before to menstruation. Estrogen exhibits negative feedback action on FSH and also on LH at the higher concentrations in the blood.

ACTIONS:

1. Sex organs- It brings pubertal changes in the females including growth of vagina, fallopian tubes and uterus and it is responsible for proliferation endometrim in the preovulatory phase. Even in the absence of progesterone withdrawal of estrogen itself can cause menstrual bleeding

2. Secondary sexual characters- Estrogen produced after puberty leads to growth of breast by inducing proliferation of stroma , duct and accumulation of fat . it is also responsible for axillary and pubic hair growth and feminine body structures.
3. Metabolic effects – it is a anabolic hormone and involved in maintaining bone mass primarily by inhibiting bone resorption. It supports positive calcium balance by inducing hydroxylase enzyme which involved in production of active form of vitamin D3.

ESTROGEN RECEPTORS:

The two estrogen recptors gene are located on separate chromosomes.ESR1 encodes ERα, and ESR2 encodes ERβ. Both estrogen receptors are estrogen-dependent nuclear transcription factors that have different tissue tissue tissue distributions and transcriptional regulatory effects on a wide number of target genes.

Two types of estrogen receptors identified.

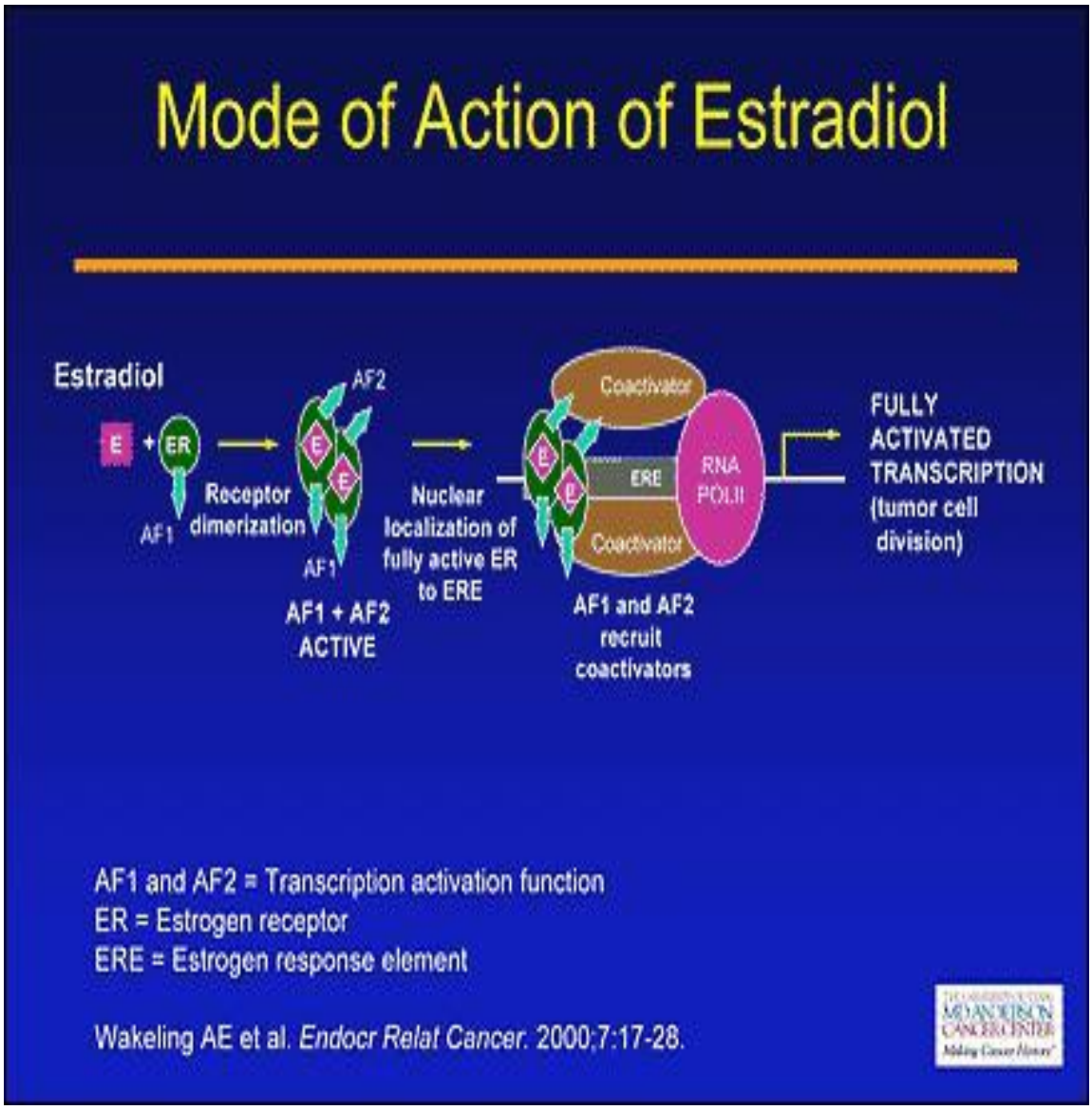
1.ERα

2.ERβ.

Most of the tissues has both subtypes. ERα predominantly seen in breast, uterus, vagina, hypothalamus, and blood vessels. ERβ predominantly seen in ovaries in female and prostate in males. Estradiol binds with both receptors equally.

MECHANISM OF ACTION

Estrogen bind to particular nuclear receptors and exhibits specific effect by regulating protein synthesize. ER are found in female sex organs, liver, pituitary,heart, cns, bones. When it binds to the ligand binding domain it leads to receptor dimerization and interaction with ERE of target genes. Gene transcription is promoted by certain coactivator proteins. When estrogen antagonist bind the receptor get a different conformation and interact with other corepressor proteins inhibiting gene transcriptions



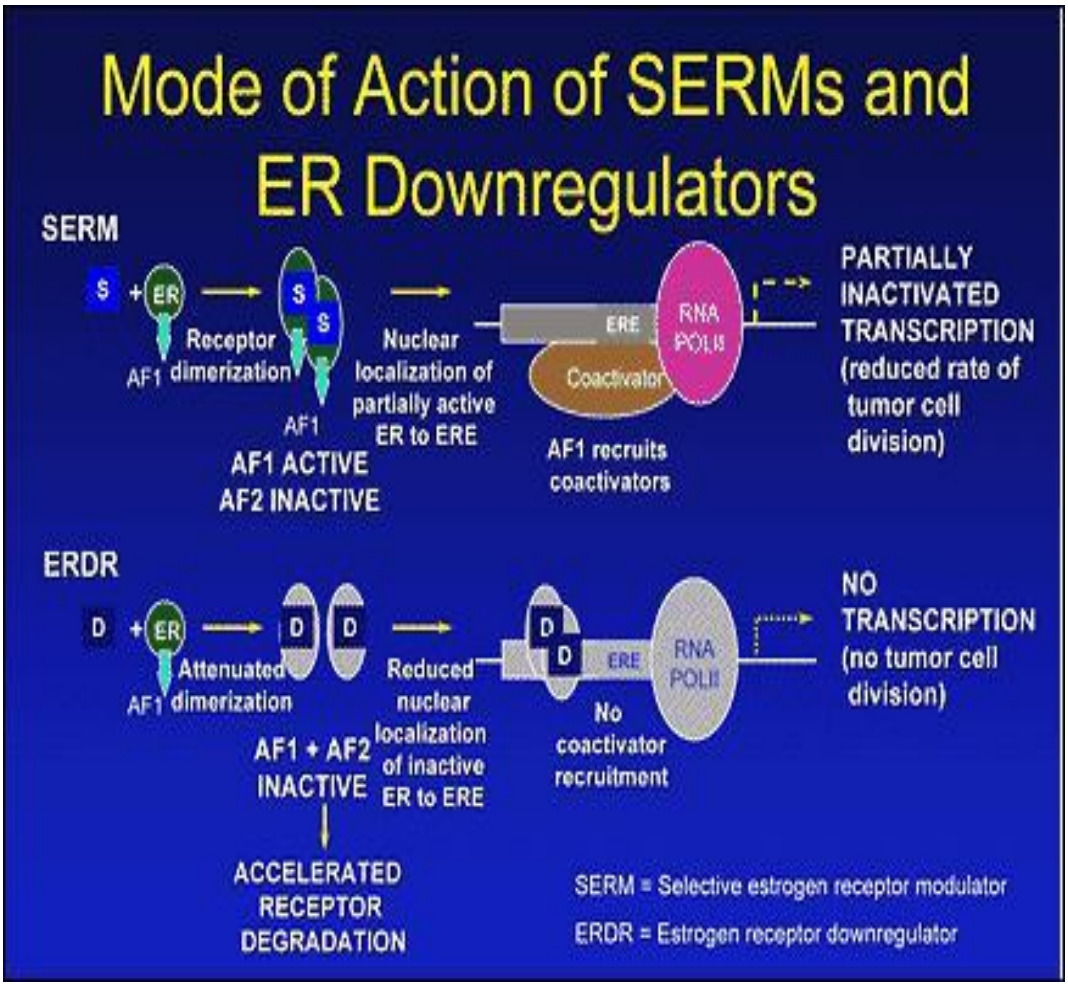
THERAPEUTIC USES-

The two major uses ofestrogens are for menopausal hormone therapy (MHT) and as components of combination oral contraceptives

Menopausal Hormone Therapy.-The established benefits of estrogen therapy in postmenopausal women include amelioration of vasomotor symptoms and the prevention of bone fractures and urogenital atrophy.

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERM)

It is a synthetic molecule. SERM can bind to both estrogen receptors and exhibits both estrogen agonist and antagonist action depends upon the target tissue.



