“CONTRACEPTIVE EFFICACY AND SAFETY OF CENTCHROMAN WITH BI-WEEKLY CUM WEEKLY SCHEDULE IN POSTNATAL WOMEN IN A TERTIARY CARE HOSPITAL - A PROSPECTIVE STUDY”

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CERTIFICATE

This is to certify that this dissertation titled **— "CONTRACEPTIVE EFFICACY AND SAFETY OF CENTCHROMAN WITH BI-WEEKLY CUM WEEKLY SCHEDULE IN POSTNATAL WOMEN IN A TERTIARY CARE HOSPITAL-A PROSPECTIVE STUDY"** is a bonafide work of **DR**. **DIVYA. A**, and has been prepared under my guidance, in partial fulfillment of regulations of The Tamilnadu Dr. M.G.R. Medical University, for the award of M.S. Degree in Obstetrics and Gynecology during the year 2019 - 2022.

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DECLARATION

I, solemnly declare that the dissertation titled **"CONTRACEPTIVE EFFICACY AND SAFETY OF CENTCHROMAN WITH BI-WEEKLY CUM WEEKLY SCHEDULE IN POSTNATAL WOMEN IN A TERTIARY CARE HOSPITAL-A PROSPECTIVE STUDY"** was done by me under the guidance and supervision of **PROF. DR. MOHANA, MD., DGO.,** Professor, Institute of Obstetrics and Gynaecology, Government Madras Medical College, Chennai - 08. The dissertation is submitted to The Tamil Nadu Dr.M.G.R. Medical University towards the partial fulfilment of the requirements for the award of M.D. degree (Branch II) in Obstetrics and Gynecology.This has not been previously submitted by me for award of any degree or diploma from any university.

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Last but not the least, I convey my heartfelt gratitude to all the patients participated in this study

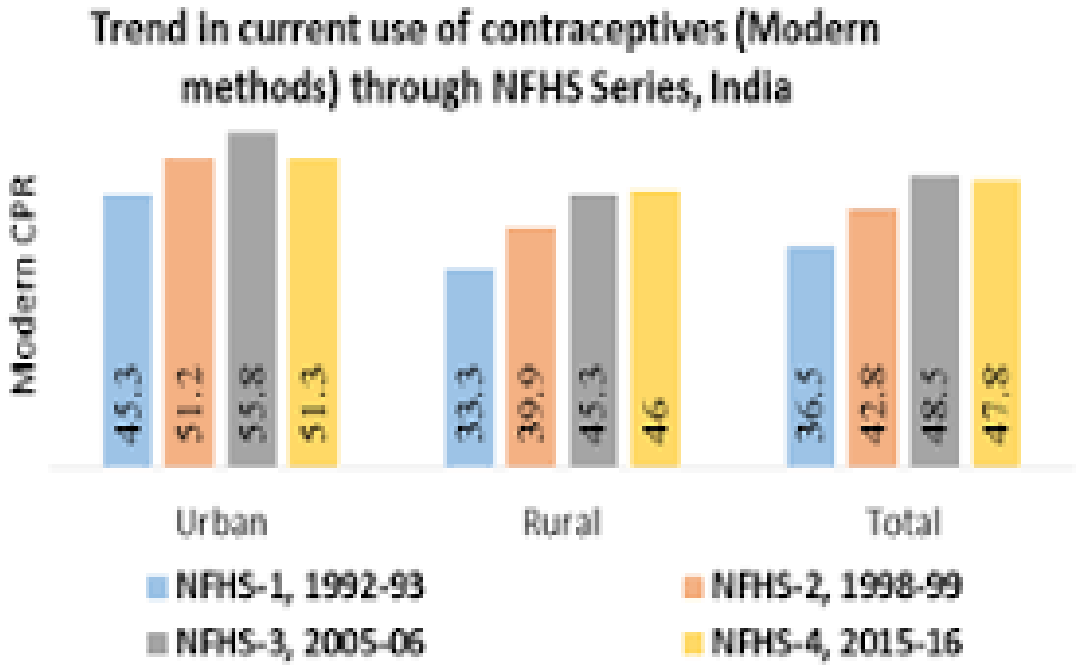
CONTENTS

INTRODUCTION

- 25% of world's eligible couples with an unmet need for contraception lives in India[1]
- Family planning has been of great interest to the Indian Government since our Independence.
- In 1952, India because the first country in the world to launch "National Family Planning Program" [2]

One of the goals enunciated in the National population policy 2000 is to achieve the replacement level total fertility rate of 2.1% by the year 2020. Even though several interventions have been made TFR was still 2.3 per woman in the year 2013. Because of this relatively high TFR there was a paradig shift in our National Policy from "POPULATION CONTROL APPROACH" which was focused on sterilization to "REPRODUCTIVE RIGHTS BASED APPROACH"

Under our national health mission ,family planning is now positioned as critical intervention for improving women's health, thereby reducing MMR and NMR



India's commitments made in the London Summit are articulated in "India's Vision FP2020" [3]

These include

1. Expanding the basket of choices and scaling up the use of the currently available methods
2. Ensuring availability of free commodities and providing services to all clients (including adolescents) through the integrated Reproductive Maternal Neonatal child and Adolescent Health (RMNCH + A) strategic approach.
3. Ensuring access to family planning services to an additional 48 million women by 2020

4. Increasing financial commitment on family planning to more than 2 billion USD.

Key Strategies under Family Planning and Achievements

1)Introduction of new contraceptive choices

- The new contraceptives Injectable MPA (under Antara programme) and Centchroman (Chhaya) were recently added in the contraceptive basket and are available across the country.
- In 2018-19, 9.71 lakh doses of Injectable MPA have been administered and 14.42 lakh Centchroman tablet shave been distributed all over the country.

2) Mission Parivar Vikas:

Mission Parivar Vikas (MPV) was launched in 2016 for substantially increasing access to contraceptives and family planning services in 146 high fertility districts of seven high focus States (Uttar Pradesh, Bihar, Rajasthan, Madhya Pradesh, Chhattisgarh, Jharkhand and Assam) with TFR of 3 and above.

The following Key Strategic Initiatives have been undertaken in MPV Districts:

Delivering Assured Services

- Roll out of Injectable Contraceptive
- Augmentation of PPIUCD services across all delivery points
- Augmentation of Sterilization services through HFD compensation Scheme
- Condom boxes at strategic locations in health facilities
- IEC campaigns

Promotional Schemes

- New Contraceptives have been made available till the Sub-center level.
- Nayi Pehel Kit: A family planning kit to the newlywed couple is being distributed through ASHA.

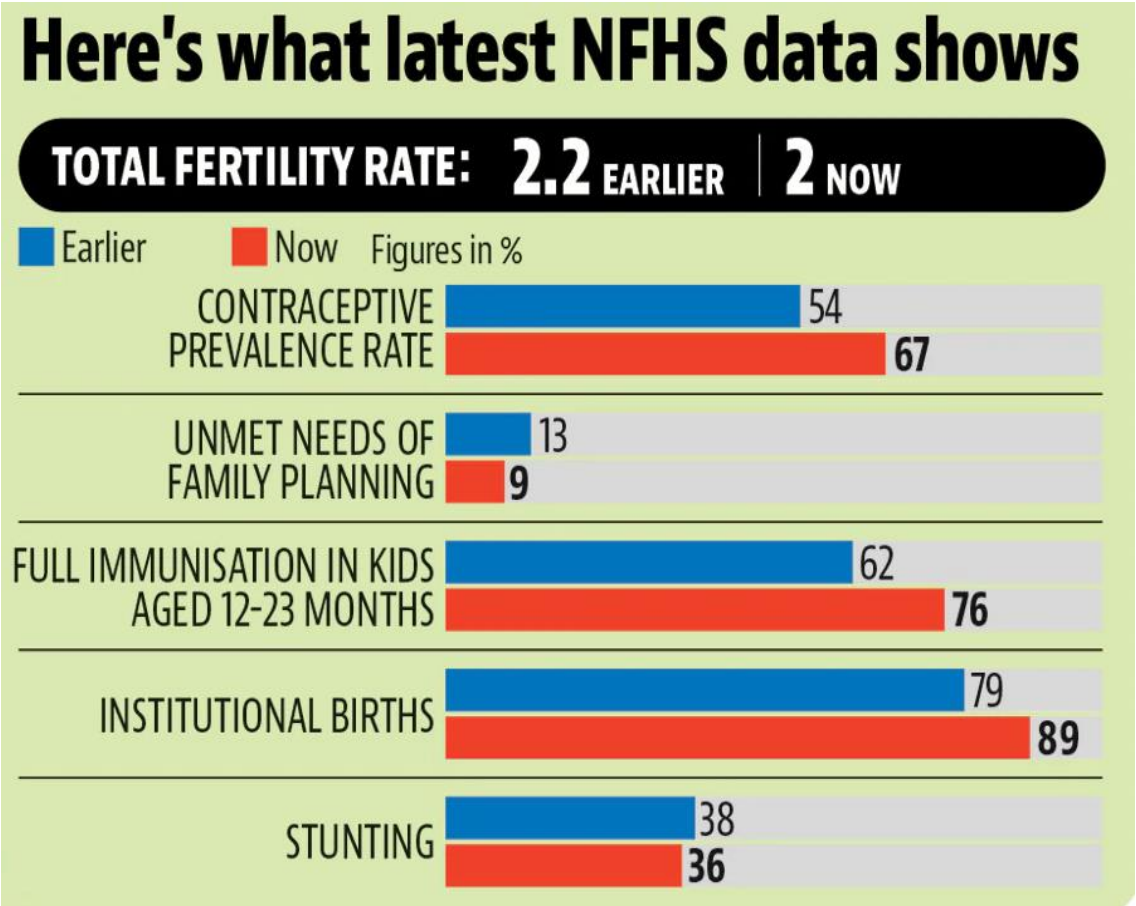
Saas Bahu Sammelans: facilitates and encourages communication between young married women and their mother in laws, to freely discuss matters related to family planning and reproductive health.

1,86,991 Saas bahu Sammelans have been organized in the year 2018-19.

- Saarthi: Family planning mobile van offering information and services at community door step

Approximately, following quantities of Centchroman Contraceptive were procured for supply to States during the year 2017-18 and 2018- 19 (including procurement by CMSS)

ITEM	2017-2018	2018-2019
Chayya contraceptive pills (lakh strips)	**23.99**	**170.27**



QUOTED IN NFHS SURVEY 2019-2021

“Delay the first, postpone the second, prevent the third”

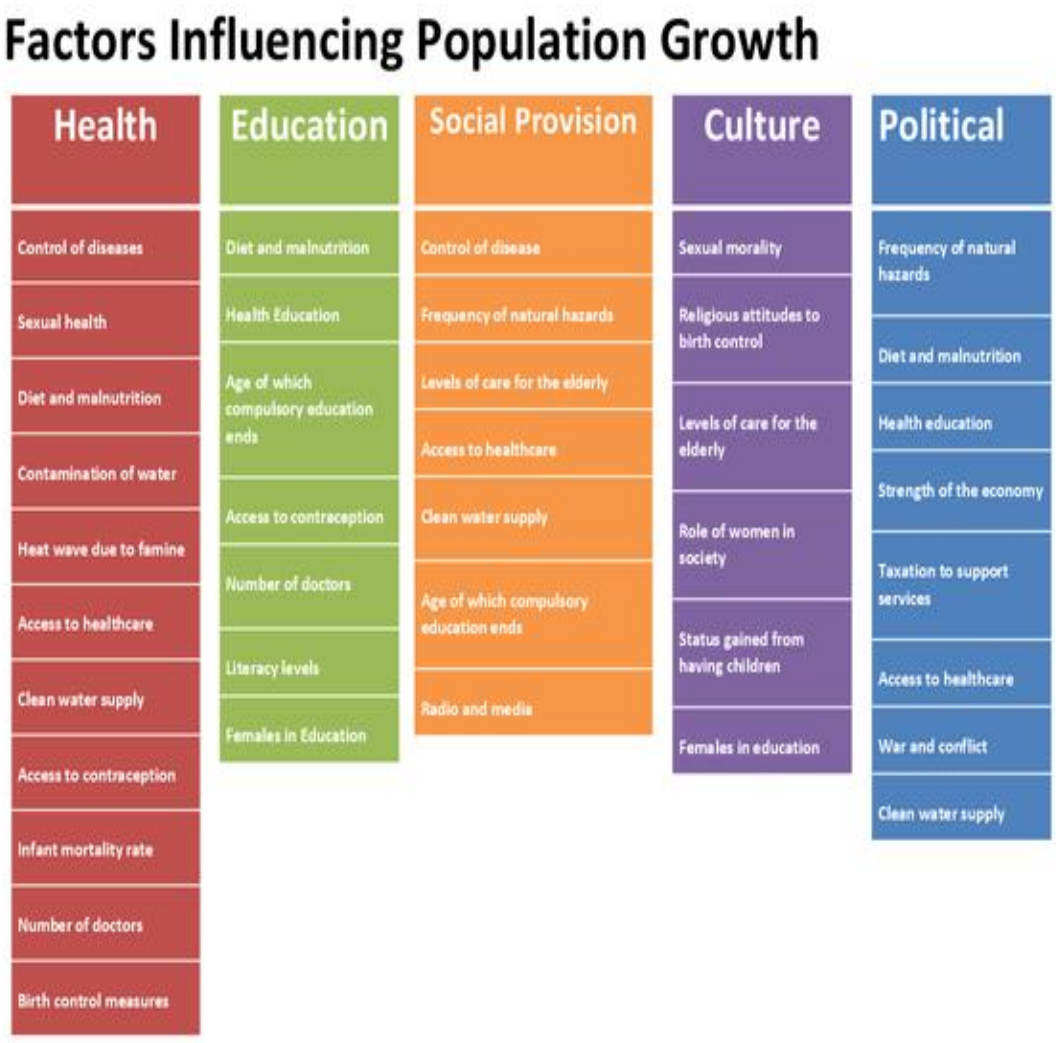
-TAMILNADU GOVERNMENT

Family is a basic unit of society. It is Unit of Service. The independency of family members is an important concept in defining family. Every family is a social system. It has its own cultures, values and rules has structured and basic functions and moves through stages .The fact that some methods of Natural family planning methods can be 99% effective in the avoidance of pregnancy seems unknown to most of the general public including many health care professional .

According to WHO family planning program, it has been defined as a way of knowledge, attitude and also responsible decision by the individuals and couples in order to promote the health and welfare of the family group and thus contribute effectively to the Social development of the country.

Family planning refers to the practice to help the individuals or couples to attain certain objectives.

1. To avoid unwanted births
2. To bring about wanted births.
3. To regulate the interval between pregnancies.
4. To control the time at which births occur in relation to the ages of the parents.
5. To determine the number of children in the family.



Contraception should also be viewed in the widen context of sexual and reproductive health of the individual. The capacity to enjoy and control sexual and reproductive behavior is a key element of sexual health but the same time it is accepted that birth intervals of at least 2 years improve maternal and infant mortality .

In addition survey conducted Post – Partum indicate that women may wish to discuss contraception antenataly post hospital discharge, preferably in the contest of general education about maternal and child health .

The National program in India offers five modern contraceptive options

1. Combined oral contraceptive pills
2. Condoms
3. IUDs

Two limiting methods

1. Male sterilization
2. Female sterilization

A significant development in the recent years is the policy decision of “Government of India” to introduce injectable contraceptives (DEPOT MEDROXY PROGESTERONE ACETATE) in the public health delivery system.

Contraception in the postpartum periods

Since India has an exponential increase in Institutional deliveries of more than 80%. There is a need to increase the choices other than postpartum sterilization and PPIUCD

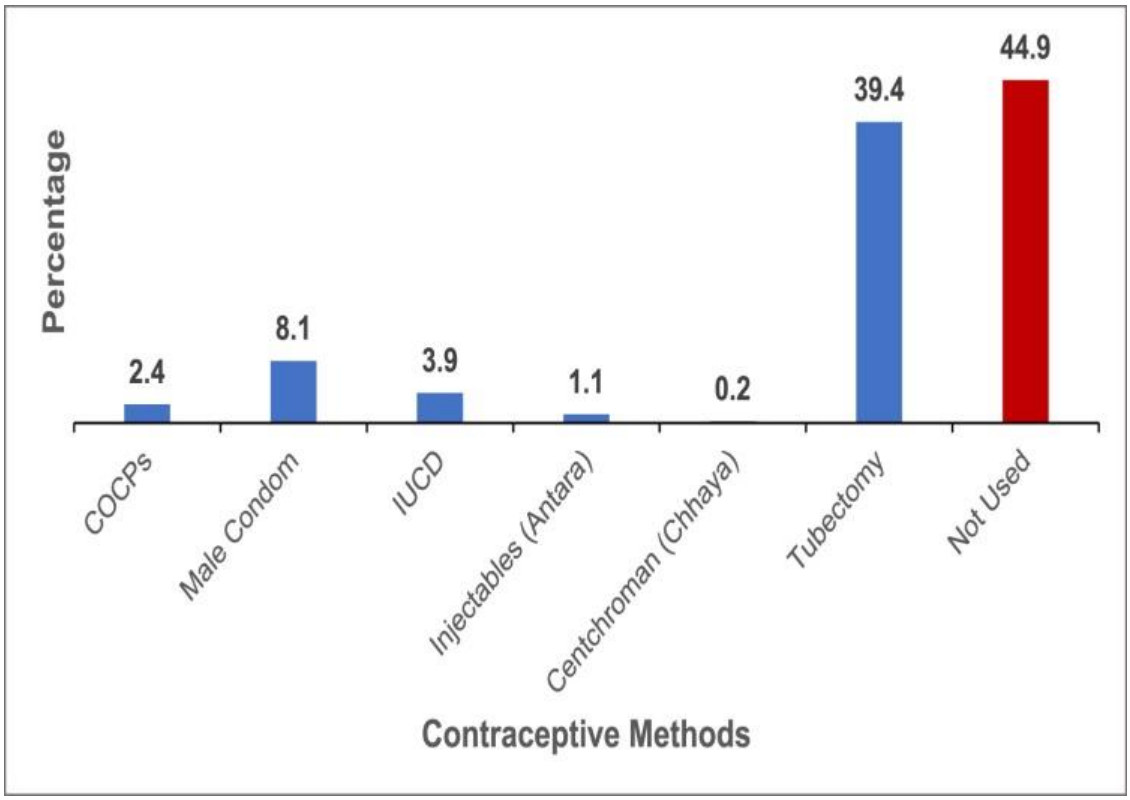
Two more promising agents were introduced

1. Progesterone only pills
2. Centchroman

The potential of Progestin – Only Pills (POPs) as option for spacing births in the postpartum period is well recognized. In the revised World Health Organization's (WHO) Medical Eligibility Criteria (MEC) for POPs have been moved from Category 3 to Category 2 for < 6 weeks breastfeeding women. Which means that they can be used in the immediate postpartum period as the advantages outweigh the risks. [4]

Centchroman is a promising non hormonal option for spacing which is known as once-a-week oral contraceptive under the name "Saheli" [5]

Clinical trials conducted on women of reproductive age and market surveys has demonstrated the drug safety, efficacy and also acceptability. [6]



REVIEW OF LITERATURE

History in India[5 & 6]

- In 1960 to 1990 extensive research has been done by CSIR - CDRI / ICMR
- In 1990 Centchroman has been approved by DCGI
- In 1992 the drum has been marketed as a contraceptive under the Trade name SAHELI
- In 1995 the drug has been subsidized under social marketing scheme of Government of India.
- In 2005 launch of NovexDX for DUB
- In 2010 included in United State Pharmacopoeia as "ORMELOXIFENE HYDORCHOLORIDE"
- In 2012 launch of TATKAL as emergency contraceptive
- In 2013 launch of Novex for mastalgia and fibroadenoma of breast
- In 2016 launch under the brand name " CHHAYA" for public health sector

Key milestones on evolution of centchroman. CDRI, Central Drug Research Institute.