The pharmacological goal of these drugs is to produce beneficial estrogenic actions in certain tissues like bone , brain and liver during postmenopausal hormone therapy but antagonist activity in tissues such as breast and endometrium where estrogen action might be deleterious. Currently approved drugs in the USA are tamoxifen citrate, raloxifene hydrochloride and toremifene which is chemically related and has similar actions to tamoxifene..

Tamoxifene and toremifene are used for the treatment of breast cancer. Raloxifene is used primarily for the prevention and treatment of osteoporosis and to reduce the risk of invasive breast cancer in high risk postmenopausal women.

ORMELOXIFENE (CENTCHROMAN)

It is a nonhormonal nonsteroidal antiestrogen (Selective estrogen receptor modulator, SERM) drug produced by the Central Drug Research Institute, Lucknow, India.

It has weak agonist action on endometrium and strong antagonist action on breast ductolobular epithelium . Well absorbed from the GI tract. Peak serum levels attained in 4 hrs. widely distributed in body tissues with little affinity to plasma proteins

.Currently used as contraceptive and for DUB . centchroman has been available in india for birth control since 1990.It is marketed in the trade name as saheli, centron, sevista and novex.

ADVERSE EFFECTS:

Only significant adverse effect is menstrual abnormality.Others are nausea, headache, rise in BP, Weight gain. Menstrual periods will resume at the end of 12 weeks.

Table 16.1 Variety of therapeutic targets in which established SERMs are used in comparison with estrogens

Therapy	*Hot flashes*	*Genital atrophy*	*Endometrial proliferation*	*Ovulation*	*Osteoporosis*	*Breat cancer*	*CVD*
Estrogen* ERT/HRT	↓	↓	NA	NA	↓	↑	↑
Clomifen	NA	↑	↓	↑	NA	NA	NSC
Tamoxifen	↑	↑	↑	NA	↓	↓	↑
Raloxifene	↑	NSC	↓	NA	↓	↓	↑
Genistein	↓	↓	NSC	NA	↓	NSC	↓
Centehroman	NA	NSC	NSC	NSC	↓	↓	NSC

* ERT alone not used without hysterectomy
CVD = Cardiovascular disease including Deep Venous Thrombosis
NA = Not applicable in the clinical situation
NSC = No significant change

Contraindications

1.Hypersensitivity to Ormeloxifene

2.Renal impairment

3.Hepatic impairment

4.Jaundice

5.Polycystic ovarian disease

6.Chronic cervicitis

7.Cervical hyperplasia

8.Tuberculosis.

OBSERVATIONS AND RESULTS

Mastalgia study group

VAS score	Day 0	4th week	8th week	12th week	24th week
0	0	0	2	8	12
2	2	3	5	4	1
4	8	9	5	1	0
6	5	3	3	2	2
8	0	0	0	0	0
10	0	0	0	0	0

Mastalgia control group

VAS score	Day 0	4th week	8th week	12th week	24th week
0	0	0	1	1	2
2	2	2	2	2	1
4	8	8	8	8	9
6	5	5	4	4	3
8	0	0	0	0	0
10	0	0	0	0	0

Fibroadenoma volume change study group

Volume change	4th week	8th week	12th week	24th week
Complete regression C	0	2	10	12
Decrease in size D	4	10	5	3
No change N	11	3	0	0
Increase in size I	0	0	0	0

Fibroadenoma volume change control group

Volume change	4th week	8th week	12th week	24th week
Complete regression C	0	0	0	0
Decrease in size D	0	0	3	3
No change N	15	14	11	11
Increase in size I	0	1	1	1

Fibroadenoma 4th week

Volume change	Study	Control	
C	0	0	0
D	4	0	4
N	11	15	26
I	0	0	0
	15	15	30

Chi- Square test: 4.615
P value:0.0317

Fibroadenoma 8th week

Volume change	Study	Control	
C	2	0	2
D	10	0	10
N	3	14	17
I	0	1	1
	15	15	30

Chi- Square test: 20.118
P value:0.0002

Fibroadenoma 12th week

Volume change	Study	Control	
C	10	0	10
D	5	3	8
N	0	11	11
I	0	1	1
	15	15	30

Chi- Square test: 22.500
P value:0.0001

Fibroadenoma 24th week

Volume change	Study	Control	
C	12	0	12
D	3	3	6
N	0	11	11
I	0	1	1
	15	15	30

Chi- Square test:16.000
P value:0.0001

MASTALGIA 4th week

VAS score	Study	Control	
0	0	0	0
2	3	2	5
4	9	8	17
6	3	5	8
8	0	0	0
10	0	0	0
	15	15	30

Chi- Square test: 0.759
P value:0.6843

MASTALGIA 8th week

VAS score	Study	Control	
0	2	1	3
2	5	2	7
4	5	8	13
6	3	4	7
8	0	0	0
10	0	0	0
	15	15	30

Chi- Square test:2.454
P value:0.4836

MASTALGIA 12th week

VAS score	Study	Control	
0	8	1	9
2	4	2	6
4	1	8	9
6	2	4	6
8	0	0	0
10	0	0	0
	15	15	30

Chi- Square test: 12.222
P value:0.0067

MASTALGIA 24th week

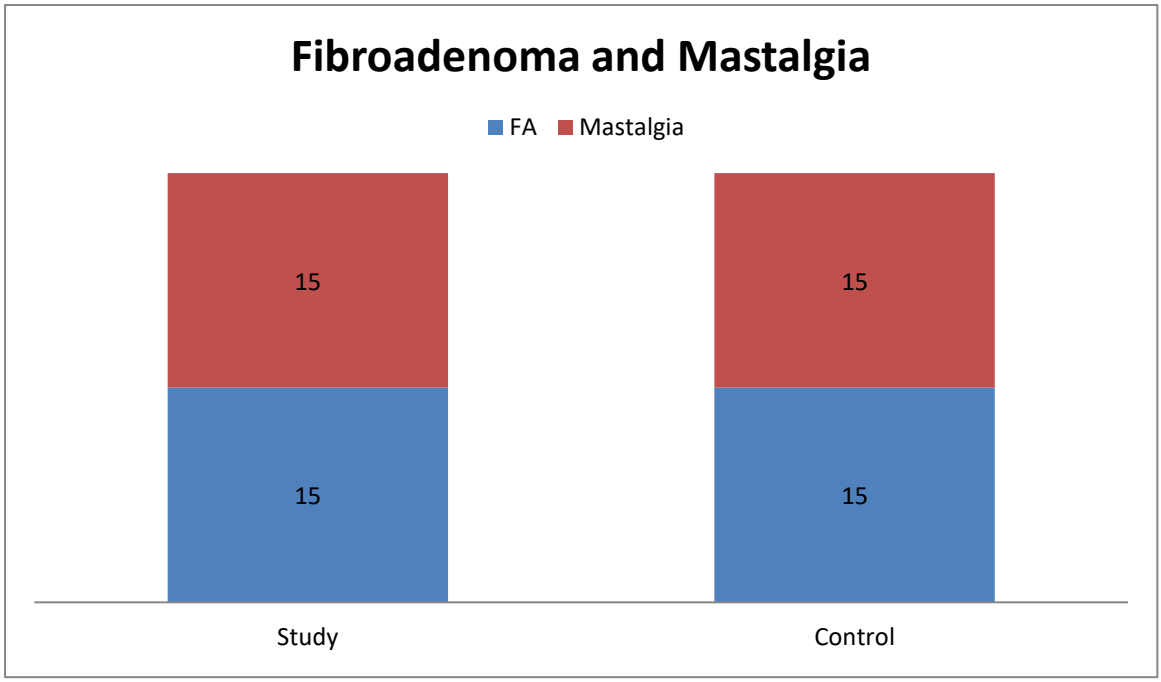
VAS score	Study	Control	
0	12	2	15
2	1	1	2
4	0	9	9
6	2	3	5
8	0	0	0
10	0	0	0
	15	15	30

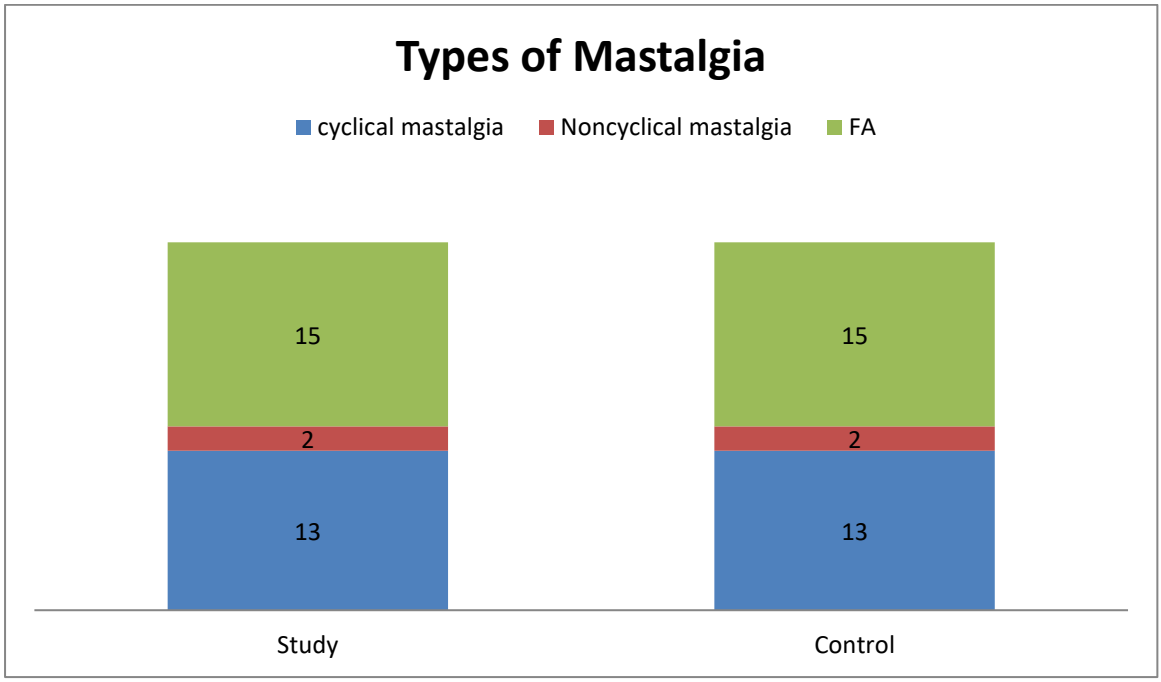
Chi- Square test: 16.343
P value:0.0010

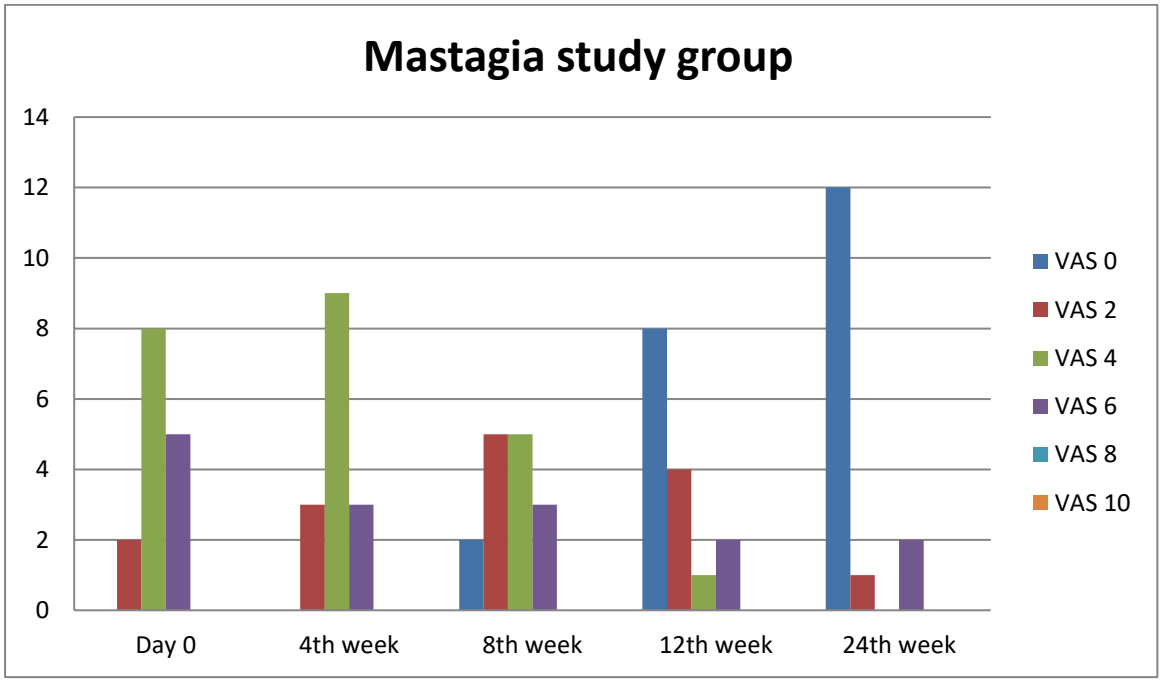
Side effects

Side effects	Study	Control	
None	25	28	53
Menstrual delay	4	0	4
Gastritis	1	2	3

Chi- Square test: 4.543
P value:0.1032


Fibroadenoma and Mastalgia
FA
Mastalgia
15
15
15
15
Study
Control


Types of Mastalgia
cyclical mastalgia
Noncyclical mastalgia
FA
15
2
13
15
2
13
Study
Control


Mastagia study group
14
12
10
8
6
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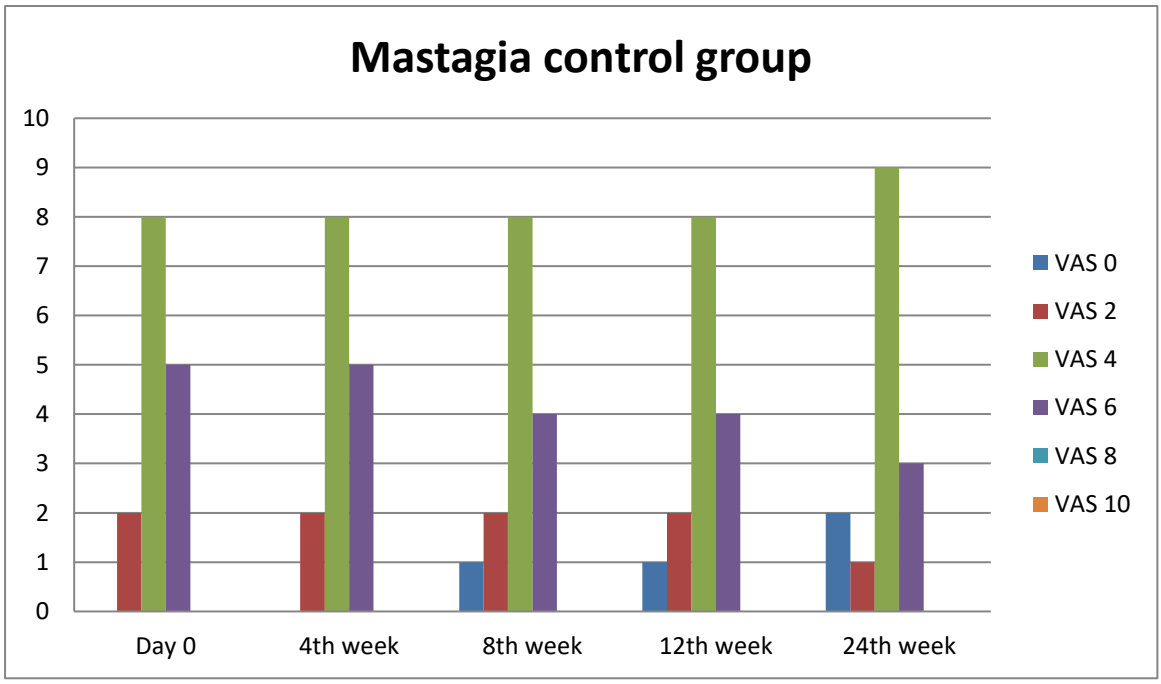
Day 0
4th week
8th week
12th week
24th week
VAS 0
VAS 2
VAS 4
VAS 6
VAS 8
VAS 10


Mastagia control group
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24th week
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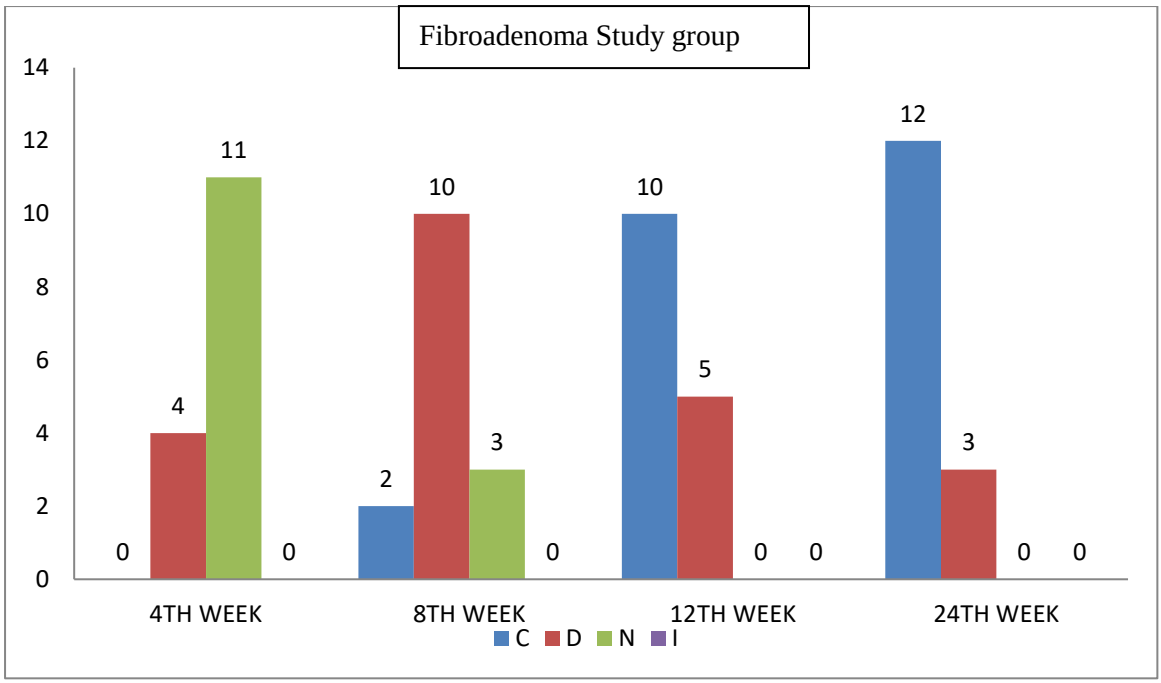
VAS 10