SCOPING REVIEW

- In a scoping review, which was conducted in the year 2019 based on 5 stages of Arksey & O'Malley's scoping review frame work, a research was conducted beginning in the year 1970

Excluding the studies conducted in animals, conducted before 1970 and excluding the studies which were focused mainly on non-contraceptive uses of Centchroman there were 33 studies reported on effectiveness, side effects, pharmacokinetics and mechanism of action of drugs.[7]

Among the 33 studies 8 studies which included 5 clinical trails & 3 observational studies reported the effectiveness of Centchroman.

One of the clinical trial which was in its phase 3, conducted among 1500 individuals, [8] Centchroman was given us a “30 mg once-a-week” contraception on the first day of cycle and then one tablet was taken on the same day every subsequent week. An additional tablet has to be taken on the first day of every subsequent cycle irrespective of the weekly tablet. Analysis of the study was method failure-4.1% and effectiveness was 95.9%

Phase 4 clinical trial in its post marketing surveillance conducted by ICMR, INDIA which was a non randomized clinical trial with CuT users being the comparison group. In the study 30 mg Centchroman twice a week for 2 weeks followed by once a week there after. Analysis of the trail was method failure 2.6%, nil user failure and the effectiveness was 97.4%.[9,10]

Among the 3 observational studies conducted, the effectiveness of the Centchroman was 93% to 100%[11,12]

` Amount 33 studies, 13 studies reported the side effects of Centhchroman as a weekly contraceptive pill. Most common side effects documented were menstrual irregularities and changes on Ultra sound examinations

Among the menstrual irregularities 4 studies reported short cycle less than 20 days, 6 studies reported prolonged cycles greater than 4 days and the 3 studies reported continuous bleeding among continuous users. **13,14,15**

Out of 13 studies 7 studies reported Ultra sound findings among Centchroman users such as bulky Uterus with distorted endometrial cavity and transient unilateral ovarian enlargement.**16**

OBSERVATIONAL STUDIES IN INDIA

- In another prospective study conducted about Centchroman with special reference to its contraceptive benefits in 2016 in Kerala, India which was conducted among 153 patients concluded Centchroman as a safe non steroidal contraceptive for pregnancy spacing, not altering carbohydrates or liquid metabolism and hence can be used in women in whom OC pills are contra indicated. This study also reported Centhroman does not cause pathological ovarian enlargement **17.**

  In the analysis of the study 60% patients were in the age group of 20-24 yrs,93 % of patients had one child,43% of the acceptance was following MTP,35% were following delivery and 22% were interval acceptance.

Menstrual complaints were noted in 45 % of acceptors which was high compared to 8-10%.Pearl index of the study is 2 which was higher compared to 1-1.8.Resumption of fertility following discontinuation of centchroman was prompt.

- In yet another study conducted regarding Centhchroman and its contraceptive benefits at Arunachal Pradesh, India in 2019 which was conducted among146 women also concluded the compliance of therapy with this drug duo to its convenient dosage schedule. The drug has good therapeutic efficay under favorable side effects profile. [18]

38.35% were in post abortal group,36 % were following delivery and the interval was 25.4%.Pearl index was 2.05.The major menstrual complaint was delayed cycles seen in 15 % of acceptors.The study also recommended proper stratagies to make it easily accessible to women at various stages of reproductive cycle ,giving counseling and follow up messages in complete and easily understandable language will improve te contraceptive pill user in India.

STUDIES RELATED TO PHARMACO-KINETICS OF THE DRUG

- Among the various studies conducted for analysis of the pharmacokinetic and pharmaco dynamic actions of the drug,conducted in 1992,at Dr.Ambedkhar university agra among female rats, it is concluded that the half life of cenchroman in the the target tissue that is uterus is 5 days.The still more long half life of centchroman of 7 days in the women is attributed due to entero hepatic circulation and its large volume of distribution.The rationale for using centchroman as once a week contraceptive is supported because of the long half life of 7 days in the clinic pharmacological study.

- Another study conducted in 1996 by J.k.Paliwal analyzing the pharmaco kinetic behavior and tissue distribution of centchroman and its 7-desmethyl centchroman after a single dose of 12.5 mg per kg per orally in young female rats concluded that high tissue to plasma concentration ratio of desmethyl cenchroman than the centchroman indicates its greater affinity for tissues.**19**

- In a study conducted in CDRI,Lucknow in 2009 by Jawahar lal regarding the drug interaction,coadministration of tetracycline

yielded significantly higher concentration and shorter time to reach maximum concentration of the drug.They also concluded that amount of drug ingested by infants through breast milk is unlikely to be of any physiological significance and also they did not recommend excluding breast feeding mothers from mass centchroman therapies .

STUDIES RELATED TO EFFECTIVENESS OF CENTCHROMAN

- Roy et al in 1976 concluded centchroman as a potent anti estrogen and week estrogen **20**
  - When given daily induces ovulation by increasing FSH/LH ratio
  - When given once a week no change in FSH/LH ratio
- Singh et al in 1986 concluded that in humans contraceptive effect of centchroman is due to
  - Slight increase in zygote transport
  - Accelerated blastocyst formation
  - Suppression of endometrial maturation

  The net effect is implantation is prevented
- In a study conducted in 1988 by Puri et al ,30 mg dosage given weekly in 10 centres among 398 women followed for 13 months ,the pregnancy rate is 2.84%

When 30 mg dose given weekly the rate of delayed menses is 8%

When the same dose is given twice weekly the rate of delayed menses is 6%

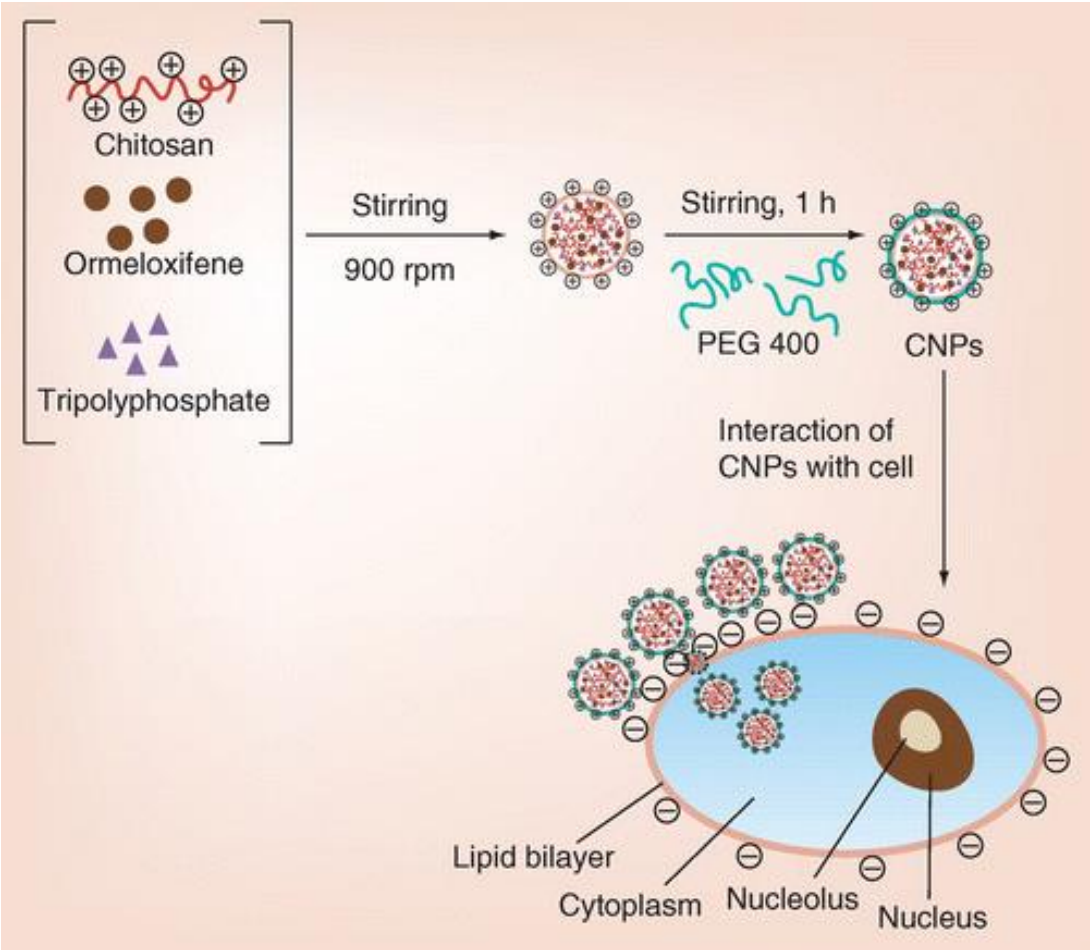
STUDIES REGARDING NEW FORMULATIONS OF THE DRUG

- Regarding various formulation of the drug ,an article was published in 1997 regarding the formulation and invitro evaluation of centchroman loaded biodegradable microspheres .

  The present investigation analysis the microspheres of centchroman with some long acting biodegradable carriers namely Alginate,Chitosan ,Ovalbumin and poly lactico glycolic acid(PLGA).All the carriers have classified as non toxic and are biodegrable in nature and have been extensively used to achieve controlled release of a variety of drugs.

- Pluronic Polymer-Based Ormeloxifene Nanoformulations Induce Superior Anticancer Effects in Pancreatic Cancer Cells. This research article presented in 2020 at university of TEXAS provides a proof-of-concept foundation that pluronic polymers can be used a successful delivery vehicle for ormeloxifene therapeutics. These formulations have superior anticancer activities against pancreatic cancer cell lines than free ormeloxifene. ORM nanoformulations induced apoptosis through decreasing the mitochondrial membrane

potential and altering the expression of apoptosis-related two key proteins and the ultrastructure of these cells. Based on these results, we believe that ORM nanoformulations could be a promising treatment regimen for pancreatic cancer. These results are warranted to further examine the anticancer efficacy of ORM nanoformulations in clinically relevant mouse models.**21**



STUDIES REGARDING NON CONTRACEPTIVE BENEFITS OF CENTCHROMAN

- In recent studies, one hundred women participated in a clinical study,60 mg of ormeloxifene was given to each woman twice a week for three months followed by once a week administration for one month. Patients were monitored for six months. Menstrual blood loss was observed by a pictorial blood loss assessment chart (PBAC) score as well as visual analog scale (VAS).

The results showed a significant reduction in median PBAC score ranging from 252 to 102.8 in patients treated with Ormeloxifene and the presence of blood clot reduced from 64 to 12%. On the other hand, the incidence of dysmenorrhea 18 drastically suppressed from 22 to 8% and the mean endometrial thickness was decreased from 9.7 to 6.7 mm45.

However, there was an increase in PBAC score to 112.7% when treatment was stopped after six months but lower than the pretreatment level. There was a significant reduction from 64 to 12% in patients with initial passage of clot and massive improvement of patients with mild or severe dysmenorrhea (22 to 12%). The fact that ormeloxifene is a safe and effective therapeutic option for the management of Menorrhagia

cannot be disputed because of its higher potency and minimal side effects.

Pictorial blood loss assessment chart:

	Level of soiling	Score
Pads	Light	1
	Moderate	5
	Saturated	20
Clots	Size of a rupee coin or smaller	1
	Larger than a rupee coin	5

Regulatory safety studies of centchroman

Pharmacological effects

- Three months of toxicity studies of centchroman in rats and rhesus monkeys were found to be non-toxic.
- The compound showed no adverse impact on humans during preclinical trial up to a dose of 120 mg per day**22**. Centchroman has a lower ulcerogenic index (0.8) compared to phenylbutazone (1.7) and is less likely to cause gastric irritation. Its intraperitoneal and oral LD50 is higher compared to phenylbutazone and does not in any way produce leucopoenia and eosinopenia as seen in phenylbutazone.

- Its anti-inflammation and anti-implantation effect is exerted directly on inflamed tissues and does not mediate its weak estrogenic agnostic activity or via pituitary- adrenal **axis 23**
- Using 30 mg weekly dose of centchroman in women for one year did not cause any hyperaggregability of platelets.**24** The antiaggregatory effects of centchroman are as a result of platelet cyclooxygenase inhibition, and it is an evidence of thromboxane–B2 synthesis as well as inhibition of in malonaldehyde .
- No significant effect on thyroid weight, 134Iuptake, and conversion ratio or excretion rate of 24-hour urinary 17-OH ketosteroids was observed when upon five consecutive administration of centchroman to female rhesus mon.
- When the dose of centchroman was increased to 30, 60 and 120 mg/day for six weeks in normospermic men, it resulted in decreased in urinary 17 –OH ketosteroids in all cases. **25**

Toxicological effect Centchroman has shown an excellent therapeutic index, upon 12 months administration in rats and rhesus monkey

- With no evidence of biochemical, hematological or histopathological toxicity. **26**

- No evidence of congenital abnormalities of fetuses, anomalies 21 or aborting was reported during six weeks of oral administration to rabbits and mice.
- DLcentchroman and its enantiomers possess no mutagenicity, genotoxicity and with a reduced toxic effect on known mutagens and no carcinogenic effects have been observed following life-term administration to rats **27**
- . Ormeloxifene has a few side effects which include Delayed menstruation, Nausea, Vomiting, headache and Weight gain62 . Also, women with the desire of becoming pregnant must discontinue taking the drug. However, Ormeloxifene should not be taken by patients with any of the following problems such as polycystic ovarian disease, cervical hyperplasia, the recent history of jaundice or hepatic impairment, severe allergic state, TB, renal impairment. **28**

ROLE OF CENTCHROMAN IN FERTILITY CONTROL AND REPRODUCTIVE HEALTH

- India's population stands second in the world and is growing rapidly.

- Fertility control plays an important role in promoting reproductive health of female from teens to perimenopausal epoch.It is also important for socio-economic development of the country.

By imparting effective control,we can decrease the colossal MATERNAL MORTALITY RATE by atleast 25 percent.In the international conference on population and development,it was rightly pointed out that the main aim of contraception is promotion of reproductive health.

Eventhough several contraceptive methods have been there throughout the century,the need for a safer alternative to OC pills has been there since the sixties.This provoked the scientists to discover a non steroidal oestrogen antagonists.

Centchorman was derived from benzofuran and ethamoxytriphetol (MER-25) compounds as an orally taken birth control/family planning drug after several years of perseverance and hard work of Dr. Nitya Anand & team in 1971. The Centchroman was tested in experimental animals, rats, dogs, and monkeys before human use for contraceptive purposes. The preclinical harmful effects have also been

tested on experimental animals such as rats, beagle dogs, rhesus monkeys, and rabbits and found safe.

After 22 years of extensive research,scientists at the CDRI,LUCKNOW has developed CENCTCHROMAN ,the world's first non steroidal contraceptive agent.The drug was finally approved in 1991.It was marketed as SAHELI and CHOICE 7 in 1992.India has now licensed centchroman in NEHP under the name CHHAYA from APRIL 2016.

NEED FOR EMERGENCE OF CENCHROMAN AND HOW IT WAS

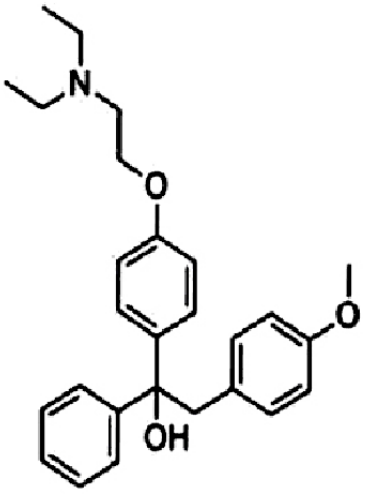
The Ministry of health and family welfare called upon CDRI,Lucknow in 1960 to develop ideal contraceptive for family planning.

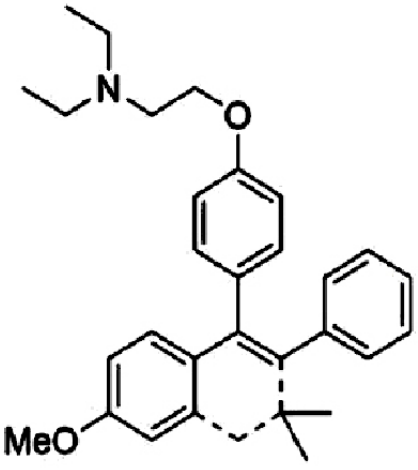
In 1960,US –FDA approved steroidal OC pills with a few riders due to patient worrisome sideaffects.Further the OC Pills prevented pregnancy by suppressing ovulation,by disturbing HPA axis.

CDRI was very particular of the fact that contraceptives are used by young women and they should not be disturbing their normal reproductive function.At that time,LERNER ET AL published the first non steroidal estrogen antagonist,MER-25 which antagonized the activity of estrogen without disturbing ovulation.Surprisingly it also prevented pregnancy in rats when given post coitally.

CDRI from the beginning was interested in the development of post coital contraceptive which will neither affect ovulation nor HPO axis and also free from side effects of steroidal contraceptives.

MER-25 seemed to meet the the above mentioned requirements and CDRI had decided to design a non steroidal post coital contraceptive .It was nemed Centchroman ,a chroman derivative developed by CDRI.





At CDRI,it is also known as 67/20,as it is the 20 th compound synthesized in the year 1967.WHO has approved ORMELOXIFENE as INN(International non proprietary name for the product CENTCHROMAN.Under the WHO ATC system,the code for ormeloxifene is GO3*C04

Ormeloxifene is a mixture of d and l isomers.Both the isomers have been isolated and had post coital contraceptive action in rat.

This is a selective estrogen receptor modulator(SERM) and it has selective estrogenic and anti-estrogenic effects.It suppresses the oestrogen receptors in ovaries ,uterus and breasts but stimulate bones.

PHYSICAL PROPERTIES OF CENTCHROMAN

- Ormeloxifene is a white crystalline solid with molecular weight 457 g/mol and has a melting point of 165 -166°C.
- It is soluble in organic solvents such as Ethyl acetate, dichloromethane, chloroform, acetone, methanol, and ethanol, but sparingly soluble in water, HCl, NaOH, and isobutanol**29** .
- It is a very stable compound under normal conditions and can retain its physical characteristics and biological activities for over

three years when stored in aluminum strips or glass container at room temperature.

- Previous studies have shown that the racemic mixtures of Ormeloxifene can be resolved into D- and L- enantiomers with L-isomer showing more receptor binding potency and about two-fold higher anti-implantation activity in rat than D and DL-ormeloxifine**30**

Pharmacokinetics and bioavailability of Centchroman.

- Centchroman is a lipophilic drug and possesses both pharmacodynamics and pharmacokinetic properties. **31**
- This drug shows low binding affinity to plasma albumin ,which is an evidence of its low binding affinity to albumin and has no interaction with steroids such as cortisol, testosterone, progesterone, and estradiol**32** . It is clear that centchroman does not compete with steroids to a specific binding site and also shows no competition with nonsteroidal agonistics such as diethylstilbestrol nor steroidal antagonistic like tamoxifen**33**.
- Studies have demonstrated that the liver metabolized centchroman and is quickly excreted from the body through faces**34**. It has also been proved that perfused organs like spleen, liver, and lungs can

retain more of this drug as compared to the less perfused organs such as muscles and pancreas

- 7- Desmethylated ormeloxifene, the active metabolite of centchroman is formed in a matter of an hour after a patient has taken the drug and peaks within 24 hours**35** . A higher 13 concentration of this drug as well as its metabolites can be detected in the spleen, liver, lungs, adipose tissues as well as the uterus after administration**36** . It is factual that centchroman and its metabolites accumulate higher in tissues than the plasma and its concentration in tissue or plasma is higher compared to its major metabolite . In human, the overall half-life of ormeloxifene and its primary metabolites with either single dose administration of 30 mg or 60 mg was detected to be around 168 hours whereas that of rats and lower mammals was about 26 hours for 12.5 mg/kg of centchroman**37** . Studies have shown that rats and lower mammals metabolize centchroman faster than humans.
- The maximum serum concentration (Cmax) of centchroman depends on the dose used, 30 mg dose has a Cmax of about 55.53 ± 15.43 ng/ml while 60 mg dose has Cmax of 122.57 ± 6.25 ng/ml32 .

- Also, the Cmax for 30 mg dose (twice a week for 12 weeks) in breast cancer patients is 54.98 ± 14.19 ng/ml and 60 mg dose for a month or a year is 135 ± 15.5 ng/ml.
- The Cmax of Centchroman and its half-life are quite similar in both nursing and non–lactating mothers and it is estimated, about 2.5% of the drug is excreted in milk but this is less likely to have any physiological effect on a breastfeeding child.
- No significant differences were observed in an amount of drug accumulated or time taken for maximum accumulation when multiple repeating doses were administered to adult female volunteers**38** . In rats, a low dosage of centchroman does not affect the hypothalamuspituitary-ovarian response, but the opposite occurs at much higher dose**39** . The above data is proof that ormeloxifene is a favorable and safe drug candidate for various health problems.

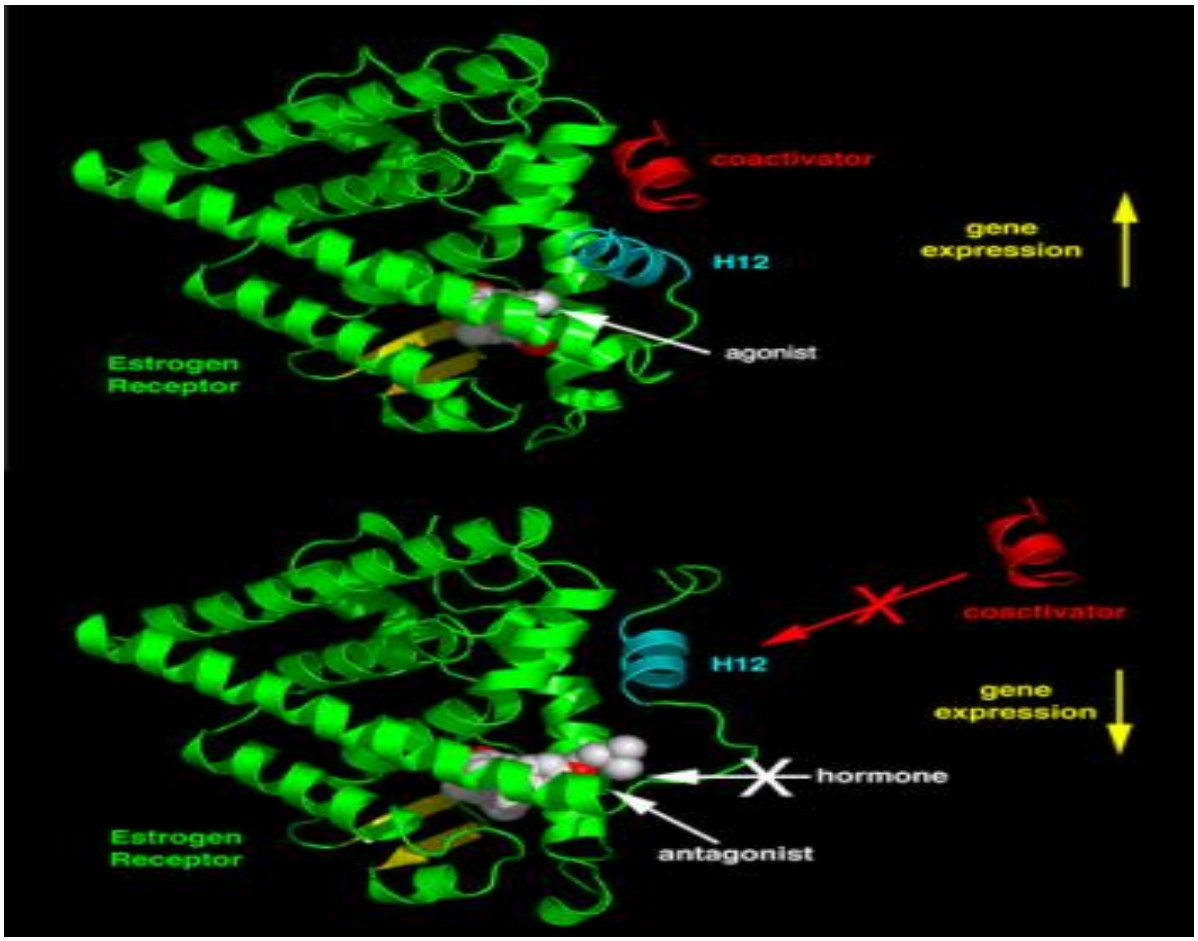
STRUCTURAL ACTIVITY RELATIONSHIP OF CENTCHROMAN

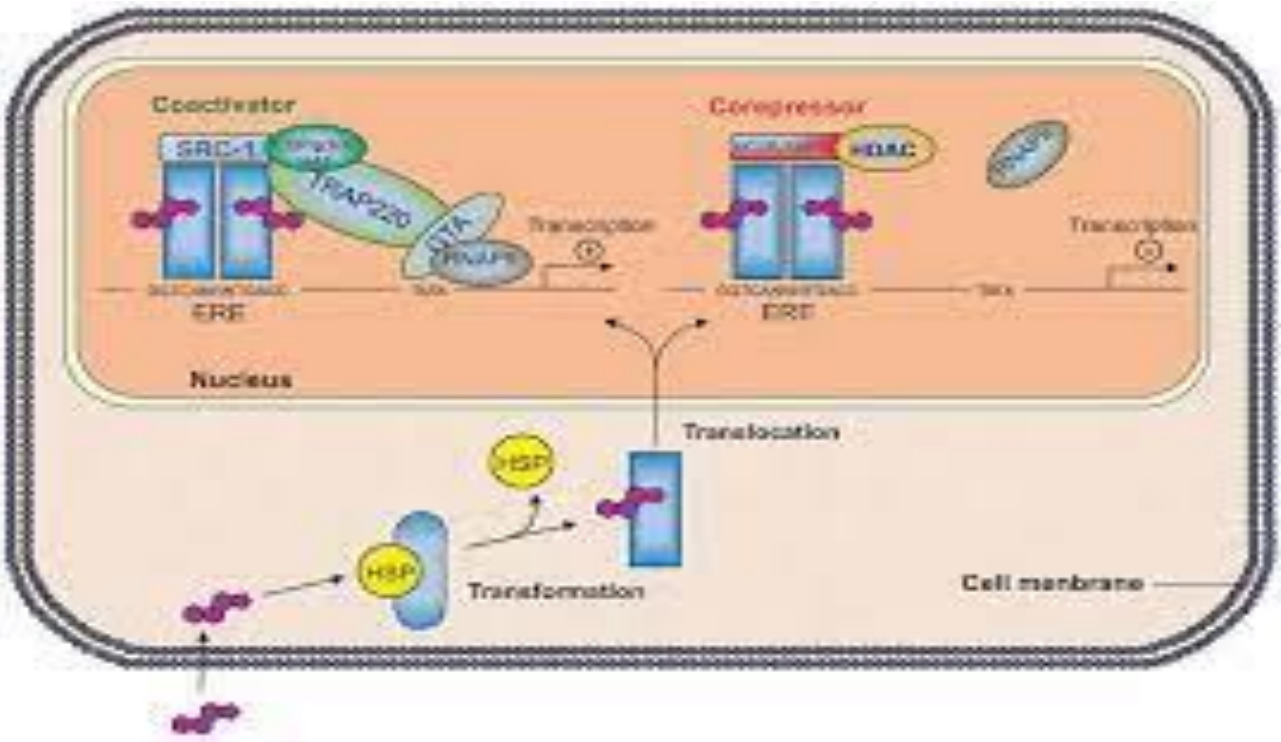
- Methoxy group at position C-7 is replaced with a phenolic group improves receptor binding affinity35 . Therefore, a free OH group at the C-7 position is essential for dynamic binding to the estrogen receptor (ER)

- The receptor binding affinity, estrogen antagonistic and anti-implantation activities of centchroman is as a result of the pyrrolidinoethoxy side chain at p-4-phenyl position37
- Replacement of 3-nbutylamino-2-hydroxypropyloxy moiety with tertbutyl-aminoethoxy increased the anti-implantation activity of centchroman, 3,4-diaryl coumarins, and chromans to 2.5 – 5 fold40 .
- Stepwise increase in relative binding activity was observed when α- and β- methyl groups were introduced at the C-2 of both cis and trans-3,4-chroman

MECHANISM OF ACTION

- Ormeloxifene is a Selective Estrogen Receptor Modulator which acts as an estrogen antagonist and has anti progestogenic activity .
- It has significant antioxidant activity which could be the reason for its use in various gynaecological and other conditions.
- Ormeloxifene is a 3 rd generation SERM. It is a nonsteroidal estrogen antagonist which has high affinity to the estrogen and shows estrogenic activity in some tissues such as vagina, bone, cardiovascular, and central nervous system and it has antiestrogenic effect in breast and uterus.


coactivator
H12
gene expression
agonist
Estrogen Receptor
coactivator
H12
gene expression
hormone
Estrogen Receptor
antagonist


Coactivator
Corepressor
SRC-1
TRAP220
HDAC
ERE
ERE
Nucleus
Translocation
HSP
HSP
Transformation
Cell membrane

The chemical structure of ormeloxifene is trans-7-methoxy -2, 2-dimethyl-3-phenyl-4 (4-(2-pyrrolidinoethoxy) phenyl (-chromanhydrochloride) .The drug competitively binds with the cytosol receptors and it not only blocks them but also cause prolonged depletion of the receptors, so that its action lasts longer even after withdrawal of drug.

It is well absorbed from the GI tract and it attains a peak level in 4 hours and its terminal half life is 170 h. It has little affinity to plasma proteins.

The contraceptive action is probably due to its action on utero-embryonic asynchrony and failure of implantation.It has no deleterious effect on gonadotropin release.It does not inhibit ovulation but it delay the the ovulation by prolonging the follicular phase.It also does not inhibit corpus luteal function.Contraception action is due to disorganized endometrial end organ response to the reproductive steroids.

The antifertility effect of ormeloxifene is due to

1. Its potent ostrogenic effect completely blocks the mitosis in uterine epithelial tissues.the endometrial development is reduced leading to poor mitotic activity in the luminal glandular epithelium and

stroma. The effect is achieved at a lower dose of 30-60 mg per week.

2. It also has week partial inhibitory effect on stromal mitosis reflecting a week anti progestational action.These strong anti-estrogenic and weak anti-progestational actions prevent proper endometrial decidualisation.
3. Defect in ovum transport is another added contraceptive benefit. Tubal blocking of embryos at the ampullary isthmic junction occurs either because of direct action of the drug on pre-implantation embryos or mediated through an alteration of tubal function.
4. Other actions include delayed implantation and reduced rate of zonal shedding by pre-implantation blastocyst'
5. By its anti oestrogenic effect,it inhibits cervical mucus sperm interaction and transport.

If user failure could be taken care of the drug is comparable that of the best low dose OCP such as desogestrel and ethinyl estradiol combinations.

It is a very good post coital contraceptive agent with 1% failiure rate.The dosage is 60 mg taken 2 doses ,12 hours apart within 24 hrs of

coital exposure.It is 100% effective when taken between days 1 to 4 of exposure.The post coital contraception is because of its effect on zygote and ovum transport and blastocyst development.

The advantages of ormeloxifene over hormonal oral contraceptives are lesser incidence of vomiting, vertigo, weight gain, hypertension and breakthrough flow. It does not cause any thrombotic episodes, adverse effects on lipid profile and also no risk of cancer. It does not have any androgenic, antiandrogenic or progestational properties. It does not affect the secretions of pituitary, thyroid or adrenal hormones in its contraceptive doses.

If pregnancy occurs when the patient is on ormeloxifene, the treatment should be discontinued and pregnancy should follow the natural course as there is no risk of teratogenesis with centchroman.

Prominent side effects are nausea, headache, prolongation of menstrual cycles. Jaundice or hepatic dysfunction, polycystic ovarian disease, cervical hyperplasia, tuberculosis, renal disease or hypersensitive are contraindications for its use.

It is being investigated for the treatment of osteoporosis, breast and endometrial carcinoma. There is a considerable evidence for its Anti-inflammatory activity and used for various gynaecological conditions.

The anti oestrogenic action of chhaya varies with the concentration gradient of the drug

1) At 30-60 mg dosage per week,it blocks mitosis in the uterine epithelial tissue.This prevents decidualisation of endometrium and affects the implantation and act as a contraception
2) In a dose of 60-120 mg per week,it changes cervical mucus transportation and affects the contraception
3) At 120 mg dosage per week,it affect the neuroendocrine axis and induce gonadotropin synthesis,its release and ovulation.At this concentration the anti oestrogenic effect is released by decreased maturation index in vaginal cytology

Drug-drug interactions

- Oral administration of tetracycline and other non-steroidal anti-inflammation drugs like ibuprofen produces no effect on efficacy or terminal half-life of centchroman, but there was a significant increase in maximum serum concentration, (Cmax) from 22 to 30 ng/ml and decrease tmax from 12 to four hours in rats **40 .**

- Similar effects were observed when lactic acid bacillus spores were included in the regimen, Cmax increased to 47% and AUC0- ∞ of 34% of centchroman with a drastic reduction in tmax **41.** There is, therefore, no known drug-drug interaction with centchroman, devoid of side effects and safe for prolonged use.

CONTRACEPTIVE BENEFITS OF CENTCHROMAN

The main effect of centchroman appears to be on endometrial receptivity.Centchroman appears to exert its contraceptive action by producing asynchrony between blastocyst movement and endometrial receptivity to blastocyst resulting in inhibition of implantation in the uterus

.

It is the only contraceptive which neither suppress ovulation nor interferes with the hypothalamic-pituitary and ovarian axis. It has high level of safety and is virtually free fom side effects except for a delay in about of 8% of menstrual cycles which is not confined to any women.

The published data with centhroman at the 30 mg bi weekly dose regimen has reported an acceptable pregnancy protection rate of 1.83 and cumulative pregnancy protection(PEARL INDEX-1.83) and cumulative pregnancy protection life table analysis at 12 months of 1.63

NON-CONTRACEPTIVE BENEFITS OF CENTCHROMAN

- Other than its contraception and interception benefits,it also has benefits to the patients with the use of low dose oral contraceptives. Many of these benefits are shared by cenchroman. But centchroman does not cause any alteration in endocrine, biochemical and metabolic synthesis.
- These benefits are based on selective estrogenic and non-estrogenic properties of the drug.
- Specific Antagonist action on uterine endometrium.Ormeloxifene also inhibits the growth of cisplatin resistant ovarian cancer cells.It also decreases the incidence of epithelial ovarian cancer,pelvic inflammatory disease,ectopic pregnancy and iron deficiency anemia.
- Due to its estrogenic action,centchroman can be used to relieve pre menopausal symptoms such as hot flushes,fatigue,insomnia and headache.It can also used as contraceptive in pre menopausal subject.
- On bone merabolism,it supports bone metabolism like combined oral contraceptives pills without affecting the coagulability of blood.It also inhibits osteoclastic bone resorption .

- Regular and prolonged use can also improve the pattern of menstrual cyclicity.

Centchroman and hormone-related disorders

❖ **Abnormal uterine bleeding**

- Menorrhagia affects about 33% of women at some stage in their life and its management has been a challenging task and available drugs prescribed for this disorder don't have consensus for medical treatment.
- Menorrhagia occurs as a result of uterine abnormalities or large fibroid and is sometimes associated with systemic disorders.There have been several medical options such as anti-inflammatory drugs, Danazol and cyclical combined oral contraceptive pills for the treatment of AUB but cost and adverse affects are concerning features.

Centchroman is an estrogen antagonistic on uterine and breast tissues but have agonistic action on bone, vagina, cardiovascular and the central nervous system. It has been revealed that it has no uterine stimulation; it maintains a better function of the brain, lower cholesterol level and has no increased risk of breast cancer and prevents bone loss.

The effect of centchroman on the management of menorrhagia and endometriosis was observed when administered as a contraceptive.

- **Bone loss (Osteoporosis)**
  - According to world health organization , Osteoporosis is a condition where the patient spinal bone mineral density is less than 2.5 standard deviations below the mean of young, average adult of the same gender.
  - It is a condition of increased concern in adults where the bone has been lost to the extent that it is unable to function very well to support its regular activities and this may result in the risk of spontaneous or mild trauma fractures.
  - This condition is highly observed in postmenopausal women with about 75% lifetime risk **42** . There has been an unmet medical need as a result of yearly increased in the number of aged people due to continual increased in life expectancy worldwide.
  - The FDA has recently approved many drugs including selective estrogen receptor modulator, Evista, that can be used to suppress further bone loss in postmenopausal women, but they are not so useful in replacing a significant amount of lost bones **43** . To treat or prevent osteoporosis there has been considerable

development of animal models and analytical methods for osteoporosis research.