Fibroadenoma Study group
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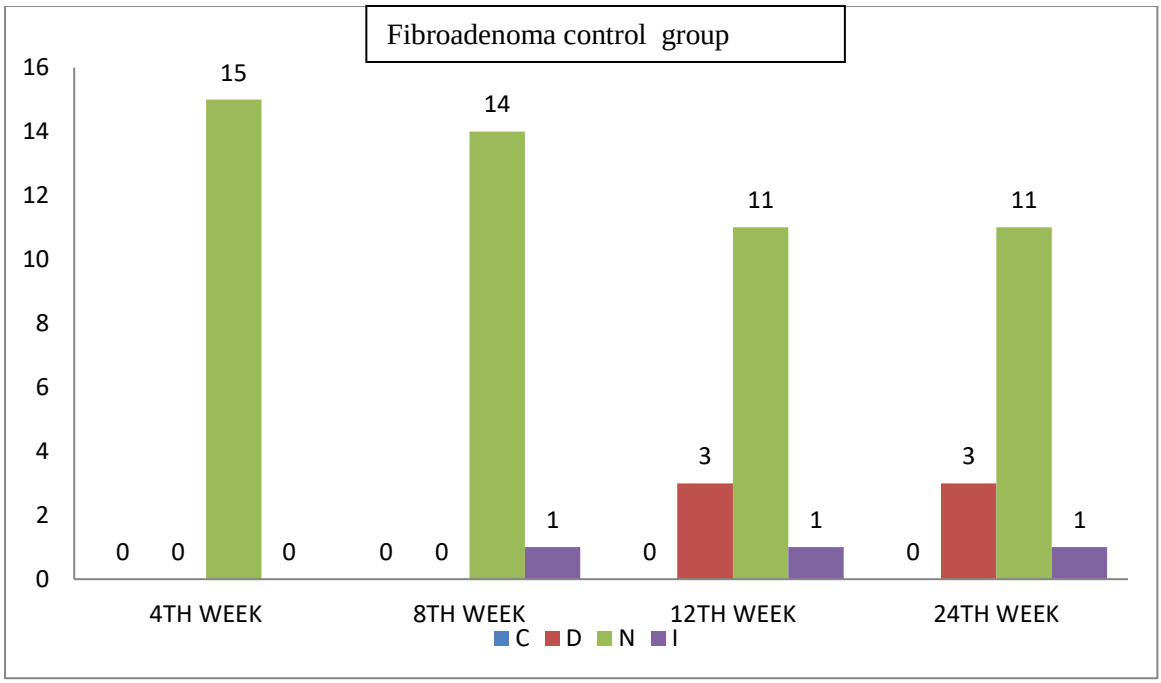
8TH WEEK
12TH WEEK
24TH WEEK
C D N I


Fibroadenoma control group
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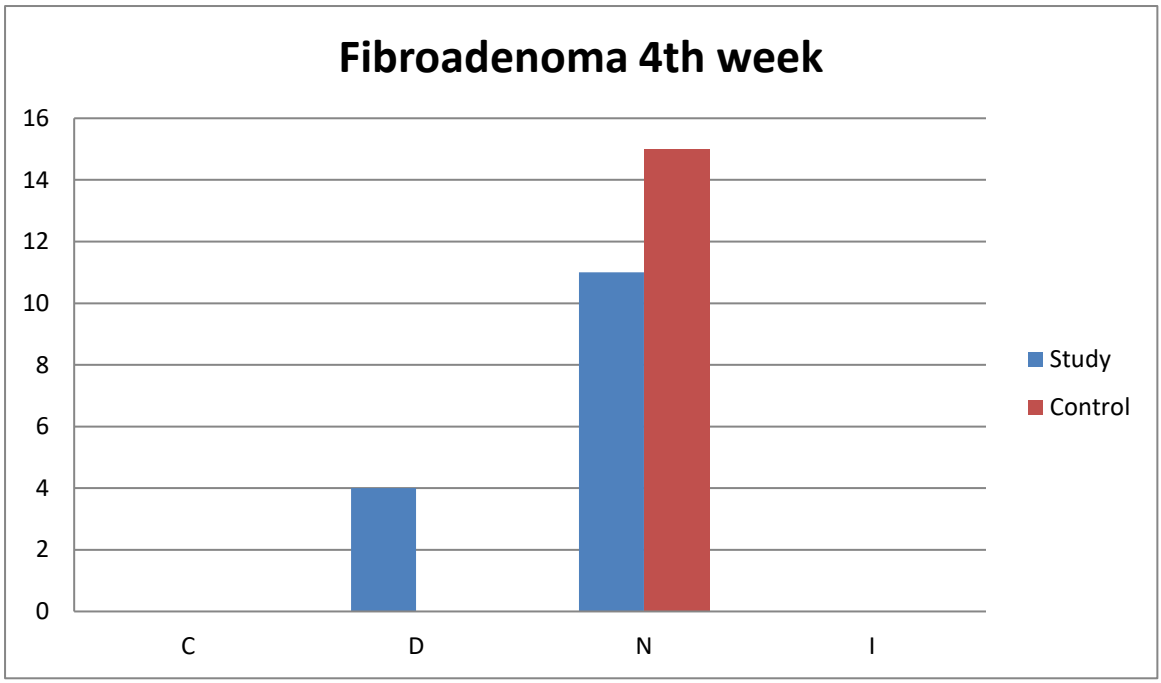
8TH WEEK
12TH WEEK
24TH WEEK
C D N I


Fibroadenoma 4th week
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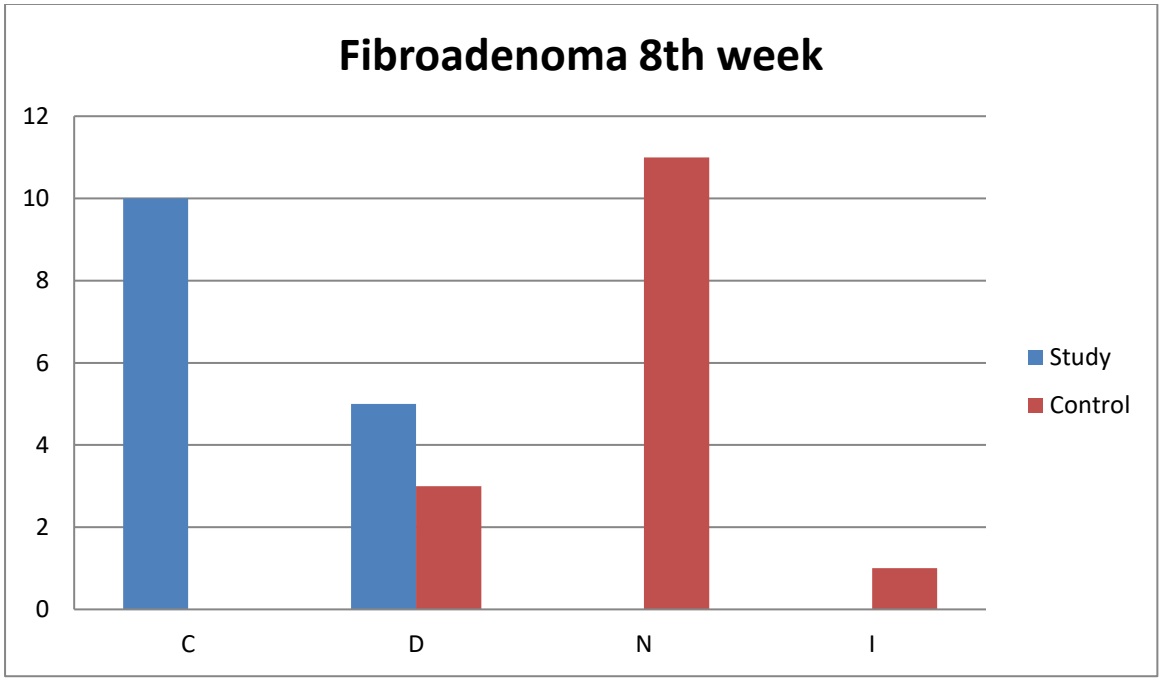
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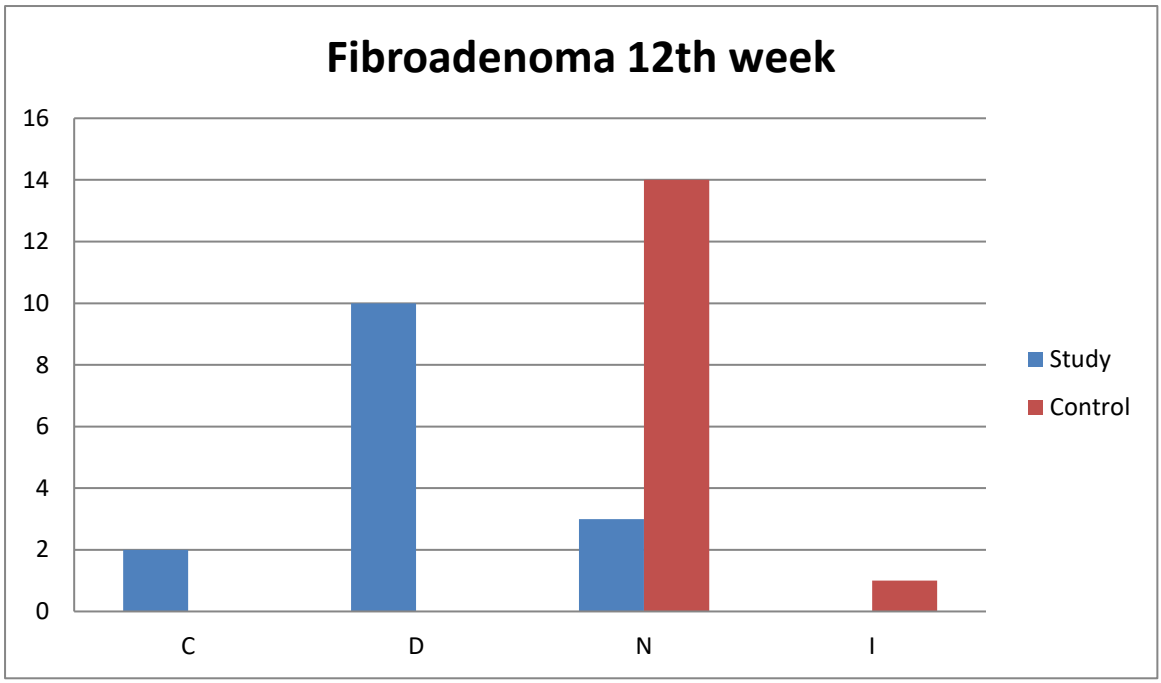
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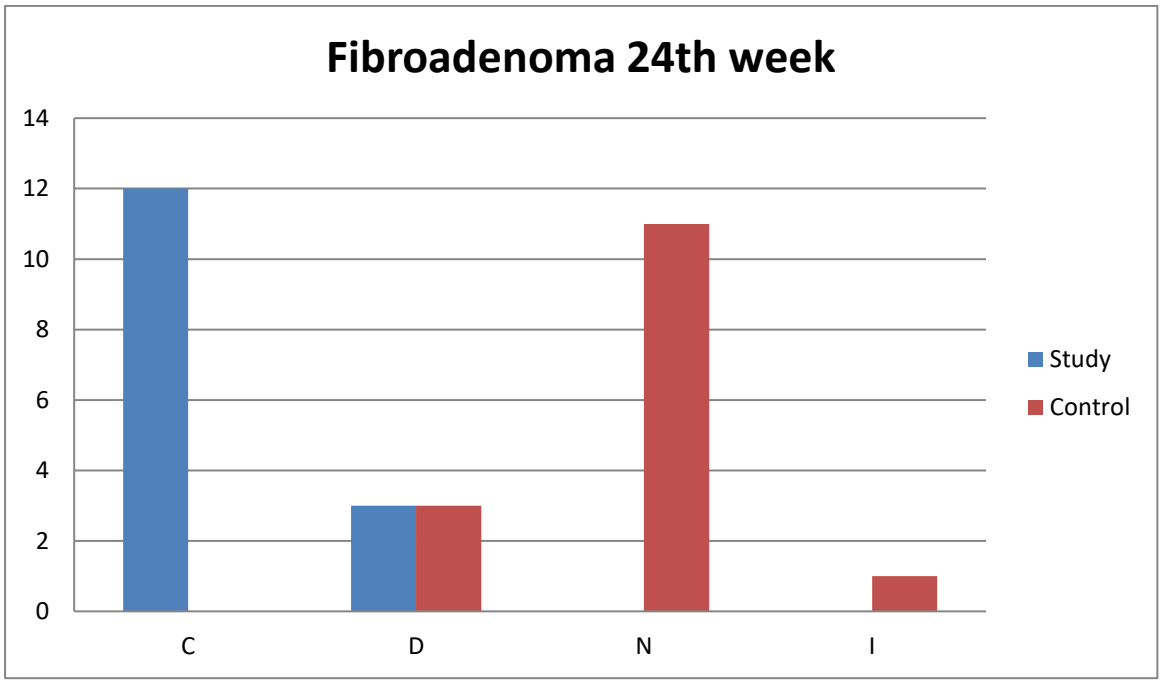
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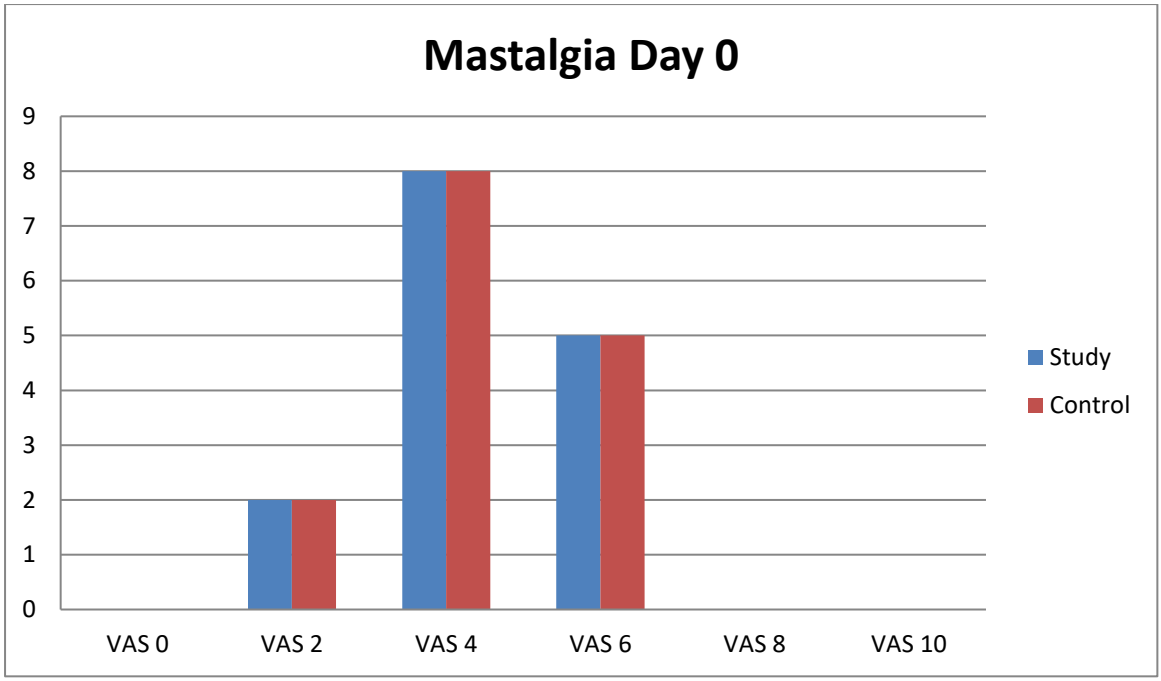
Mastalgia Day 0
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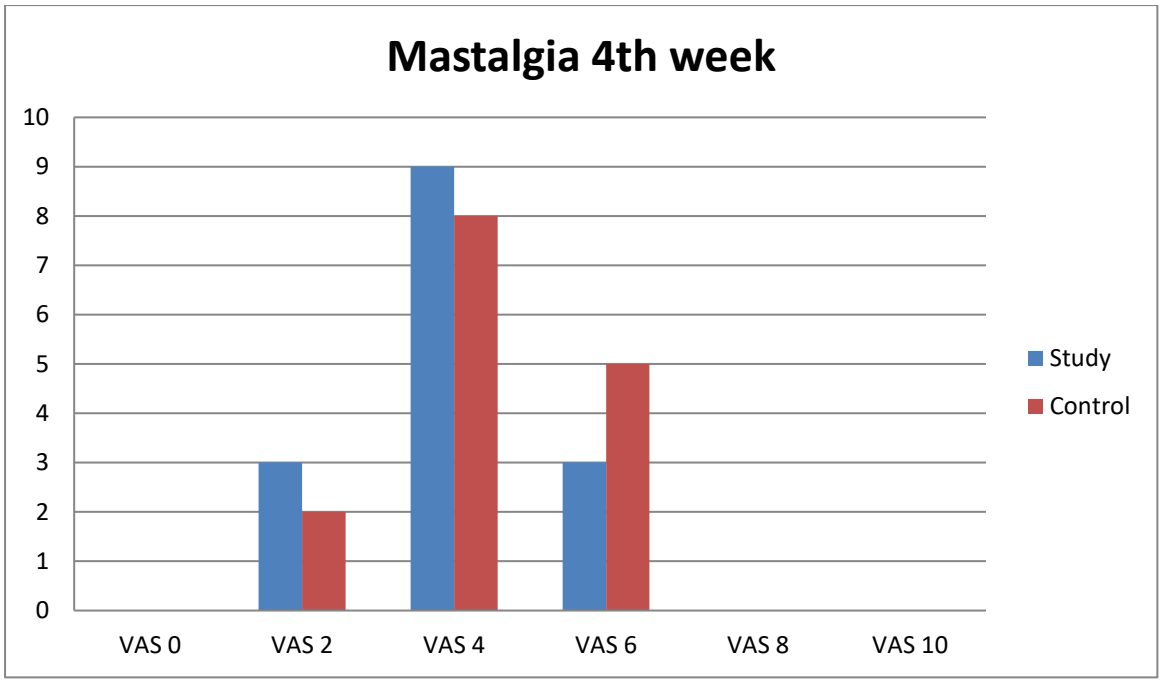
VAS 10
Study
Control