- It has recently been reported that L-centchroman (Levormeloxifene) is capable of preventing bone loss as well as lowering cholesterol level in the rat model and suppress uterine stimulation relative to 17 β estradiol **44** Studies have also shown that Lcentchroman was able to reduce serum cholesterol and biochemical markers of bone turnover in postmenopausal women during clinical trials **45** .
- On the other hand, Ormeloxifene has demonstrated its antiosteoporotic activity as evidenced by concentration-dependent inhibitor in PTH –induced resorption of calcium from pre-labeled chick and rat fetal limb bones

❖ **Role in Male infertility**

- Administration of 30 mg per day of centchroman in oligospermic men for six weeks showed a dramatic increase in sperm count in three individuals with the history of infertility. However, there was a decrease in sperm count in one of the patient, while 4 of the patients were identified to have lower plasma testosterone with no effect on seminal parameters,

however, increased in acidic phosphatase and GPC were observed in two of the patients **46** .

- Increasing dose of centchroman from 30 to 60 and 120 mg a day (twice a week) for six weeks resulted in a significant decreased in sperm count in one of the patients during phase II and III of treatment, but the percentage of nonmotile and abnormal spermatozoa in all the patients escalated. No plasma testosterone or seminal acid phosphatase, Salic acid, GPC or fructose effect was observed in any of the patients53.
- The epididymal motility and vassal spermatozoa pattern nor testicular histology were not affected after up to 10 mg/kg of centchroman was administered throughout the spermatogenic cycle in rats. No adverse effect was observed on the testicular tissue in cholesterol-clamped rabbits after three weeks of administration of L-centchroman**47**

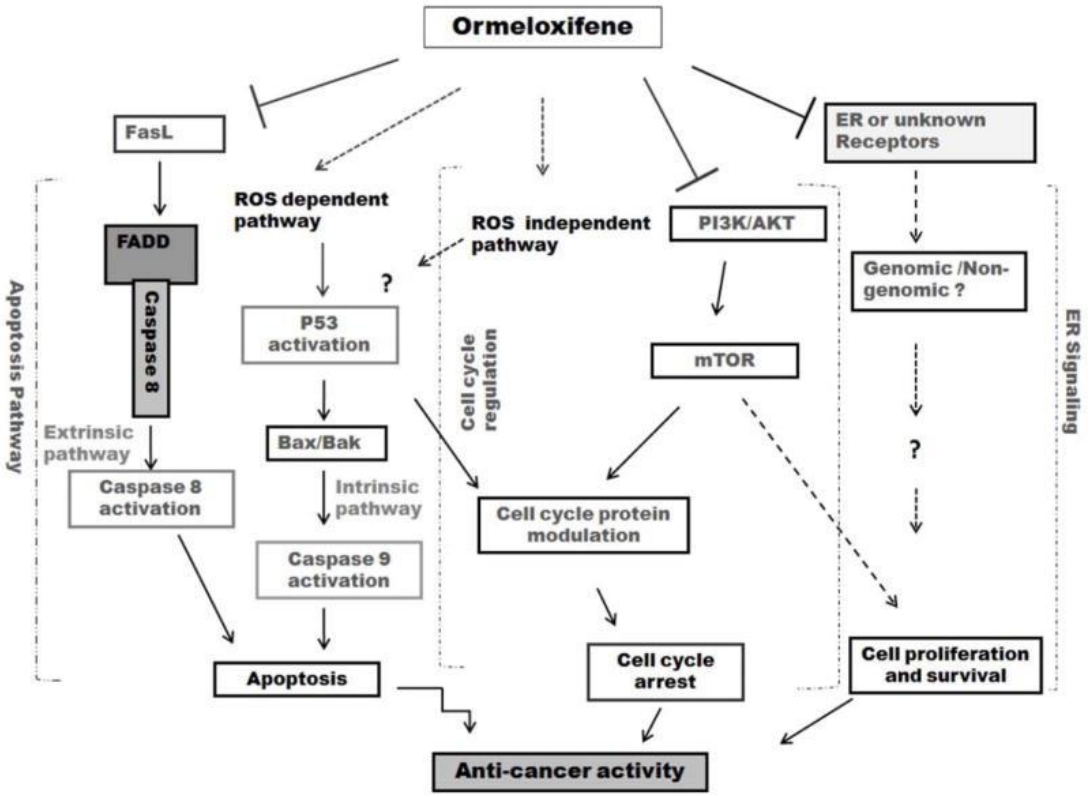
❖ **Centchroman as an anti-cancer agent**

- The established records of the safety of Ormeloxifene along with its favorable bioavailability and ability to inhibit rapid cell proliferation in the endometrium during embryonic implantation has made it a potential drug candidate for controlling

undesirable rapid cell growth such as endometriosis and cancerous tumor conditions**48** .

- Previous studies have confirmed the effectiveness of Ormeloxifene in preventing and suppressing various 22 cancer cell lines due to its potent estrogen agonist and antagonists functions of the reproductive tissues as well as non-reproductive **tissues 49** .

Investigations have revealed that Ormeloxifene induced apoptosis, inhibit s Akt/mTOR, signal transducers and activators of transcription protein 3 (STAT3) signaling. It can also alter proteins associated with cell cycle regulations and DNA damage and inhibits colony forming efficiency of Head and neck squamous cell carcinoma (HNSCC) cells



❖ **Ormeloxifene as an anti-breast cancer agent**

- Ormeloxifene is known to suppress breast cancer cell migration and invasion in vitro and breast cancer metastasis in vivo. In another development, it has been shown that Ormeloxifene induces G0/G1 phase cell cycle arrest and cellular apoptosis in human breast cancer MDA-MB-231 and MCF-7 cells with IC50 of 10μM and 20μM respectively69 .
- On the other hand, the migratory and invasion capacity human breast cancer MDA-MB-231 and mouse mammary cancer 4T1 cells were inhibited upon treatment with ormeloxifene.

- A lower dose of ormeloxifene (< 5M) on breast cancer cells was able to suppress migration and invasion of cells while higher dose inhibited cell proliferation and induced apoptosis which is evidence that suppression of migration and invasion is independent on cell growth or apotosis **50 .**
- Combination of ormeloxifene with other sensitizing agents such as resveratrol and curcumin has also proven to be effective. Combination of these agents relatively lowers the concentration of ormeloxifene induced apoptosis in breast cancer cells **51** .

❖ **Ormeloxifene as anti-head and neck cancer agent**

- According to the WHO, the 6th most common cancer in the world is Head and Neck squamous cell carcinoma with approximately fifty thousand new cases diagnosed in the United States alone in 2012 **52** .
- The role of the ER in HNSCC is very controversial. While some previous reports have revealed little to no expression of ER in HNSCC because of the controversial role of ER in HNSCC **53.** Recent investigations have shown a significant role for ER in enhancing migration and proliferation of cell in HNSCC **54** .

- Ormeloxifene has been known to exert its cytotoxicity via ER-dependent and ER-independent pathways in cancer cells, and its potential utilization for HNSCC treatment has been investigated68 .
- Dual inhibition of ormeloxifene on Akt and mTOR could be a significant therapeutic breakthrough as these signaling pathways are massively activated in HNSCC which explains how Akt/mTOR inhibitor effectiveness to overcome the effects of feedback loops better than a single inhibitor that selectively targets mTOR **55**.
- It is worth noting that ormeloxifene inhibits multiple HNSCC cell line growth by inducing apoptosis through caspase 3 activation. Treatment with ormeloxifene inhibits phosphorylation of Akt which leads to attenuate downstream Akt signaling thereby suppressing Akt/mTOR, STAT3 signaling and enhanced p21 and p27 protein expressions associated with cell cycle progression77 . These promising in vitro results have shown ormeloxifene to be a potential drug candidate for the treatment of HNSCC and warrants for further clinical studies.

❖ **Ormeloxifene as an anti-prostate cancer agent**

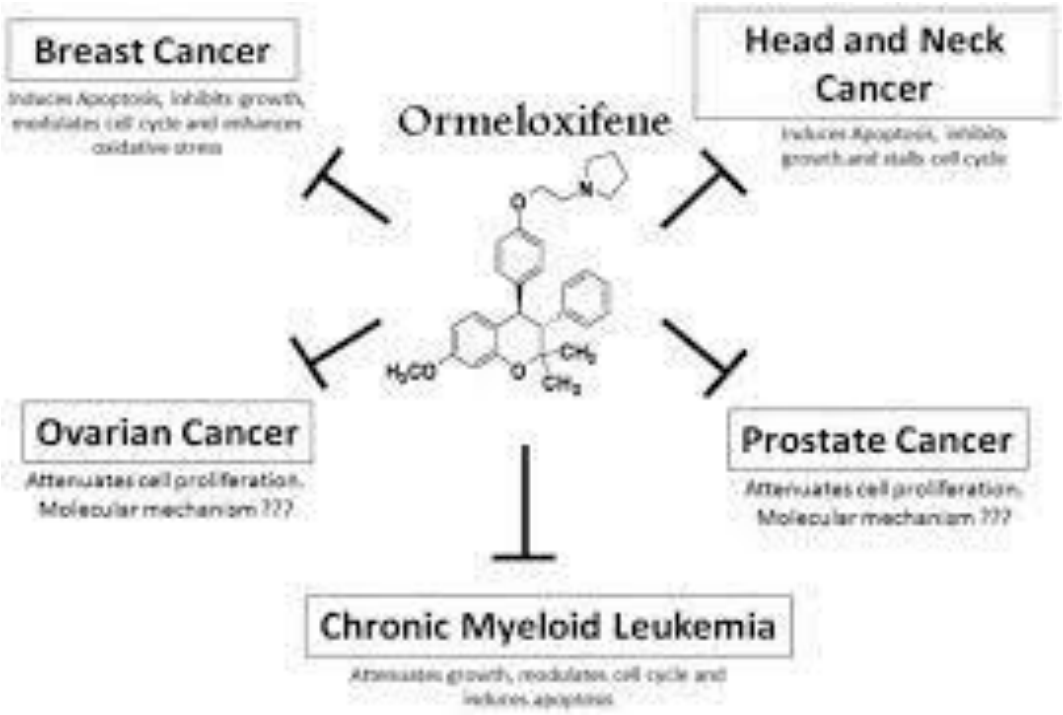
- The second most common leading cause of cancer death in male is prostate cancer **56**. ER is found in both the stroma and epithelium of the prostate. Studies have revealed estrogen as the genesis of prostate cancer.
- Rising estrogen and decreasing androgen levels in aged males triggers prostate cancer, and this is where SERM comes in as a potential treatment of prostate cancer where it selectively inhibits ER.
- There have been several reports where tamoxifen, and in combination with other anticancer agents have been used to suppress the proliferation of prostate cancer **57** . Other SERM such as raloxifene has been reported to inhibit prostate cancer cell growth expressing in different levels of ERα and ERβ and has efficiently induced apoptosis and inhibited proliferation of prostate cancer cells by modulating multiple signaling pathways **58.**
- The use of ormeloxifene as a prostate cancer agent has however not been reported, but the initial report has predicted the effectiveness of ormeloxifene to arrest androgen-dependent and independent androgen growth of prostate cancer cell growth.

❖ **Ormeloxifene and Chronic Myeloid Leukemia**

- Recent studies have revealed that Ormeloxifene induces apoptosis in several leukemia cells in a dose-dependent manner especially in K562. 2-DE-gel electrophoresis of K562 cells, 57% of the cells induced apoptosis when treated with ormeloxifene while 30% of proteins belong to cell cycle pathways.
- Activation of the extracellular signal-regulated kinase (ERKs) and further cytochrome C release, leading to mitochondria-mediated caspase-3 activation are evidence of ormeloxifene-induced apoptosis81 . Moreover, Ormeloxifene suppresses the proliferation of K562 cells by blocking them in the G0/G1 phase and suppressing c-myc promoters via ormeloxifene induced MBP-1 and upregulation of p21 25 expression **59** .
- The ability of ormeloxifene to induce apoptosis in K562 cell via phosphorylation or ERK and block them in G0/G1 through reciprocal regulation of p21 and c-myc has been demonstrated **60** . Ormeloxifene efficiently attenuates the growth of multiple types of cancer cells .

❖ **Role in Ovarian Cancer**

- Ovarian cancer remains the leading clinical challenge in gynecological oncology. It is among the leading cause of death (approximately 140,000 per year) worldwide and estimated to be diagnosed in over 220,000 women every year **61** .
- Ovarian cancer is the second most frequent malignancy after cancers of the uterine corpus in the United States with 20,880 estimated cases each year. About 13,850 women die from ovarian cancer annually representing the most common cause of death among women with gynecological malignancies **62** . The lifetime incidence for ovarian cancer is approximately 1.39% (1 in 72) and about 1.04% death risk from ovarian cancer for women living in the united states. The higher mortality rate of ovarian cancer is attributed to its late stage of diagnosis as approximately 75% of patients present with evidence of metastasis spreads beyond the ovaries **63**. The median survival rate is as between 24 to 60 month depending on the magnitude of residual disease following initial surgery.



RECENT ADVANCES IN DRUG DELIVRY OF ORMELOXIFENE

INTRA UTERINE DRUG DELIVERY SYSTEM

- In a study conducted in Department of pharmacology ,Delhi university, New delhi, formulated an intrauterine system of centchroman which should be safe and acceptable
- This new drug delivery system surpasses the first pass metabolism, thus increasing the bio availability and reducing the drug load.
- This formulation delivered the drug upto 21 days.Polylactic –co-glycolic acid served as the best fit polymer for delivering the drug.

INJECTABLE FORMULATION

- In another study stability and anti fertility effect of injectable and bio degradable formulations of centchroman was investigated
- The formulations included an insitu gelling preparation namely POLY LACTIDE CO GLYCOLIDE(PLGA) in triacetin prepared by solution method
- These formulations showedcontrolled drug release and enhanced stability and promising anti-fertility activity
- It was concluded from the study that PLGA in triacetin was a better candidate for the development of a biodegradable ,bio-erodable ,long acting ,injectable contraceptive formulation.

AIMS AND OBJECTIVES

1. The aim of this study was to assess the

- ❖ Effectiveness
- ❖ side effects
- ❖ compliance
- ❖ discontinuation rates
- ❖ resumption to fertility after stoppage of drugs
- ❖ failure rate

among the users of Centchroman (Chhaya)

in our tertiary center after its introduction in 2016 under National Family Planning Programme.

1) To study the effectiveness of centchroman as a non steroidal oral contraceptive
2) To study the possible causes of centchroman failure
3) To study the incidence of other side effects of centchroman

Moreover, there are very few studies and literature available on efficacy of Centchroman as contraceptives other than published report from Central Drug Research Institute, Lucknow (CDRI).

A Systematic review demonstrates that despite evidence of effectiveness of centchroman,more research is needed on side effects and mechanism of action .

MATERIALS AND METHODOLOGY

This study is a observational study conducted in the department of obstetrics and gynecology, Madras Medical college, Chennai during the period October 2020- octoberv2021.The above study is approved by the ethical and research committee of Madras Medical College.

PARTICIPANTS

During the research period about 320 post natal patients including patients following abortions who were uncovered for some reasons have been given the option of chhaya and discharged with packs for 3 months and were followed through phone calls for the persistent motivation

Only 118 cases of post natal mothers including both post LSCS and labour natural mothers and also including those who have undergone MTP were willing to participate in the study .All these mothers were given chhaya on 6 th week postnatal period which is available in our family planning department.Intial regular follow up of the patient is ensured since all the mothers will come to our hospital for routine check up and for vaccination to the baby on the 6^{th} ,10^{th} and 14^{th} week and compliance and complaints of the patient are addressed in these visits.

Difficulty in follow up comes only for post abortal patients who are routinely followed up through phone for any complaints.

AIMS AND OBJECTIVES

Objective of the study to study the contraceptive efficacy ,safety and return to fertility of centchroman

INCLUSION CRITERIA

1) Patient with normal menstrual cycles
2) Not on any other method of contraception
3) Willing to come for follow up
4) Medical illness where steroidal pills are contraindicated such as heart disease and diabetes mellitus

EXCLUSION CRITERIA

1) Women with PCOD
2) Cervical hyperplasia
3) History of jaundice or liver
4) Renal disease
5) Tuberculosis

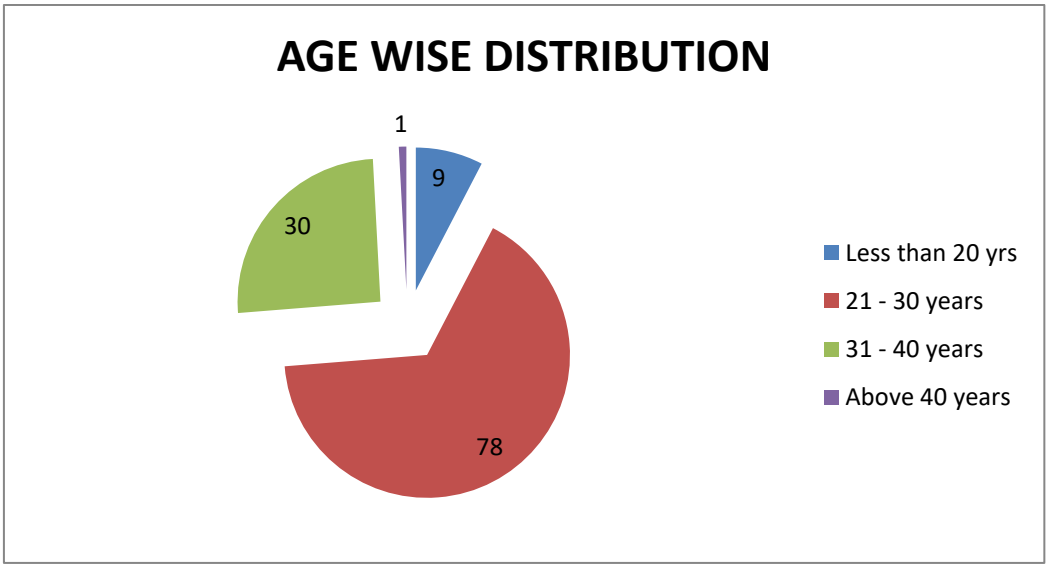
METHOD OF STUDY

- For intiation of centchroman ,the first pill is taken on the 6 th week of post natal period and the second pill three days later .
- This pattern of days is repeated through the first three months.Starting from the fourth month ,the pill is to be taken once a week on the first pill day and should be continued on the weekly schedule regardless of her menstrual cycle
- If the pill is missed by 1 or 2 days but lesser than 7 days ,the normal schedule should be continued and client needs to use a back up method (eg.condoms)till the next period starts.
- If the pill is missed by more than 7 days ,client needs to start taking it all over again like a new user that is twice a week for 3 months and then once a week.