Mastalgia 4th week
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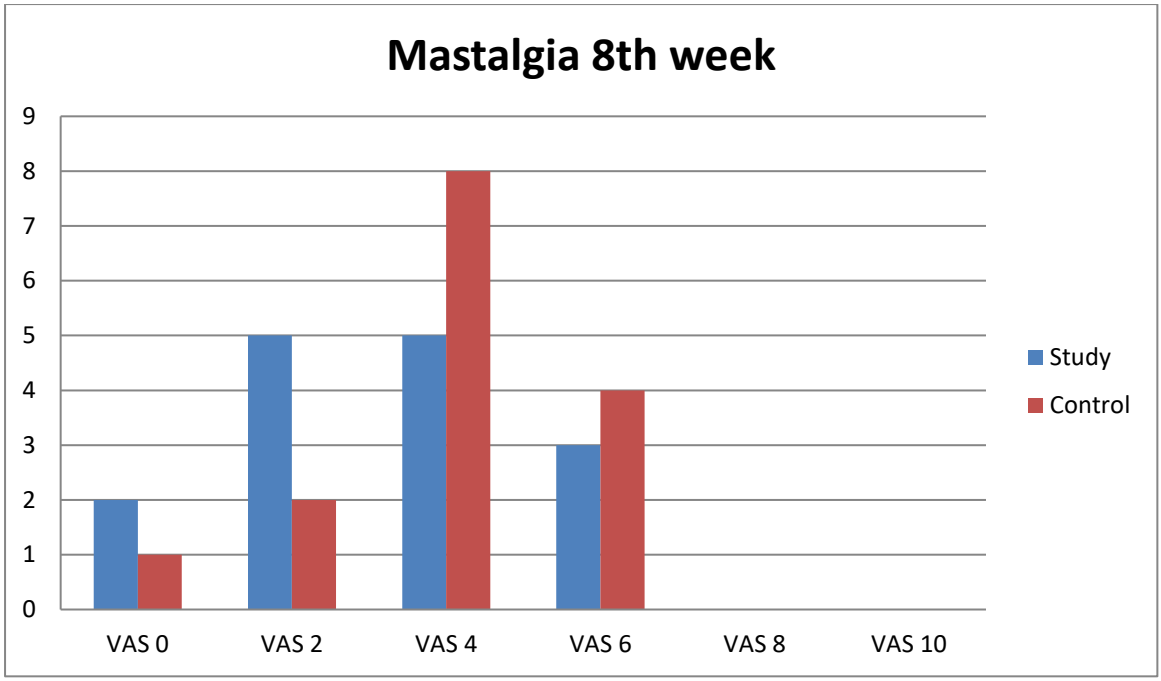
Mastalgia 8th week
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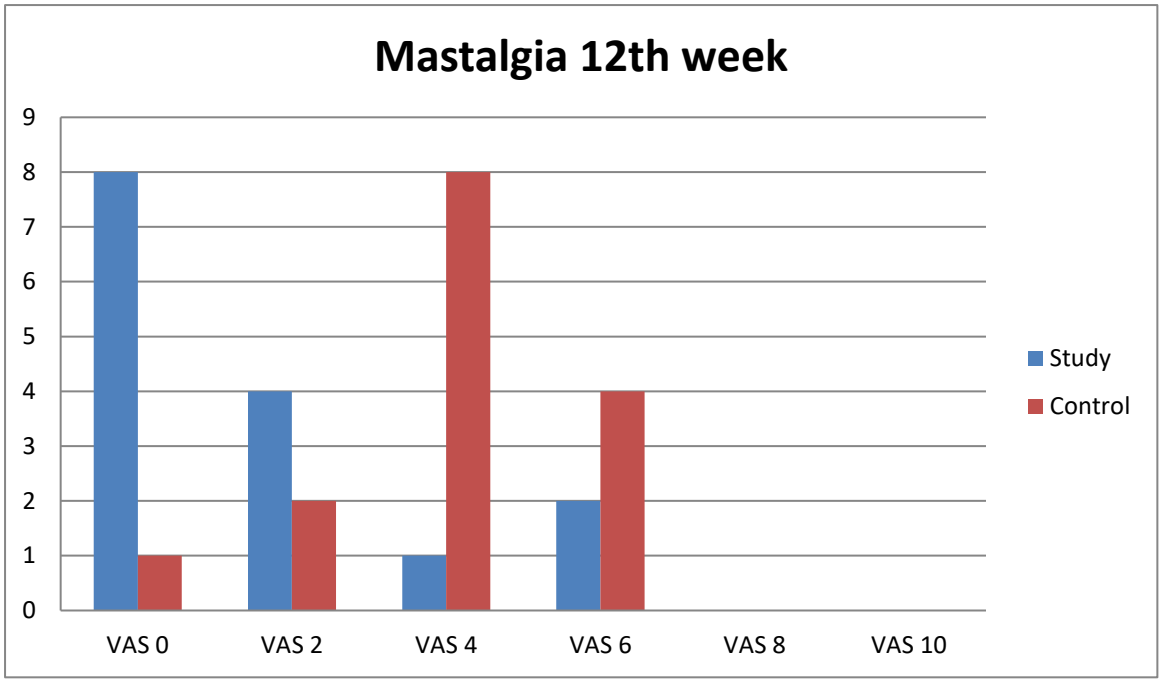
Mastalgia 12th week
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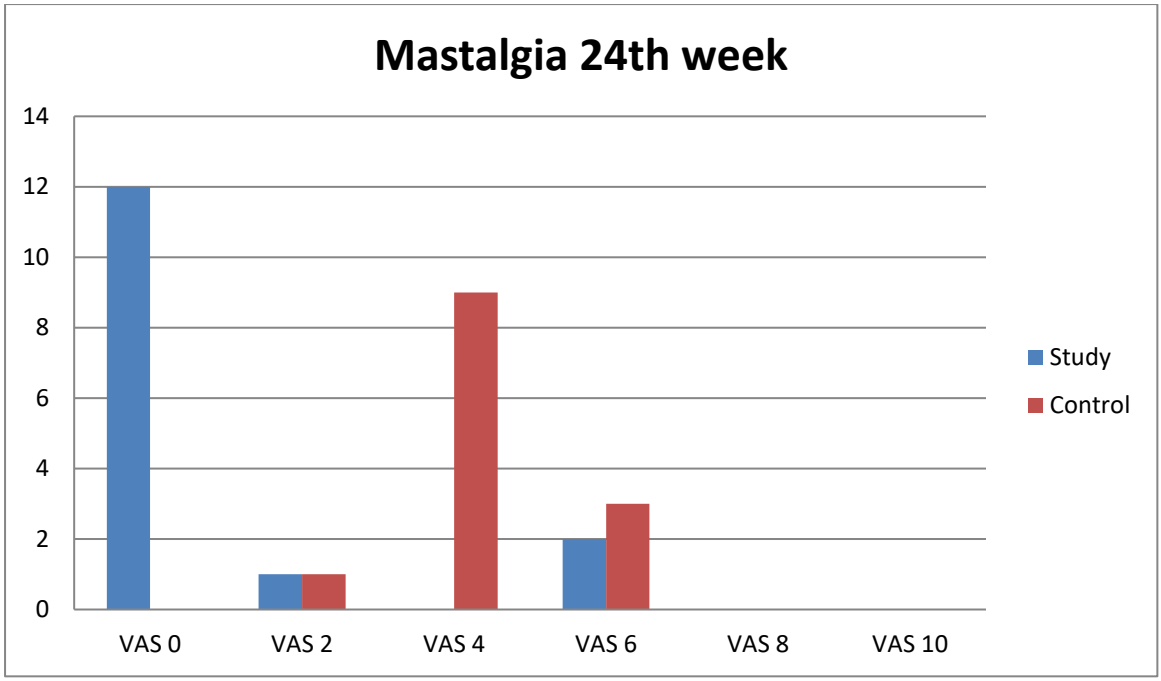
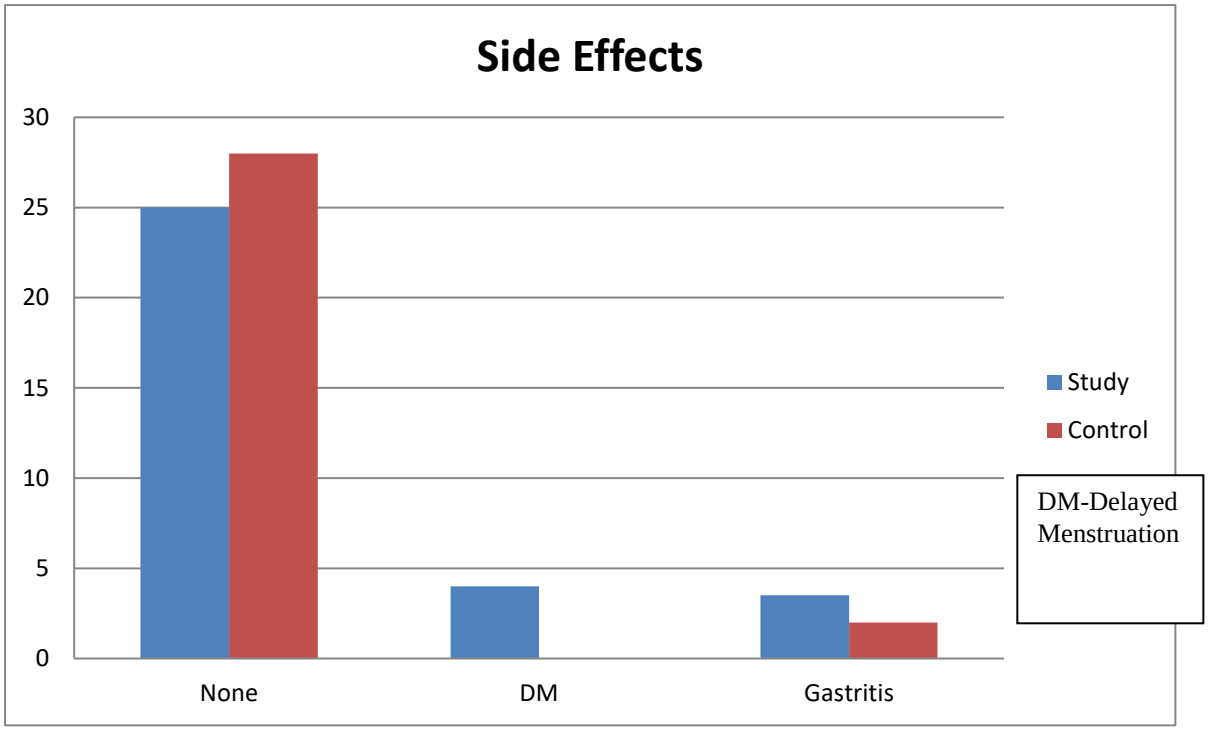
VAS 10
Study
Control


Mastalgia 24th week
14
12
10
8
6
4
2
0
VAS 0
VAS 2
VAS 4
VAS 6
VAS 8
VAS 10
Study
Control


Side Effects
30
25
20
15
10
5
0
None
DM
Gastritis
Study
Control
DM-Delayed Menstruation

DISCUSSION

DISCUSSION

Fibroadenomas and mastalgias are the most common benign breast disorders. Fibroadenomas are the second most common neoplasm of females. After verifying lot of studies regarding conservative management of mastalgias and benign breast conditions, I decided to conduct this study in my hospital for my dissertation comparing with patients kept under simple observation. It is well known fact that 15 % of fibroadenomas will regress spontaneously over one to six years of observation.

As per my study patients on centchroman were put on alternative day single dose regimen of dose 30 mg. Both study group patients and control group patients were regularly followed at 4^{th} week, 8^{th} week, 12^{th} week and finally at 24^{th} week. Totally 60 patients were taken in this study, out of which 30 patients were categorised into fibroadenoma group and the other 30 patients into mastalgia group. Out of 30 patients in fibroadenoma group, 15 patients were randomised into study group and the remaining 15 patients were put into control group. Similarly in mastalgia group of 30 patients, 15 were taken into the study group and the rest 15 patients were randomised into control group.

Results in fibroadenoma group:

In fibroadenoma group, at each visit patients were measured the volume of lump using ultrasonography and compared with the volume of lump they had in their previous visit. By this method, patients were categorised into four groups by their response to intervention. Those four groups were of the following

C- complete regression

D- decrease in volume

N- no change in volume

I-Increase in volume

At the end of four weeks, in study group, 0/15 patients had complete regression, 4/15 patients had decrease in volume of the breast lump comparing with their first visit, 11/15 patients had same volume of the breast lump as their first visit, 0/15 patients showed increase in volume compared with their first visit. Whereas in control group, 0/15 patients had complete regression, 0/15 patients had decrease in volume of the breast lump comparing with their first visit, all of the control group patients i.e., 15/15 patients had no change in volume of the breast lump when compared with their first visit, 0/15 patients had increase in size of the lump compared with their first visit. when the results were compared, p value(0.0317) was found to be statistically significant.

At the end of eight weeks, in study group, 2/15 patients had complete regression, 10/15 patients had decrease in volume of the breast lump comparing with their second visit, 3/15 patients had same volume of the breast lump as

their second visit, 0/15 patients showed increase in volume compared with their second visit. Whereas in control group, 0/15 patients had complete regression, 0/15 patients had decrease in volume of the breast lump comparing with 0 second visit, 14/15 patients had no change in volume of the breast lump when compared with their second visit, 1/15 patient had increase in size of the lump compared with their second visit. when the results were compared, p value(0.0037) was found to be statistically highly significant.

At the end of twelve weeks, in study group, 10/15 patients had complete regression, 5/15 patients had decrease in volume of the breast lump comparing with their third visit, 0/15 patients had same volume of the breast lump as their third visit, 0/15 patients showed increase in volume compared with their third visit. Whereas in control group, 0/15 patients had complete regression, 3/15 patients had decrease in volume of the breast lump comparing with their third visit, 11/15 patients had no change in volume of the breast lump when compared with their third visit, 1/15 patient had increase in size of the lump compared with their third visit. when the results were compared, p value(0.0001) was found to be statistically highly significant.

At the end of twenty four weeks, in study group, 12/15 patients had complete regression, 3/15 patients had decrease in volume of the breast lump comparing with their fourth visit, 0/15 patients had same volume of the breast lump as their fourth visit, 0/15 patients showed increase in volume compared with their fourth visit. Whereas in control group, 0/15 patients had complete regression, 3/15

patients had decrease in volume of the breast lump comparing with their fourth visit, 11/15 patients had no change in volume of the breast lump when compared with their fourth visit, 1/15 patient had increase in size of the lump compared with their fourth visit. when the results were compared, p value(0.0001) was found to be statistically highly significant.

Results in mastalgia group:

In mastalgia group, patients were randomly categorised into study and control groups each containing 15 patients. Patients were followed up in each visit with visual analog score for mastalgia ranging from 0 to 10.

At first visit on Day 0, both groups had two patients with VAS 2, both groups had eight patients with VAS 4, and both groups had five patients with VAS 6. Hence both groups were found to be comparable initially before any intervention to be provided.

At second visit on 4^{th} week, 0/15 patients in study group had VAS 0, 3/15 patients in study group had VAS 2, 9/15 patients in study group had VAS 4, 3/15 patients in study group had VAS 6, 0/15 patients in study group had VAS 8 and 0/15 patients in study group had VAS 10. Whereas 0/15 patients in control group had VAS 0, 2/15 patients in control group had VAS 2, 8/15 patients in control group had VAS 4, 5/15 patients in control group had VAS 6, 0/15 patients in control group had VAS 8 and 0/15 patients in control group had VAS

10. When the results were compared, p value (0.6843) was not found to be statistically significant.

At third visit on 8th week, 2/15 patients in study group had VAS 0, 5/15 patients in study group had VAS 2, 5/15 patients in study group had VAS 4, 3/15 patients in study group had VAS 6, 0/15 patients in study group had VAS 8 and 0/15 patients in study group had VAS 10. Whereas 1/15 patients in control group had VAS 0, 2/15 patients in control group had VAS 2, 8/15 patients in control group had VAS 4, 4/15 patients in control group had VAS 6, 0/15 patients in control group had VAS 8 and 0/15 patients in control group had VAS 10. When the results were compared, p value (0.4836) was not found to be statistically significant.

At fourth visit on 12th week, 8/15 patients in study group had VAS 0, 4/15 patients in study group had VAS 2, 1/15 patients in study group had VAS 4, 2/15 patients in study group had VAS 6, 0/15 patients in study group had VAS 8 and 0/15 patients in study group had VAS 10. Whereas 1/15 patients in control group had VAS 0, 2/15 patients in control group had VAS 2, 8/15 patients in control group had VAS 4, 4/15 patients in control group had VAS 6, 0/15 patients in control group had VAS 8 and 0/15 patients in control group had VAS 10. When the results were compared, p value (0.0067) was found to be statistically highly significant.

At fifth visit on 24th week, 12/15 patients in study group had VAS 0, 1/15 patients in study group had VAS 2, 0/15 patients in study group had VAS 4,

2/15 patients in study group had VAS 6, 0/15 patients in study group had VAS 8 and 0/15 patients in study group had VAS 10. Whereas 2/15 patients in control group had VAS 0, 1/15 patients in control group had VAS 2, 9/15 patients in control group had VAS 4, 3/15 patients in control group had VAS 6, 0/15 patients in control group had VAS 8 and 0/15 patients in control group had VAS 10. When the results were compared, p value (0.0010) was found to be statistically highly significant.

Centchroman drugs were found to have safety profile with minimal side effects. In this study conducted, delayed menstruation and gastritis were the two side effects to get manifested. In study group, 25/30 patients had no side effects whereas 4/30 patients had menstrual delay and 1/30 patient had gastritis. In control group, 28/30 patients had no side effects, 0/30 patients had menstrual delay and 2/30 patients had gastritis. When these results were statistically analysed, they were found to be insignificant. Hence two groups are comparable in view of side effects.

The study showed statistical difference in fibroadenoma patients with significant reduction in their sizes in patients treated with centchroman even at 4^{th} week. Further the difference between study and control group became statistically highly significant at 8^{th}, 12^{th} and 24^{th} week.

The study did not show any statistical difference in mastalgia patients treated with centchroman at 4^{th} and 8^{th} week. But the difference between study and

control group became statistically significant at 12^{th} and 24^{th} week with greater reduction in pain.

LIMITATION OF THE STUDY:

This study presents data based on 6 months follow-up only. Long term results of centchroman on recurrent and further decrease in size require further studies in future.

CONCLUSION

CONCLUSION:

1. .Centchroman therapy in FA treatment showed statistically significant regression of volume.
2. .Centchroman therapy in mastalgias treatment showed statistically significant regression of pain
3. Long term results beyond 6 months needs further study
4. It is useful in patient who is willing for observation instead of enucleation of FA
5. Patients more than 35 yrs old and young patients (<35 yrs) with suspicious histology, recurrence, family h/o carcinoma breast, anxiousness and no response to conservative management are the ideal candidate for active management as excisional biopsy (enucleation of FA).

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ANNEXURES

Masterchart fibroadenoma study group

S.No	Name	Age	Side	Day (	4th week		8th week		12th week		24th week		Side effects	
				volume	volume	chart	volume	chart	volume	chart	volume	chart	DM	Gastritis
1	Rakammal	22	R	5.5	3.9	D	1.2	D	0	C	0	C		
2	Rani	21	R	5.1	5.1	N	5.1	N	2.5	D	0	C		
3	Irulayee	30	L	14	14	N	4.7	D	0	C	0	C		
4	Mary	24	R	4.5	4.5	N	4.5	N	1.4	D	0	C		
5	Usha	25	L	12.2	12.2	N	5.1	D	3.6	D	1.4	D		
6	Rajee	20	L	12.2	4.1	D	0	C	0	C	0	C		
7	Mani	19	L	8.5	3.6	D	0	C	0	C	0	C		Yes
8	Petchi	24	R	10.5	10.5	N	5.1	D	0	C	0	C	Yes	
9	Kanmani	21	R	4.7	4.7	N	1.1	D	0	C	0	C		
10	Uma	23	R	14	14	N	8.5	D	4.7	D	2.5	D		
11	Radhika	21	R	5.1	5.1	N	1.4	D	0	C	0	C		
12	Devi	23	R	10.5	10.5	N	10.5	N	6.4	D	3.6	D		
13	Vidhya	20	R	8.5	5.5	D	3.6	D	0	C	0	C		
14	Latha	22	L	5.1	5.1	N	2.5	D	0	C	0	C		
15	Divya	20	L	4.5	4.5	N	1.2	D	0	C	0	C		