IF THE FIRST DAY OF PILL TAKEN ON	**FIRST THREE MONTHS**	**AFTER 3 MONTHS**
SUNDAY	SUNDAY AND WEDNESDAY	SUNDAY
MONDAY	MONDAY AND THURSDAY	MONDAY
TUESDAY	TUESDAY AND FRIDAY	TUESDAY
WEDNESDAY	WEDNESDAY AND SATURDAY	WEDNESDAY

IF THE FIRST DAY OF PILL IS TAKEN ON	FIRST THREE MONTHS	AFTER 3 MONTHS
THURSDAY	THURSDAY AND SUNDAY	THURSDAY
FRIDAY	FRIDAY AND MONDAY	FRIDAY
SATURDAY	SATURDAY AND TUESDAY	STURDAY

RESULTS AND ANALYSIS



Age Group	AGE GORUP TOTAL	Percentage
Less than 20 years	9	8%
21 - 30 years	78	66%
31 - 40 years	30	25%
Above 40 years	1	1%
TOTAL	118	100%

Of the 118 acceptors,most of the post natal and post abortal patients who have taken centchroman fall in 21 to 30 yrs of age category.Another cluster of 30 patients were in 31-40 age group.Majority of patients fall in 21-40 yrs of age who were in high need of contraception.My target group of 20-40 years of age is achieved in my study group.In the extremes of age of less than 20 yrs,9 patients were there in the study group and there is one patient more than 40 yrs of age.

Discussion

The prime target is young ,low parity couples for family planning services to be over emphasized

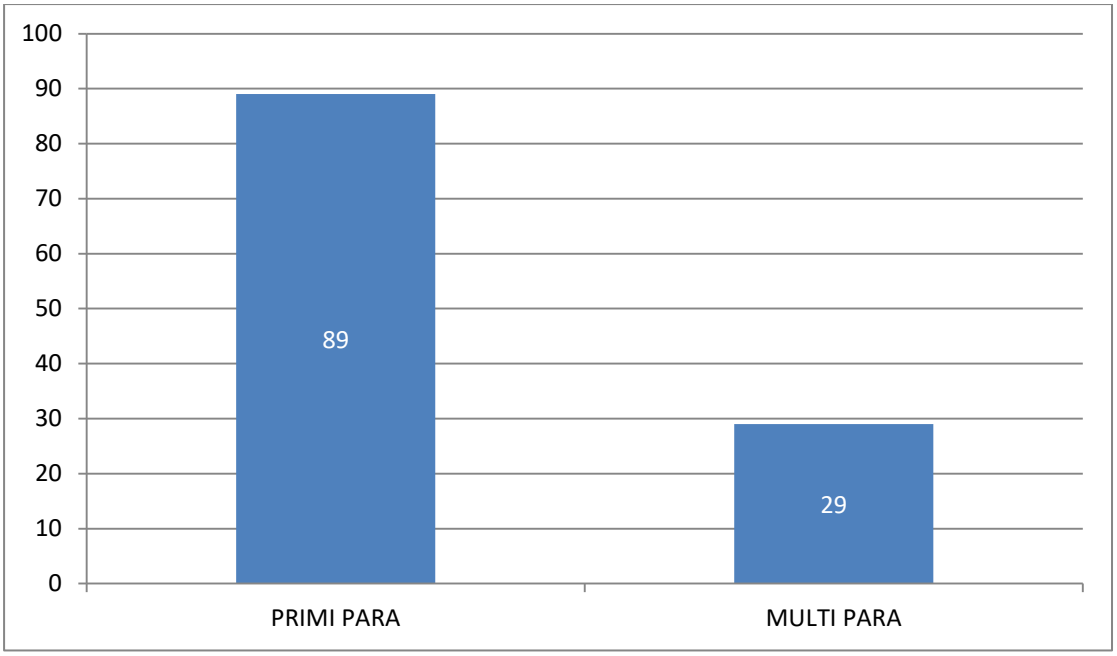
Women of 15-24 years of age group make 44% of all women of reproductive age group.

In our study group 90% women lie in the 20-40 age group.

Conclusions

Of less than 20 yrs and more than 40 yrs who have undergone LSCS, there is only one patient in each category and they are highly motivated and are educated about adequate spacing of atleast 2years is required and they are on regular follow up.

Only one of above more than 40 years ,explained about the risk any plan for future pregnancy and patient also explained about the other non contraceptive benefits of centchroman and the patient is on regular follow up

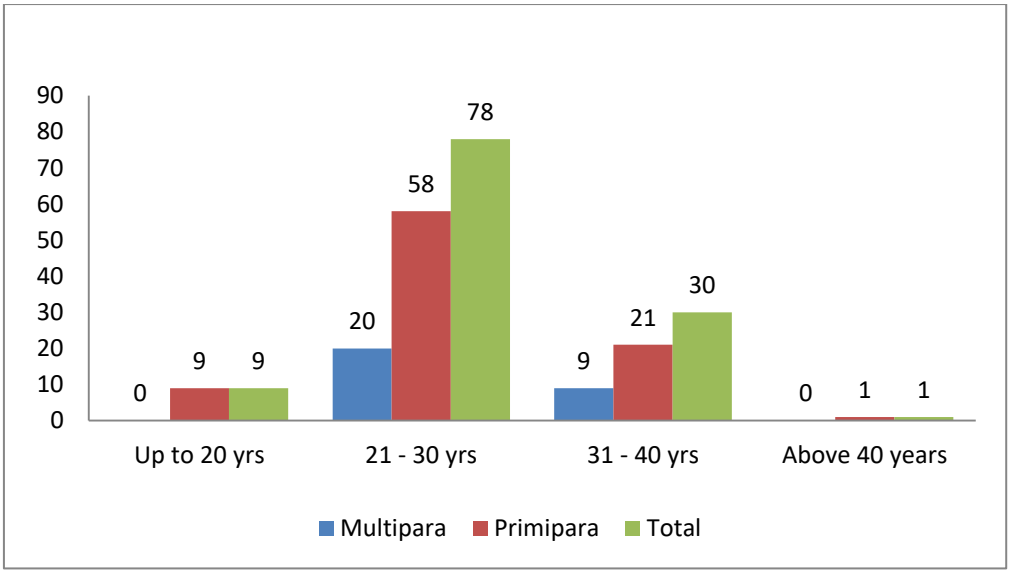


PARITY WISE DISTRIBUTION		
PRIMI PARA	89	25%
MULTI PARA	29	75%

Among 118 acceptors,29 were multiparous women and 89 were primi parous women.70% of women Have one child ,22% of women having 2 living child.Only 0.8% of women has three living child whom Permanent method of sterilisation has been planned on an interval basis due to post partum Hemorrhage ,providing time for anemia correction.

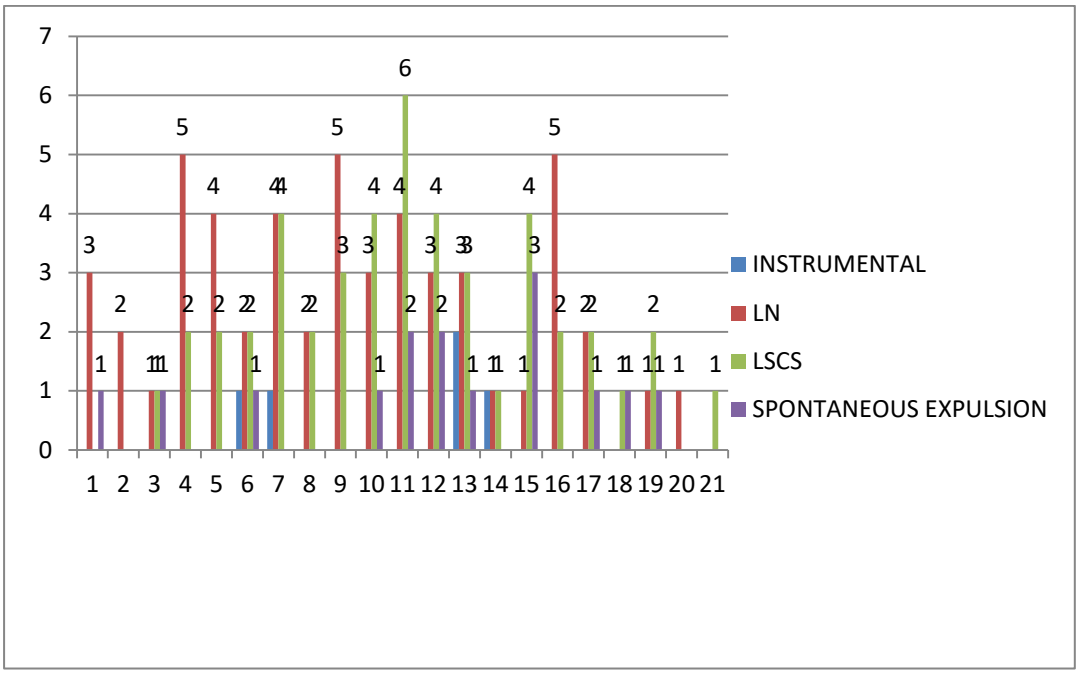
Permanent contraceptive metrhods were accepted by Women with 2 or more living children while Temporary methods of contraception were accepted mainly by women with one living child.

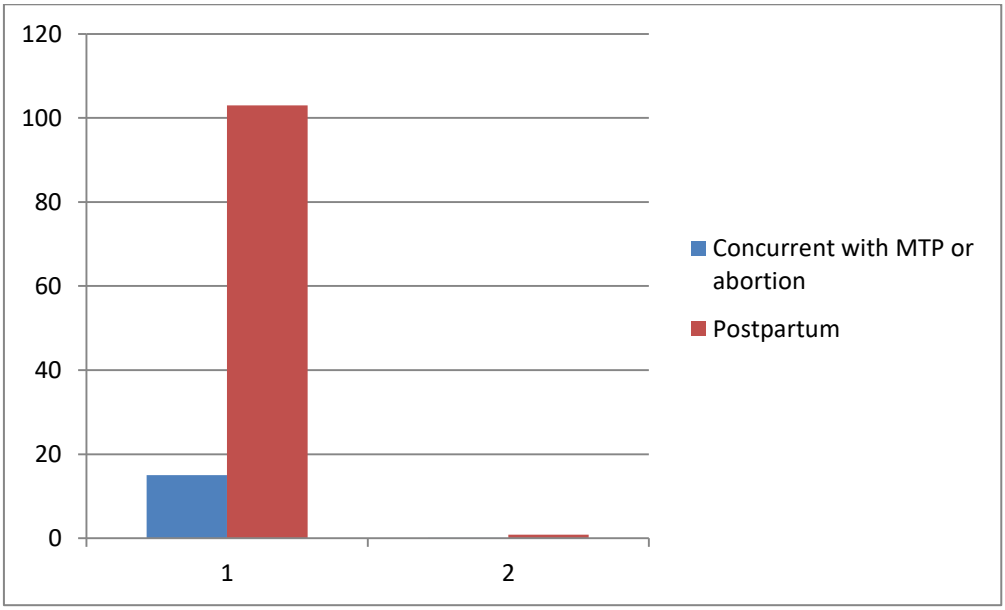
		Count	%
OBSTETRICSCORE	A1	2	1.7%
	P1L1	71	60.1%
	P1L1A1	11	9.3%
	P1L1A10	1	.8%
	P1L1A2	1	.8%
	P1L1A3	1	.8%
	P1L2	2	1.7%
	P2L1	1	.8%
	P2L1A1	1	.8%
	P2L2	23	19.5%
	P2L2A1	1	.8%
	P2L2A2	1	.8%
	P3L2	1	.8%
	P3L3	1	.8%



Age band	Multipara	Primipara	Total
Up to 20 yrs	0	9	9
21 - 30 yrs	20	58	78
31 - 40 yrs	9	21	30
Above 40 years	0	1	1
	29	**89**	**118**

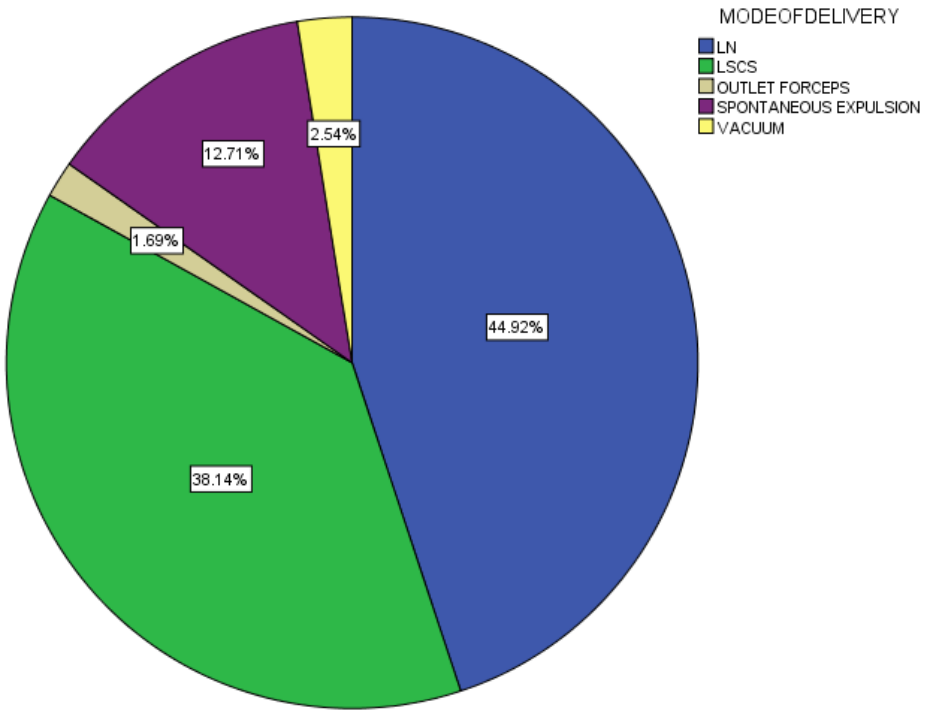
DISTRIBUTION BASED ON MODE OF DELVERY





Obsteric Status	Number	Percentage
Concurrent with MTP or abortion	15	12.71%
Postpartum	103	87.29%

MODE OF DELIVERY	LN	53	44.9%
	LSCS	45	38.1%
	OUTLET FORCEPS	2	1.7%
	SPONTANEOUS EXPULSION	15	12.7%
	VACUUM	3	2.5%



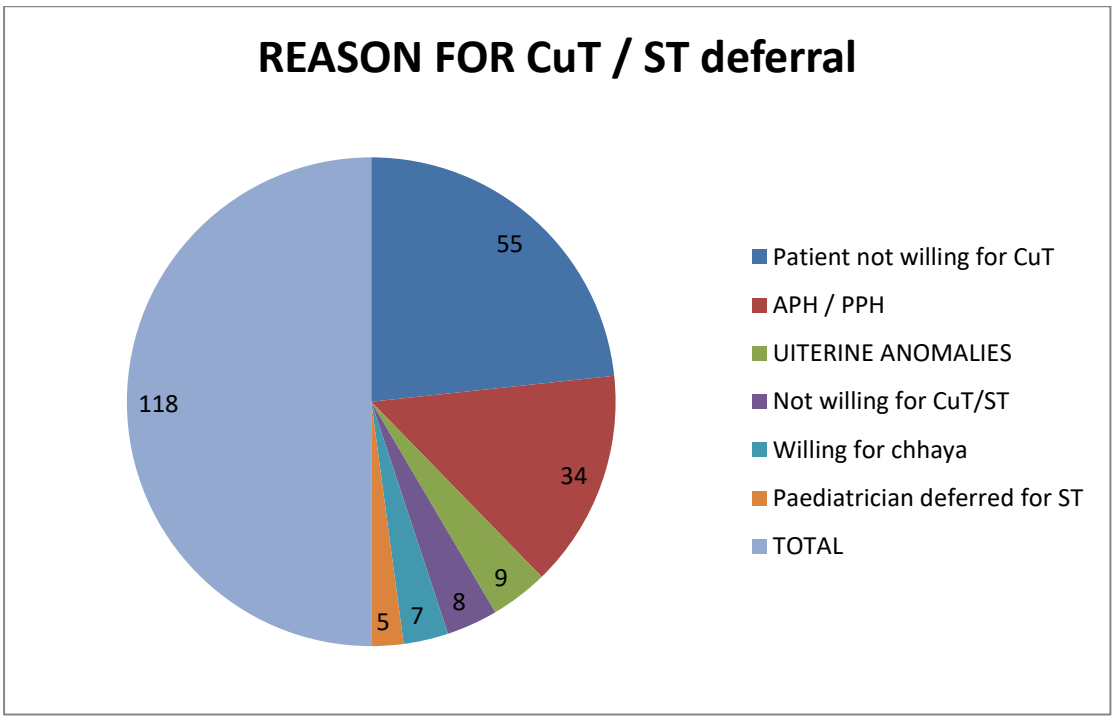
While analysing the mode of delivery,49% patients had labour natural ,38 % patients had been taken for LSCS and 12.7 % patients had spontaneous expulsion. Among the 21-30 years of age ,35 patients had labour natural ,32 patients taken up for LSCS and 7 had Spontaneous expulsion.

age Vs MODEOFDELIVERY		MODEOFDELIVERY					Total
		LN	LSCS	OUTLET FORCEPS	SPONTANEOUS EXPULSION	VACUUM	
age	<20 yrs	6	1	0	2	0	9
	21 to 30	35	32	2	7	2	78
	31 to 40	12	11	0	6	1	30
	>41	0	1	0	0	0	1
Total		53	45	2	15	3	118

Chi-Square Tests

	Value	df	P value
Pearson Chi-Square	8.706[a]	12	.728
N of Valid Cases	118		

a. 15 cells (75.0%) have expected count less than 5. The minimum expected count is .02.



Conditions	Count	Percentage
Patient not willing for CuT	55	47%
APH / PPH	34	29%
UITERINE ANOMALIES	9	8%
Not willing for CuT/ST	8	7%
Willing for chhaya	7	6%
Paediatrician deferred for ST	5	4%
TOTAL	118	100%

Among the 118 patients who have been given chhaya ,majority of them almost 54% not willing for CuT.

Hence given chayya after explaining the contraceptive and many other non contraceptive benefits of chayya.

29% of patients had APH/PPH whom CuT cant be placed and were adviced chayya as a contraceptive Option.Among 8%of patients had uterine anomalies hence CuT was not paced and were given chayya.

Only minor group of people had been deferred for ST by paediatrician and hence given chayya.6% of patients were willing for chayya and majority of them were following expulsion.

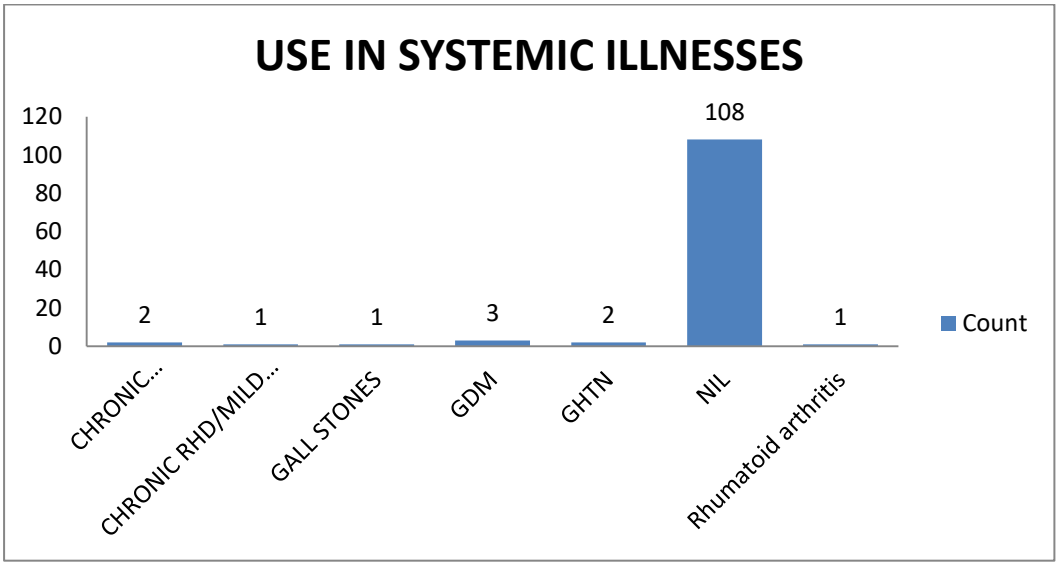
PARITY * Not wiling for CuT				
			Not wiling for CuT	Total
			Yes	
PARITY	MULTI PARA	Count	7	7
		% within Not wiling for CuT	12.7%	12.7%
	Primi para	Count	48	48
		% within Not wiling for CuT	87.3%	87.3%
Total		Count	55	55
		% within Not wiling for CuT	100.0%	100.0%

Among the patients who are not willing for CuT,majority of them are primi parous women hence awareness should be created about the availability of other methods of contraception since many of these mothers would have been uncovered if they were not given an option of other ease methods of contraception like chayya.

A survey can be conducted for analyzing why most of the patients who have adviced for CuT are not willing.

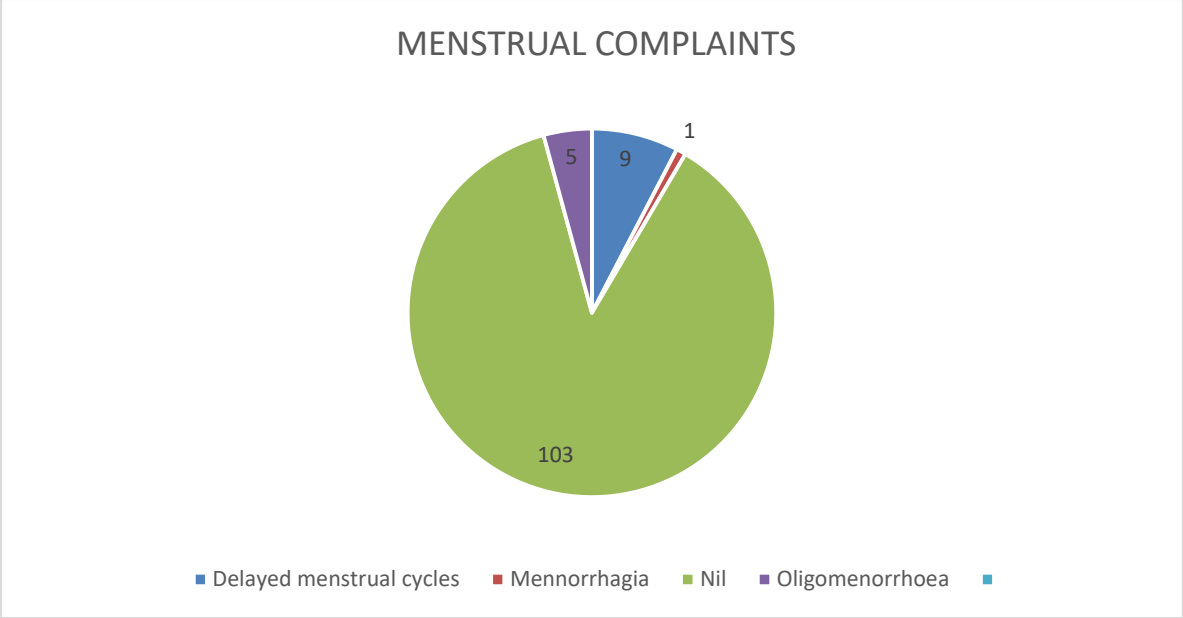
REASONFORCuTSTDIFFERAL * re_age Crosstabulation				
Only mutipara (N=29)		Age		Total
		21 to 30	31 to 40	
REASON FOR CuT ST DIFFERAL	ABRUPTIO PLACENTA	1	0	1
		5.0%	0.0%	3.4%
	Atonic PPH	1	0	1
		5.0%	0.0%	3.4%
	Bicornuate uterus	3	0	3
		15.0%	0.0%	10.3%
	Fibroid uterus	1	0	1
		5.0%	0.0%	3.4%
	Not wiling for CuT	2	2	4
		10.0%	22.2%	13.8%
	Not willing for CuT/ST	3	0	3
		15.0%	0.0%	10.3%
	Not willing for ST	3	0	3
		15.0%	0.0%	10.3%
	Outside delivery as PPH	1	0	1
		5.0%	0.0%	3.4%
	Paediatrician deferred for ST	1	3	4
		5.0%	33.3%	13.8%
	Patient not willing for CuT	1	2	3
		5.0%	22.2%	10.3%
	Patient not willing for PS	1	0	1
		5.0%	0.0%	3.4%
	Placenta previa	1	0	1
		5.0%	0.0%	3.4%
	PPH	1	1	2
		5.0%	11.1%	6.9%
	Septate uterus	0	1	1
		0.0%	11.1%	3.4%
Total		20	9	29
		100.0%	100.0%	100.0%

Among the multi parous women who have been on chayya follow up ,most of the patients were not done permanent method of sterilisation because for baby sake since paediatrician deferred ST.



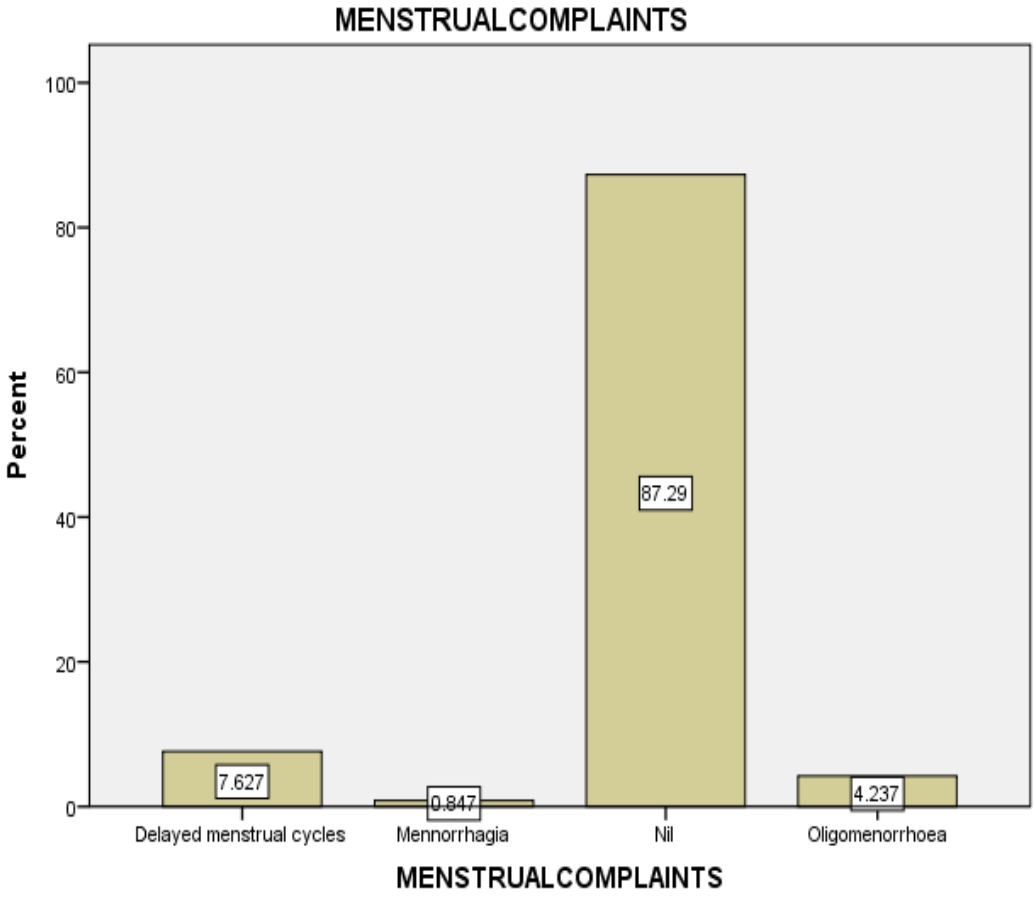
USE IN SYSTEMIC ILLNESSES		
Systemic Illness	**Count**	**Percentage**
CHRONIC HYPERTENSION	2	2%
CHRONIC RHD/MILD MS	1	1%
GALL STONES	1	1%
GDM	3	3%
GHTN	2	2%
NIL	108	92%
Rhumatoid arthritis	1	1%
Grand Total	118	100%

Centchroamn was used in 9 patients having systemic illness,among which 3 patients have GDM ,2 Patients have chronic hypertension,one with chronic RHD ,another patient with gall stones and one more with rheumatoid arthritis. Unlike steroidal pills which are relatively contraindicated,none of the above systemic illness develop any Complication with centchroman in my study.



Menstrual complaints were noted in 13% of acceptors ,which was found to be slightly higher compared to the standard claimed by the manufacturer of 8-10%.

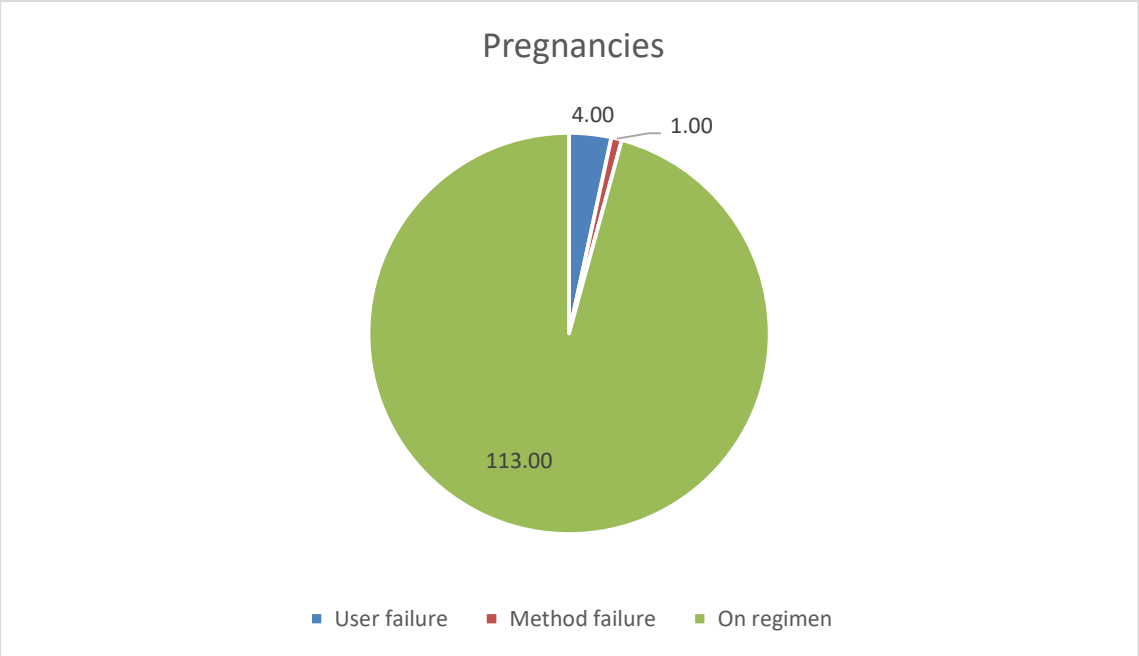
Major menstrual complaint was delayed menstrual cycles seen in 7.5% of acceptors.In case of delay , a PREGNANCY TEST was done afterv 2 wks of delay.



Row Labels	Count of MENSTRUAL COMPLAINTS	Percentage
Delayed menstrual cycles	9	8%
Mennorrhagia	1	1%
Nil	103	87%
Oligomenorrhoea	5	4%
Grand Total	118	100%

Side effects		
Side effects	**Count**	**Percentage**
backache	3	3%
headache	3	3%
nausea	5	4%
Nil	106	90%
vomiting	1	1%
Grand Total	**118**	**100%**

Other minor side effects noted were nausea(4%),headache and back ache(3),nausea (5%) which were present in 10 5 of individuals.All were minor side effects which were mostly present in the first three months of usage.



Pregnancies		
Particulars	**Count**	**Percentage**
User failure	5.00	4%
Method failure	0.00	0%
On regimen	113.00	96%
No. of patients screened	118.00	**100%**

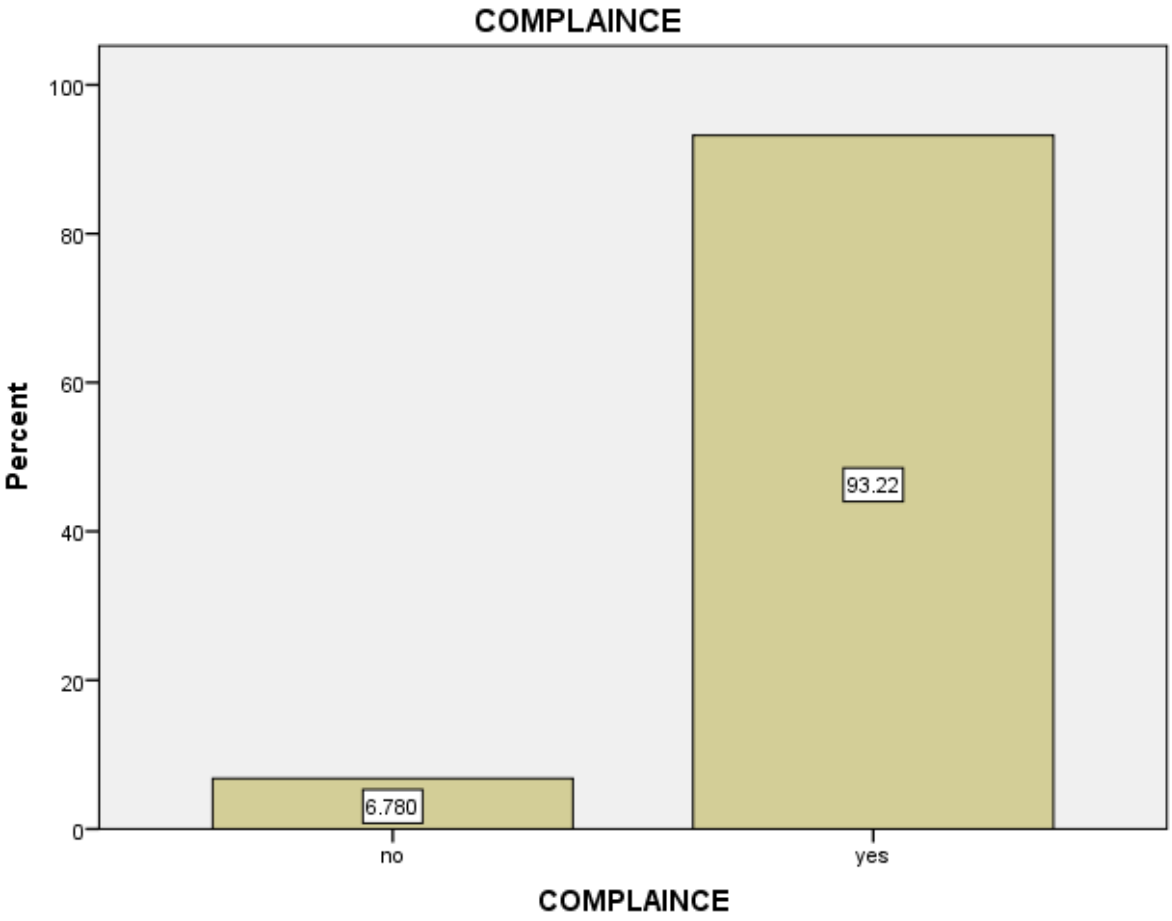
All the five patients who have been conceived were user failiure since they want to conceive ,hence they dropped from study.

Of the 118 acceptors,5 cases of pregnancies were recorded in the study.Of the 5 cases,2 cases occurred. In the first three months of use.3 more cases occurred after 6 months of usage.