Masterchart fibroadenoma control group

S.No	Name	Age	Side	Day (	4th week		8th week		12th week		24th week		Side effects	
				volume	volume	chart	volume	chart	volume	chart	volume	chart	DM	Gastritis
1	Kanamal	22	L	7.2	7.2	N	7.2	N	7.2	N	7.2	N		
2	Manju	21	L	9.6	9.6	N	9.6	N	96	N	9.6	N		
3	Muni	24	R	8.1	8.1	N	8.1	N	8.1	N	8.1	N		Yes
4	Poorni	23	R	4.7	4.7	N	4.7	N	2.5	D	1.3	D		
5	Veni	26	R	2.5	2.5	N	2.5	N	1.3	D	1.1	D		
6	Malar	24	L	9.1	9.1	N	10.9	I	12.2	I	13.3	I		
7	Kumari	23	L	8.1	8.1	N	8.1	N	8.1	N	8.1	N		
8	Chella	25	R	12.7	12.7	N	12.7	N	12.7	N	12.7	N		
9	Lucy	21	R	6.4	6.4	N	6.4	N	6.4	N	6.4	N		
10	Fathima	24	L	6.2	6.2	N	6.2	N	6.2	N	6.2	N		
11	Sasi	21	R	4.7		N	4.7	N	4.7	N	4.7	N		
12	Jeya	20	R	10.3		N	10.3	N	8.1	D	7.2	D		
13	Praba	23	L	9.6		N	9.6	N	9.6	N	9.6	N		
14	Bindu	21	L	6.4		N	6.4	N	6.4	N	6.4	N		
15	Eswari	22	L	7.2		N	7.2	N	7.2	N	7.2	N		

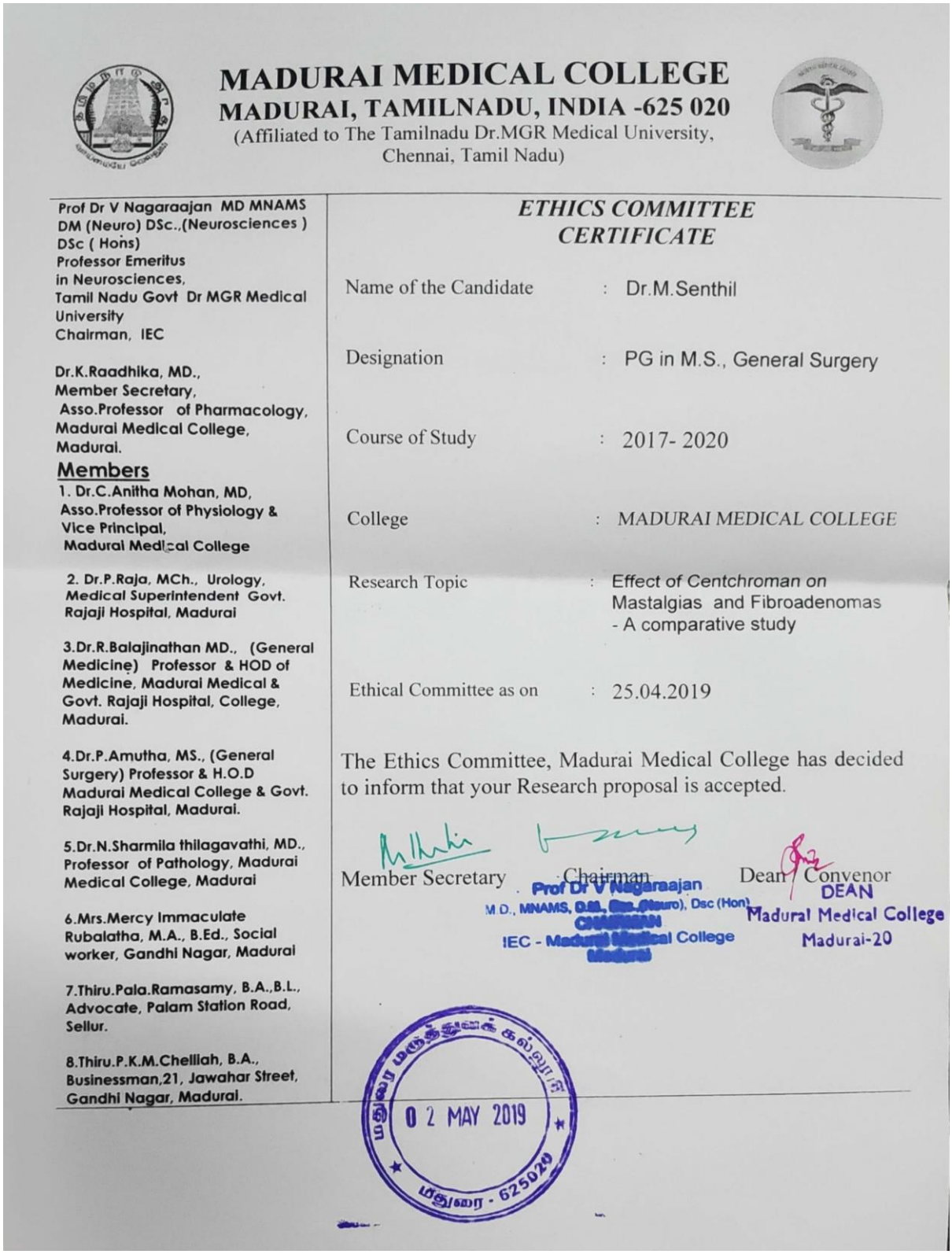
Masterchart Mastalgia study group

S.No	Name	Age	Side	VAS					Side effects	
				Day 0	4th week	8th week	12th week	24th week	DM	Gastritis
1	Saranya	26	R	4	4	2	0	0	Yes	
2	Ramayi	23	R	4	2	2	0	0		
3	Pushpa	24	R	4	4	4	2	0	Yes	
4	Sarika	28	L	6	6	6	6	6		
5	Karishma	21	L	4	4	4	0	0		
6	Thoongi	30	R	2	2	0	0	0		
7	Indira	27	R	6	4	4	2	0		
8	Janaki	24	L	6	4	4	2	0		
9	Lakshmi	23	L	4	4	4	2	0		
10	Fareena	28	L	4	4	2	0	0		
11	Vijaya	22	L	4	4	2	0	0		
12	Meena	30	R	4	4	2	0	0		
13	Selvi	26	R	6	6	6	4	2		
14	Jayanthi	25	L	6	6	6	6	6		
15	Rosy	23	R	2	2	0	0	0	Yes	

Masterchart Mastalgia control group

S.No	Name	Age	Side	VAS					Side effects	
				Day 0	4th week	8th week	12th week	24th week	DM	Gastritis
1	Arivu	22	L	4	4	4	4	4		
2	Selli	24	R	4	4	4	4	4		
3	Ammaponu	25	R	4	4	4	4	4		
4	Semba	29	L	4	4	4	4	4		
5	Reka	27	L	6	6	4	4	4		
6	Shailu	26	L	2	2	2	2	0		
7	Priya	25	R	4	4	2	2	2		
8	Sakthi	26	L	6	6	6	6	6		
9	Pidari	25	R	6	6	6	6	6		
10	Stella	27	R	4	4	4	4	4		Yes
11	Rubini	23	R	4	4	4	4	4		
12	Kanaga	25	L	4	4	4	4	4		
13	Radha	26	L	6	6	6	6	4		
14	Seetha	25	R	2	2	0	0	0		
15	Subatra	28	R	6	6	6	6	6		

ETHICAL COMMITTEE APPROVAL CERTIFICATE



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Tamil Nadu Govt Dr MGR Medical University
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8.Thiru.P.K.M.Chelliah, B.A., Businessman,21, Jawahar Street, Gandhi Nagar, Madurai.

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.M.Senthil
Designation	:	PG in M.S., General Surgery
Course of Study	:	2017- 2020
College	:	*MADURAI MEDICAL COLLEGE*
Research Topic	:	*Effect of Centchroman on* Mastalgias and Fibroadenomas - A comparative study
Ethical Committee as on	:	25.04.2019

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc.(Neuro), Dsc (Hon)
CHAIRMAN
IEC - Madurai Medical College

DEAN
Madurai Medical College
Madurai-20

02 MAY 2019

CONSENT FORM

Title of the project: A COMPARATIVE STUDY ON EFFECT OF CENTCHROMAN ON MASTALGIAS AND FIBROADENOMAS

Participant's name : Address :

The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I have understood the above study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the above study.

Signature of the participant : _____ Date : _____

Signature of the witness : _____ Date : _____

Name and address of the witness :

Signature of the investigator:_____Date : _____

PROFORMA

Name :- O. P. No

Age :- Unit

Sex :-

Occupation :-

Address

Phone no :

DIAGNOSIS:

PRESENTING COMPLAINTS

1) Duration of breast pain
2) Type of breast pain
3) Palpable breast lump

H/O menstrual irregularities

H/O infertility

GENERAL PHYSICAL EXAMINATION

1. General survey
2. Body build and nourishment

3. Appearance

4.Anaemia/Jaundice/Clubbing/

Cyanosis/Lymphadenopathy/

Pedal oedema

5. Pulse

6. Temperature

7. Respiratory rate

8. Blood pressure

LOCAL EXAMINATION OF

BREASTS

1. INSPECTION
2. PALPATION
3. PERCUSSION
4. AUSCULTATION

HISTOPATHOLOGY Report:

ULTRASOUND BREAST Report:

ULTRASOUND ABDOMEN AND PELVIS Report

PLAGIARISM VERIFICATION CERTIFICATE

:

URKUND

Urkund Analysis Result

Analysed Document:	centchroman.docx (D57288850)
Submitted:	10/19/2019 8:55:00 PM
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CERTIFICATE II

This is to certify that this dissertation work titled, entitled "**A COMPARATIVE STUDY ON EFFECT OF CENTCHROMAN ON MASTALGIAS AND FIBROADENOMAS"** submitted by **DR.M.SENTHIL** with registration number **221711124** for the award of **MASTER DEGREE** in the branch of **GENERAL SURGERY** has been personally verified by me in urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 8% percentage of plagiarism in the dissertation.

Guide and supervisor sign with seal