Association between Obstetric Status & failure rate				
Obstetric status	**Failure**		**Total**	**Chi-square test P value**
	Absent	**Present**		
Concurrent MTP or abortion	12	3	15	0.0011
Post Partum	101	2	103	
TOTL	**113**	**5**	**118**	

Reason for drop out	
Cause	**Number**
Wants to conceive	5
Unable to come for followup	0
Menstrual Integrity	0
Alternate method	0
TOTAL	**5**

Return of fertility following discontinuation of Centhroman		
Month of discontinuation	**Conception**	**Total**
4th Month	2	5
6th Month	3	



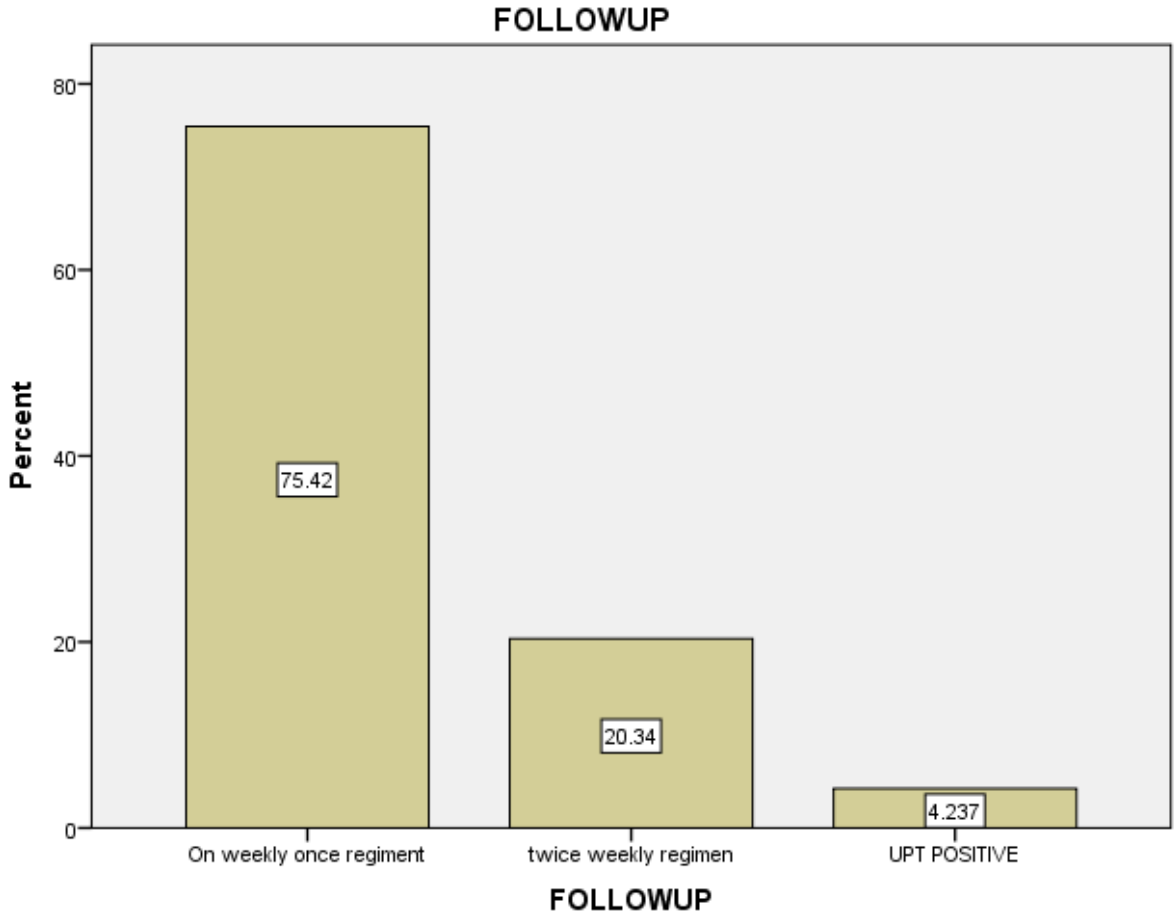
COMPLAINCE		Frequency	Percent
Valid	No	5	6.8
	Yes	113	93.2
	Total	118	100.0

SL. NO	NAME	AGE	OBSTETRIC SCORE	MODE OF DELIVERY	DATE OF DELIVERY	COMOR BIDITIES
1	Lavanya	31	P1L1	VACUUM	3-Oct-20	NIL
2	Shobana	29	P1L1A1	SPONTANEOUS EXPULSION	11-Oct-20	NIL
3	Reena joseph	34	P1L1	LN	12-Oct-20	Rhumatoid arthritis
4	Nandhini prasanth	27	P1L1A1	SPONTANEOUS EXPULSION	4-Jul-21	NIL
5	Bhuvaneshwari Parthasarathi	20	P1L1A1	SPONTANEOUS EXPULSION	23-Jul-21	NIL

REASON FOR CuT/ST DIFFERAL	COMMENCEMENT OF CHAYYA	DROPPED OUT FROM	MENSTRUAL COMPLAINTS	FOLLOW UP
Patient not willing for CuT	10-7-2020	22-1-21	Delayed menstrual cycles	UPT POSITIVE ON 6/3/21
Patient not willing for CuT	16-10-2020	4-4-2021	Nil	UPT POSITIVE ON 24/7/21
Not wiling for CuT	14-10-2020	5-5-2021	Nil	UPT POSITIVE 7/7/21
willing for chhaya	11-7-2021	10-10-21	Nil	UPT POSITIVE ON 26/12/21
willing for chhaya	28-7-2021	14-10-21	Nil	UPT POSITIVE ON 1/1/2022

1. 3 post expulsion patients and 2 patients following delivery were pregnant after using chayya as a temporary contraceptive method.

2. Among the post partum patient ,one patient who had vacuum delivery dropped out from the study since she wants to conceive,became pregnant after 6 months of usage of the drug and she resumed fertility in her second menstrual cycle after stopping the drug.
3. Similar post partum mother who also had LN also dropped out from study after 6 months of usage and resumed fertility in her 3 rd cycle.
4. Among 3 patients following expulsion,one patient conceived after 6 months of using the drug and dropped out from study and conceived in her third cycle after stopping the drug.
5. Other 2 spontaneous expulsion patients conceived after 3 months of usage of drug and discontinued the drug since they want to conceive and became pregnant in their 2 nd and 3 rd menstrual cycle respectively.
6. From these it is inferred that return to fertility is prompt with centchroman and hence can be safely recommended even in nulliparous women as temporary method of contraception.



FOLLOWUP					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	On weekly once regiment	89	75.4	75.4	75.4
	twice weekly regimen	24	20.3	20.3	95.8
	UPT POSITIVE	5	4.2	4.2	100.0
	Total	118	100.0	100.0	

age Vs REASON FOR CuTST DIFFERAL		REASONFORCuTSTDIFFERALFORCHART						Total
		APH / PPH	Not willing for CuT/ST	Paediatrician deferred for ST	Patient not willing for CuT	UITERINE ANOMALIES	Willing for chhaya	
age	<20 yrs	1	0	0	4	2	2	9
	21 to 30	27	8	2	34	5	2	78
	31 to 40	5	0	3	17	2	3	30
	>41	1	0	0	0	0	0	1
Total		34	8	5	55	9	7	118

Chi-Square Tests

	Value	Df	P value
Pearson Chi-Square	23.048[a]	15	0.083
N of Valid Cases	118		

a. 18 cells (75.0%) have expected count less than 5. The minimum expected count is .04.

Age Vs COMPLAINCE		COMPLAINCE		Total
		No	Yes	
Age	<20 yrs	1	8	9
	21 to 30	5	73	78
	31 to 40	2	28	30
	>41	0	1	1
Total		8	110	118

Chi-Square Tests

	Value	df	P value
Pearson Chi-Square	.357[a]	3	.949
N of Valid Cases	118		

a. 4 cells (50.0%) have expected count less than 5. The minimum expected count is .07.

CONCLUSION

During the study period 118 patients were screened and administered Centchroman for the study of its contraceptive efficacy.Data from the study was analysed in relation to the age at acceptance,parity,obstetric details at the time of acceptance .The salient features are summarized as follows

1. The age pattern ranged from 20 to 40 years of age with maximum number in the age group of 21-30 yrs of almost 66%
2. 75 % of patients had one living child,25 % of patients in the study group had 2 living child.
3. The maximum no of acceptors were following dellivery of almost 87.5% in my study group.
4. All patients in the study group used centchroman for one year except 5 people who dropped from study since they want to conceive.
5. The drug related side effects were very few and included headache, vomiting and nausea.
6. Menstrual complaints were noted in 13% of acceptors. Delayed Menstrual complaints were noted in 7%,menorrhagia in 2% and oligomennorhoea in 4% of cases.

7. Resumption of fertility is prompt within 2 or three menstrual cycles after stoppage of drugs is evident from my study.

FAILURES

Of the 118 patients screened,5 became pregnant.All these pregnancies were because of they want to conceive and they dropped out from the study.

Other patients who were highly motivated from the beginning and were on regular follow up,nil cases of method failiures has been observed that proves 100 % efficacy of centchroman as evidenced by some observational studies.

RECOMMENDATIONS

1. Robust study designs are needed such as RCT or longitudinal studies to compare contraceptive efficacy and safety of centchroman with other short term modern contraceptives such as combined hormonal contraceptives and progesterone only pills

2. Apart from its contraceptive benefits ,more studies to be conducted based on Non contraceptive benefits of the drug.

3. A long period of study is needed to know about other possible side. Effects of the drug.The studies done so far has not been more than a year.

LIMITATIONS

1. Since constant motivation and follow up of the patients is highly needed, it is difficult to follow up the patient.A project officer should have regular follow up of the patient.

2. The uncertainty and diversity of side effects in the studies across india implies a lack of body of evidence to make global recommendations on centchroman as a contraceptive of choice that is licensed and used in the second most populous country in the world.

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PROFORMA

Name: Age: Occupation:

Address:

Date of admission: Date of Discharge:

Inpatient number: Outpatient number:

History

Marital History:

Menstrual History: L.M.P

E.D.D

Obstetric History:

Past obstetric history:

Past History:

Medical : Diabetes, Hypertension, Renal disease, Cardiac illness, Asthma, Epilepsy.

Past surgical history:

Family history:

H/O congenital anomalies, H/O twins

H/O Diabetes mellitus, hypertension, tuberculosis, asthma, epilepsy.

Personal history:

General examination:

Weight:

Height:

Weight gain during pregnancy:

BMI:

Systemic examination:

Cardio vascular system:

Respiratory system:

Per abdomen:

Inspection:

INFORMATION SHEET

TITLE: : **"Contraceptive efficacy and safety of centchroman with bi-weekly cum weekly schedule in postnatal women in a tertiary care hospital- A Prospective study**

Name of the investigator: Dr.A.Divya

Name of the Participant:

Purpose of Research: To determine the contraceptive efficacy and safety of centchroman in postnatal women
Study Design: Prospective study

Study Population: The study would include postnatal women seeking contraception not under any other methods of contraception
Possible Risks: No risks to the patient

Confidentiality of the Information obtained from you: The privacy of the patients in the research will be maintained throughout the study.
In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Can you decide to stop participating in the study?
Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at anytime.

How will your decision to not participate in the study affect you?
Your decision will not result in any loss of benefits to which you are otherwise entitled.

Signature of Investigator Signature of Participant

Date:
Place:

PATIENT CONSENT FORM

Patient may check **( )** these boxes:

( )I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction.

( )I understand that my participation in the study is voluntary and that I am free to withdraw at anytime without giving reason, without my legal rights being affected.

( )I understand that sponsor of the clinical study, others working on the sponsor's behalf, the Ethics committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that maybe conducted in relation to it, even if I withdraw from the study I agree to this access.

( ) However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

Study title: : **"Contraceptive efficacy and safety of centchroman with bi-weekly cum weekly schedule in postnatal women in a tertiary care hospital- A Prospective study**

Study Centre: MMC,Chennai

Patient's Name:

Patient's Age:

In Patient Number:

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately in form the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.

I hereby consent to participate in this study.

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests and to undergo treatment.

Signature/Thumb impression of the patient

Patient's Name and Address:

Signature of Investigator

(Dr.Divya.A)

அனுமதியுடனான ஒப்புதல் படிவம்

-இந்த ஆய்விற்கான செயல்முறையின் நோக்கத்தை நான் புரிந்துள்ளேன் என்பதை உறுதிப்படுத்துகிறேன். எனக்கு கேள்விகளை கேட்க வாய்ப்பு உள்ளது. என்னுடைய எல்லா கேள்விகளும் சந்தேகங்களும் என் முழு திருப்திக்கு பதில் அளித்துள்ளன.

-ஆய்வில் எனது பங்கேற்பு தன்னார்வமாக இருப்பதையும், என் சட்ட உரிமைகள் பாதிக்கப்படாமல், காரணத்தைத் தெரிவிக்காமல் எப்போது வேண்டுமானாலும் விலக்கிக்கொள்ளலாம் என்பதையும் நான் புரிந்து கொள்கிறேன்.

-ஆய்வில் இருந்து நான் விலகி வந்தாலும் கூட, ஆராய்ச்சிக்கு பொருந்தக்கூடிய என் உடல்நல ஆவணங்களைப் பார்க்க என் நெறிமுறைக் குழு மற்றும் ஒழுங்குமுறை அதிகாரிகளுக்கு எனது அனுமதி தேவையில்லை என்பதை நான் புரிந்து கொள்கிறேன். இந்த அணுகலை நான் ஏற்கிறேன்.

-இருப்பினும், சட்டத்தின் கீழ் தேவைப்பட்டாலன்றி, மூன்றாம் தரப்பினருக்கு வெளியிடப்பட்ட அல்லது வெளியிட்ட எந்த தகவலிலும் என் அடையாளத்தை வெளிப்படுத்த முடியாது என்பதை நான் புரிந்து கொள்கிறேன். இந்த ஆய்விலிருந்து எழும் எந்தவொரு தரவு அல்லது முடிவுகளின் பயன்பாட்டைக் கட்டுப்படுத்துவதை நான் ஏற்றுக்கொள்கிறேன்.

-மேலே உள்ள படிப்பில் கலந்து கொள்ளவும், ஆய்வின் போது கொடுக்கப்பட்ட அறிவுறுத்தல்களுக்கு இணங்கவும், ஆய்வுக் குழுவோடு ஒத்துழைக்கவும், என் உடல்நலம் அல்லது நலம் அல்லது எந்தவொரு எதிர்பாராத அல்லது அசாதாரண அறிகுறிகளிலும் நான் பாதிக்கப்படுகையில் உடனடியாக ஆய்வு ஊழியர்களுக்கு தெரிவிக்கவும், இந்த ஆய்வில் பங்கேற்க ஒப்புக்கொள்கிறேன்.

நான் இதனுடன் முழுமையான மருத்துவ பரிசோதனை மற்றும் நோயறிதல் சோதனைகள் இரத்தம், உயிர்வேதியியல், கதிரியக்க சோதனைகள் உட்பட சிகிச்சைக்கு உட்படுத்த அனுமதிக்கிறேன்.

ஆய்வு தலைப்பு:
ஆய்வு மையம்: எம்.எம்.சி, சென்னை
பங்கேற்பாளரின் பெயர்:
பங்கேற்பாளரின் வயது:
நோயாளி எண்:

நோயாளியின் கையொப்பம்
நோயாளியின் பெயர் மற்றும் முகவரி: ஆராய்ச்சியாளரின் கையொப்பம்:

PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled "**CONTRACEPTIVE EFFICACY AND SAFETY OF CENTCHROMAN WITH BI-WEEKLY CUM WEEKLY SCHEDULE IN POSTNATAL WOMEN IN A TERTIARY CARE HOSPITAL-A PROSPECTIVE STUDY"** of the candidate **DR**. **DIVYA. A** with **Registration Number: 221916857** for the award of **M.S OBSTETRICS AND GYNECOLOGY (BRANCH II)**. I personally verified that the urkund.com website for the purpose of checking plagiarism. I found that the uploaded thesis file contains contents from introduction to conclusion and result shows **NINETEEN Percent** of plagiarism in the dissertation. (D126041462)

Guide & Supervisor sign with seal

Place : Chennai
Date :

Dr.VIJAYA, M.D DGO,
Professor,
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Egmore, Chennai – 600 008

Curiginal

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Sources included in the report

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W	URL: https://surface.syr.edu/cgi/viewcontent.cgi?article=2107&context=etd Fetched: 2021-11-29T09:38:25.7900000	1

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013/RR-16
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.DIVYA A,
Post Graduate – MS (Obstetrics and Gynaecology),
Madras Medical College,
Chennai - 600003.

Dear Dr. DIVYA A,

The Institutional Ethics Committee has considered your request and approved your study titled **"CONTRACEPTIVE EFFICACY AND SAFETY OF CENTCHROMAN WITH BI-WEEKLY CUM WEEKLY SCHEDULE IN POSTNATAL WOMEN IN A TERTIARY CARE HOSPITAL – A PROSPECTIVE STUDY"-NO.10082020.** The following members of Ethics Committee were present in the meeting held on **04.08.2020** conducted at Madras Medical College, Chennai 3.

1. Prof.P.V.Jayashankar :Chairperson
2. Prof.N.Gopalakrishnan,MD.,DM., FRCP, Director, Inst.of Nephrology,MMC,Ch : Member Secretary
3. Prof. K.M.Sudha, Prof. Inst. of Pharmacology,MMC,Ch-3 : Member
4. Prof. Alagarsamy Jamila ,MD, Inst. of Patholoy, MMC, Ch-3 : Member
5. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai : Member
6. Prof.S.Lakshmi, Prof. of Paediatrics ICH Chennai :Member
7. Tmt.Arnold Saulina, MA.,MSW., :Social Scientist
8. Thiru S.Govindasamy, BA.,BL,High Court,Chennai : Lawyer
9. Thiru K.Ranjith, Ch- 91 : Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

03/09/2020

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003.

SL.NO	NAME	AGE	OBSTETRIC SCORE	PARITY	MODE OF DELIVERY	DATE OF DELIVERY	COMORBIDITIES	REASON FOR CuT/ST DIFFERAL	REASON FOR CuT/ST DIFFERAL FOR CHART	COMMENCEMENT OF CHAYYA	COMPLAINCE	MENSTRUAL COMPLAINTS	OTHER SIDE EFFECTS	FOLLOW UP
1	Devi Raja	29	P1L1	Primi para	LSCS	21-Mar-20	NIL	PPH	APH / PPH	02-05-2020	yes	Nil	Nil	On weekly once
2	Dharani	27	P1L1	Primi para	LN	31-May-20	NIL	Not wiling for CuT	Patient not willing for CuT	12-07-2020	Yes	Nil	Nil	On weekly once regiment
3	Geetha Thiyagu	27	P1L1	Primi para	LN	31-May-20	NIL	Not wiling for CuT	Patient not willing for CuT	12-07-2020	YES	Nil	Headache	twice weekly regimen
4	Rizhwana	31	P1L1	Primi para	LSCS	21-Jun-20	NIL	Not wiling for CuT	Patient not willing for CuT	02-08-2020	YES	Nil	nil	twice weekly regimen
5	Karthiga	30	P1L1	Primi para	LSCS	12-Jul-20	NIL	Not wiling for CuT	Patient not willing for CuT	16-08-2020	Yes	Nil	Nil	On weekly once regiment
6	Lakshmi Priya	28	P1L1	Primi para	LSCS	1-Oct-20	NIL	Patient not willing for CuT	Patient not willing for CuT	12-11-2020	Yes	Nil	Nil	On weekly once regiment
7	Lavanya	31	P1L1	Primi para	VACUUM	3-Oct-20	NIL	Patient not willing for CuT	Patient not willing for CuT	14-11-2020	no	Delayed menstrual cycles	Nil	UPT POSITIVE
8	Loganayagi	38	P2L2	MULTI PARA	LSCS	5-Oct-20	NIL	Paediatrician deferred for ST	Paediatrician deferred for ST	16-11-2020	Yes	Nil	Nil	On weekly once regiment
9	Sakira	22	P1L1	Primi para	LN	7-Oct-20	NIL	PPH	APH / PPH	17-11-2020	Yes	Nil	Nil	On weekly once
10	Kalaiyarasi	30	P1L2	Primi para	LN	8-Oct-20	NIL	Patient not willing for CuT	Patient not willing for CuT	19-11-2020	Yes	Nil	Nil	On weekly once regiment
11	Janani	21	P1L1	Primi para	LN	9-Oct-20	CHRONIC HYPERTENSION	Patient not willing for CuT	Patient not willing for CuT	20-11-2020	Yes	Nil	Nil	On weekly once regiment
12	Radha	24	P2L2	MULTI PARA	LSCS	11-Oct-20	NIL	Placenta previa	APH / PPH	22-11-2020	yes	Nil	nil	On weekly once
13	Shobana	29	P1L1A1	Primi para	SPONTANEOUS EXPULSION	11-Oct-20	NIL	Patient not willing for CuT	Patient not willing for CuT	22-11-2020	no	Nil	Nil	UPT POSITIVE
14	Deepa	24	P1L1	Primi para	LN	12-Oct-20	NIL	PPH	APH / PPH	23-11-2020	Yes	Nil	Nil	On weekly once
15	Vanitha	34	P2L2	MULTI PARA	LSCS	12-Oct-20	NIL	Septate uterus	UITERINE ANOMALIES	23-11-2020	Yes	Nil	Nil	On weekly once regiment
16	Reena joseph	34	P1L1	Primi para	LN	12-Oct-20	Rhumatoid arthritis	Not wiling for CuT	Patient not willing for CuT	23-11-2020	no	Nil	Nil	UPT POSITIVE
17	Kavitha	35	P2L2A1	MULTI PARA	SPONTANEOUS EXPULSION	12-Oct-20	GDM	Patient not willing for CuT	Patient not willing for CuT	23-11-2020	Yes	Nil	Nil	On weekly once regiment
18	Bhavani	24	P1L1	Primi para	LN	14-Oct-20	NIL	PPH	APH / PPH	25-11-2020	Yes	Nil	Nil	On weekly once
19	Mahalakshmi	38	P1L1A1	Primi para	SPONTANEOUS EXPULSION	22-Oct-20	GDM	Patient not willing for CuT	Patient not willing for CuT	26-11-2020	Yes	Nil	Nil	On weekly once regiment
20	Deepika	28	P2L1	MULTI PARA	SPONTANEOUS EXPULSION	24-Oct-20	NIL	Patient not willing for CuT	Patient not willing for CuT	28-11-2020	Yes	Nil	Nil	On weekly once regiment

21	kaviya	21	P2L2	MULTI PARA	LN	25-Oct-20	NIL	Outside delivery as PPH	APH / PPH	29-11-2020	yes	Delayed menstrual cycles	nil	On weekly once regiment
22	Tamilselvi	30	P1L1	Primi para	OUTLET FORCEPS	25-Oct-20	NIL	Patient not willing for CuT	Patient not willing for CuT	29-11-2020	Yes	Nil	Nil	On weekly once regiment
23	Pavithra	27	P2L2A2	MULTI PARA	LSCS	2-Nov-20	NIL	Bicornuate uterus	UITERINE ANOMALIES	14-12-2020	yes	Nil	nil	On weekly once regiment
24	Hema	22	P1P1	Primi para	LN	15-Nov-20	NIL	PPH	APH / PPH	30-12-2020	YES	Nil	Nil	On weekly once
25	Priyanka	28	P2L2	MULTI PARA	LN	16-Nov-20	NIL	Not willing for CuT/ST	Not willing for CuT/ST	30-12-2020	YES	Nil	Nil	On weekly once regiment
26	Revathy	29	P1L1	Primi para	LSCS	17-Nov-20	NIL	PPH	APH / PPH	01-01-2021	yes	Nil	Nil	On weekly once
27	Ranjitha	26	P1L1	Primi para	LN	21-Nov-20	NIL	Not wiling for CuT	Patient not willing for CuT	05-01-2021	Yes	Nil	Nil	On weekly once regiment
28	Devipriya	28	P1L1	Primi para	LSCS	23-Nov-20	NIL	PPH	APH / PPH	07-01-2021	Yes	Nil	Nil	On weekly once
29	Gunasundhari	23	P1L2	Primi para	LSCS	24-Nov-20	NIL	Not willing for CuT/ST	Not willing for CuT/ST	08-01-2021	YES	Delayed menstrual cycles	Nil	On weekly once regiment
30	Sooriya	24	P1L1	Primi para	LSCS	28-Nov-20	NIL	PPH	APH / PPH	12-01-2021	Yes	Nil	Nil	On weekly once
31	Vimala	26	P3L3	MULTI PARA	LN	29-Nov-20	NIL	Not willing for CuT/ST	Not willing for CuT/ST	13-01-2021	Yes	Nil	Nil	On weekly once regiment
32	Deepika	25	P1L1A1	Primi para	LN	30-Nov-20	NIL	Not willing for CuT/ST	Not willing for CuT/ST	14-01-2021	Yes	Nil	Nil	On weekly once regiment
33	Menaka	21	P1L1	Primi para	LSCS	7-Dec-20	NIL	PPH	APH / PPH	21-01-2021	Yes	Nil	Nil	On weekly once
34	Jananayaki	33	P1L1A1	Primi para	LSCS	15-Dec-20	NIL	PPH	APH / PPH	29-01-2021	Yes	Nil	Nil	On weekly once
35	Vishnitha antonesh	22	P1L1	Primi para	LN	18-Dec-20	NIL	Not wiling for CuT	Patient not willing for CuT	01-02-2021	Yes	Nil	Nil	On weekly once regiment
36	Nandhini	27	P1L1	Primi para	LSCS	22-Dec-20	NIL	Placenta previa	APH / PPH	05-Feb	Yes	Delayed	Nil	On weekly once
37	Madhuri	21	P1L1	Primi para	LN	23-Dec-20	NIL	Not wiling for CuT	Patient not willing for CuT	06-02-2021	Yes	Nil	Nil	On weekly once regiment
38	Saranya	30	P1L1A1	Primi para	SPONTANEOUS EXPULSION	25-Dec-20	NIL	Not wiling for CuT	Patient not willing for CuT	08-02-2021	Yes	Nil	Nil	On weekly once regiment
39	chamundeeswari	38	P1L1	Primi para	LSCS	3-Jan-21	NIL	Atonic PPH	APH / PPH	17-02-2021	yes	Nil	nil	On weekly once
40	Jeyanthi nagaraj	38	P1L1	Primi para	LN	6-Jan-21	NIL	Not wiling for CuT	Patient not willing for CuT	20-02-2021	YES	Delayed menstrual cycles	Headache	twice weekly regimen
41	Bhuvaneshwari	30	P1L1	Primi para	OUTLET FORCEPS	7-Jan-21	NIL	Not wiling for CuT	Patient not willing for CuT	21-02-2021	YES	Nil	nil	twice weekly regimen
42	Saranya Ramathan	28	P3L2	MULTI PARA	LN	26-Jan-21	NIL	Not willing for ST	Not willing for CuT/ST	12-03-2021	Yes	Nil	Nil	On weekly once regiment
43	Nasooma	23	P1L1	Primi para	LN	13-Feb-21	NIL	Not wiling for CuT	Patient not willing for CuT	30-03-2021	Yes	Nil	Nil	On weekly once regiment
44	Nalini	33	P1L1A10	Primi para	LSCS	18-Feb-21	NIL	Not wiling for CuT	Patient not willing for CuT	04-04-2021	Yes	Nil	Nil	On weekly once regiment
45	Anusiya	34	P2L2	MULTI PARA	LN	19-Feb-21	NIL	PPH	APH / PPH	05-04-2021	Yes	Nil	Nil	On weekly once
46	Kalaiselvi	35	P1L1	Primi para	LSCS	20-Feb-21	NIL	Fibroid uterus	UITERINE ANOMALIES	06-04-2021	Yes	Delayed menstrual cycles	Nil	On weekly once regiment
47	Gayathri	29	P1L1	Primi para	LSCS	21-Feb-21	NIL	PPH	APH / PPH	07-04-2021	Yes	Nil	nil	On weekly once
48	Sakira	30	P2L2	MULTI PARA	LN	3-Mar-21	NIL	Atonic PPH	APH / PPH	17-04-2021	Yes	Nil	Nil	On weekly once
49	Kalairasi madhan	33	P1L1	Primi para	LN	3-Mar-21	NIL	Atonic PPH	APH / PPH	17-04-2021	Yes	Nil	nil	On weekly once
50	Amutha valli	24	P1L1	Primi para	LSCS	6-Mar-21	NIL	PPH	APH / PPH	20-04-2021	YES	Nil	Nil	twice weekly
51	Saraswathi	32	P2L2	MULTI PARA	LN	7-Mar-21	NIL	Paediatrician deferred for ST	Paediatrician deferred for ST	21-04-2021	YES	Nil	nil	twice weekly regimen

52	Abirami	22	P1L1	Primi para	LSCS	13-Mar-21	NIL	Not wiling for CuT	Patient not willing for CuT	27-04-2021	Yes	Nil	nil	On weekly once regiment
53	vijayalakshmi	34	P1L1A1	Primi para	SPONTANEOUS EXPULSION	15-Mar-21	NIL	Not wiling for CuT	Patient not willing for CuT	29-04-2021	Yes	Oligomenorrhoea	nil	On weekly once regiment
54	Sripriya arul	18	P1L1	Primi para	LN	17-Mar-21	NIL	Not wiling for CuT	Patient not willing for CuT	01-05-2021	Yes	Nil	nil	On weekly once regiment
55	Saideepa	18	P1L1	Primi para	LN	17-Mar-21	NIL	Septate uterus	UITERINE ANOMALIES	01-05-2021	Yes	Nil	nil	On weekly once regiment
56	shabha rafi	21	P2L2	MULTI PARA	LSCS	17-Mar-21	NIL	Not willing for ST	Not willing for CuT/ST	01-05-2021	Yes	Nil	Vomiting	On weekly once regiment
57	Rahila	33	P2L2	MULTI PARA	LN	22-Mar-21	NIL	Not wiling for CuT	Patient not willing for CuT	06-05-2021	yes	Nil	nil	On weekly once regiment
58	Nandhini	19	P1L1	Primi para	LN	25-Mar-21	NIL	Not wiling for CuT	Patient not willing for CuT	09-05-2021	no	Delayed menstrual cycles	nil	on weekly once regiment
59	Bharathi saravana kumar	32	P2L2	MULTI PARA	LSCS	25-Mar-21	GDM	Not wiling for CuT	Patient not willing for CuT	09-05-2021	yes	Oligomenorrhoea	nil	On weekly once regiment
60	Kirithika	22	P1L1	Primi para	LSCS	29-Mar-21	NIL	APH	APH / PPH	13-05-2021	YES	Nil	nil	On weekly once
61	Tamilselvi	30	P2L2	MULTI PARA	LSCS	3-Apr-21	NIL	Fibroid uterus	UITERINE ANOMALIES	18-05-2021	Yes	Nil	Nil	On weekly once regiment
62	seetha	32	A1	Primi para	SPONTANEOUS	5-Apr-21	NIL	willing for chhaya	Willing for chhaya	20-05-2021	YES	Delayed	nil	On weekly once
63	Surya	32	P1L1	Primi para	LN	7-Apr-21	NIL	Not wiling for CuT	Patient not willing for CuT	22-05-2021	YES	Nil	nil	twice weekly regimen
64	Ayesha	30	P1L1	Primi para	LSCS	15-Apr-21	NIL	PPH	APH / PPH	30-05-2021	YES	Delayed	Nil	On weekly once
65	Selvarani anand babu	33	P1L1	Primi para	LN	16-Apr-21	NIL	Not wiling for CuT	Patient not willing for CuT	31-05-2021	no	Nil	nil	On weekly once regiment
66	Gayathri Gopi	20	P1L1	Primi para	LSCS	20-Apr-21	NIL	PPH	APH / PPH	04-06-2021	YES	Nil	nil	On weekly once
67	Priyanka preethi	24	P1L1	Primi para	LSCS	20-Apr-21	NIL	Not wiling for CuT	Patient not willing for CuT	04-06-2021	no	Nil	Headache	On weekly once regiment
68	Valarmathi	23	P2L2	MULTI PARA	LSCS	30-Apr-21	NIL	PPH	APH / PPH	14-06-2021	YES	Nil	nil	On weekly once
69	Aarthi	21	P1L1	Primi para	LN	3-May-21	NIL	Atonic PPH	APH / PPH	17-06-2021	Yes	Nil	Nil	On weekly once
70	keerthi soundarajan	21	P1L1	Primi para	LN	5-May-21	NIL	Not wiling for CuT	Patient not willing for CuT	19-06-2021	YES	Nil	Nil	On weekly once regiment
71	Abirami venugopal	26	P2L2	MULTI PARA	LSCS	5-May-21	NIL	Paediatrician deferred for ST	Paediatrician deferred for ST	19-06-2021	YES	Nil	Nausea	On weekly once regiment
72	sheeba dhanraj	28	P1L1A1	Primi para	SPONTANEOUS EXPULSION	5-May-21	NIL	Not wiling for CuT	Patient not willing for CuT	19-06-2021	YES	Nil	Nil	On weekly once regiment
73	Jayanthi stalin	33	P1L1	Primi para	LN	13-May-21	NIL	Not wiling for CuT	Patient not willing for CuT	27-06-2021	YES	Nil	nil	On weekly once regiment
74	Backiyalakshmi	18	P1L1	Primi para	LN	18-May-21	NIL	Septate uterus	UITERINE ANOMALIES	02-07-2021	YES	Nil	nil	On weekly once regiment
75	Keerthika karthikeyan	24	P2L2	MULTI PARA	LN	20-May-21	NIL	Not wiling for CuT	Patient not willing for CuT	04-07-2021	YES	Nil	Nil	On weekly once regiment
76	Ramya prabhu	32	A1	Primi para	SPONTANEOUS	28-May-21	NIL	willing for chhaya	Willing for chhaya	12-07-2021	YES	Nil	Nausea	twice weekly
77	Sudha	28	P1L1	Primi para	LN	1-Jun-21	NIL	PPH	APH / PPH	16-07-2021	Yes	Nil	Nil	On weekly once
78	Durga	26	P1L1	Primi para	LSCS	3-Jun-21	NIL	Fibroid uterus	UITERINE ANOMALIES	18-07-2021	Yes	Mennorrhagia	Nil	On weekly once regiment
79	sathya madhavan	24	P1L1	Primi para	LN	4-Jun-21	NIL	Not wiling for CuT	Patient not willing for CuT	19-07-2021	YES	Oligomenorrhoea	nil	On weekly once regiment
80	Shoba Sridhar	33	P1L1	Primi para	LN	4-Jun-21	GHTN	Not wiling for CuT	Patient not willing for CuT	19-07-2021	YES	Nil	nil	On weekly once regiment

81	Parvin Davidraj	22	P1L1	Primi para	LN	5-Jun-21	NIL	Not wiling for CuT	Patient not willing for CuT	20-07-2021	YES	Nil	nil	On weekly once regiment
82	Gowthami	26	P1L1	Primi para	LN	17-Jun-21	NIL	Not wiling for CuT	Patient not willing for CuT	01-08-2021	YES	Nil	Nil	twice weekly regimen
83	Arasa kumari	26	P1L1A2	Primi para	LN	18-Jun-21	NIL	Not wiling for CuT	Patient not willing for CuT	02-08-2021	no	Nil	Backache	twice weekly regimen
84	sheeba vignesh	26	P1L1	Primi para	LSCS	18-Jun-21	NIL	PPH	APH / PPH	02-08-2021	YES	Nil	Nausea	twice weekly
85	Anjali	25	P1L1	Primi para	LSCS	19-Jun-21	NIL	PPH	APH / PPH	03-08-2021	YES	Nil	Nil	twice weekly
86	Meghashner	29	P1L1	Primi para	LN	20-Jun-21	NIL	Not wiling for CuT	Patient not willing for CuT	04--08-21	no	Nil	nil	twice weekly regimen
87	Sughashini navamani	29	P2L2	MULTI PARA	LN	24-Jun-21	NIL	Not wiling for CuT	Patient not willing for CuT	08-08-2021	YES	Nil	Nil	twice weekly regimen
88	Linju Arul pandian	23	P1L1	Primi para	LN	25-Jun-21	NIL	Adherent placenta	APH / PPH	09-08-2021	YES	Nil	Nil	twice weekly
89	Adhilakshmi	18	P1L1A1	Primi para	SPONTANEOUS	28-Jun-21	NIL	willing for chhaya	Willing for chhaya	12-08-2021	YES	Nil	nil	twice weekly
90	Vani	25	P2L2	MULTI PARA	LSCS	1-Jul-21	NIL	Not willing for CuT/ST	Not willing for CuT/ST	15-08-2021	Yes	Nil	Nil	On weekly once regiment
91	Nalini	26	P2L2	MULTI PARA	LN	1-Jul-21	NIL	Not willing for ST	Not willing for CuT/ST	15-08-2021	yes	Nil	Nil	On weekly once regiment
92	Vaitheeswari	29	P1L1A3	Primi para	SPONTANEOUS EXPULSION	1-Jul-21	NIL	Not wiling for CuT	Patient not willing for CuT	15-08-2021	Yes	Nil	Nil	On weekly once regiment
93	Aarthi balamurugan	19	P1L1	Primi para	LN	4-Jul-21	NIL	Not wiling for CuT	Patient not willing for CuT	18-08-2021	YES	Nil	nil	On weekly once regiment
94	Nandhini prasanth	27	P1L1A1	Primi para	SPONTANEOUS	4-Jul-21	NIL	willing for chhaya	Willing for chhaya	18-08-2021	YES	no	Nil	UPT POSITIVE
95	Syed ali fathima	29	P1L1	Primi para	LSCS	5-Jul-21	NIL	PPH	APH / PPH	19-08-2021	YES	Nil	Backache	On weekly once
96	Shantha malini vinoth	30	P2L2	MULTI PARA	LN	5-Jul-21	NIL	Patient not willing for PS	Paediatrician deferred for ST	19-08-2021	YES	Nil	Nil	On weekly once regiment
97	krishnaveni kumaraguru	32	P1L1	Primi para	SPONTANEOUS	5-Jul-21	Chronic hypertension	willing for chhaya	Willing for chhaya	19-08-2021	YES	Nil	nil	On weekly once
98	Devika viswanath	32	P2L2	MULTI PARA	LSCS	5-Jul-21	NIL	Patient not willing for CuT	Patient not willing for CuT	19-08-2021	YES	Nil	nil	On weekly once regiment
99	kirthika venkat	34	P2L2	MULTI PARA	LSCS	5-Jul-21	NIL	Paediatrician deferred for ST	Paediatrician deferred for ST	19-08-2021	YES	Nil	nil	On weekly once regiment
100	Surekha karthikeyan	24	P2L1A1	MULTI PARA	VACUUM	13-Jul-21	CHRONIC RHD/MILD MS	Bicornuate uterus	UITERINE ANOMALIES	27-08-2021	YES	Oligomenorrhoea	Nil	twice weekly regimen
101	Selvi ramu	28	P1L1	Primi para	LN	15-Jul-21	NIL	VLBW/Pt not willing for CuT	Patient not willing for CuT	29-08-2021	YES	Nil	Nil	twice weekly regimen
102	Gomathi karthick	31	P1L1	Primi para	LN	18-Jul-21	NIL	Not wiling for CuT	Patient not willing for CuT	01-09-2021	YES	Nil	nil	twice weekly regimen
103	Meena Dinesh	28	P1L1	Primi para	LSCS	20-Jul-21	NIL	Not wiling for CuT	Patient not willing for CuT	03-09-2021	yes	Nil	Nil	twice weekly regimen
104	Bhuvaneshwari Parthasarathi	20	P1L1A1	Primi para	SPONTANEOUS EXPULSION	23-Jul-21	NIL	willing for chhaya	Willing for chhaya	06-09-2021	yes	no	nil	UPT POSITIVE
105	Kavitha Devendran	42	P1L1	Primi para	LSCS	26-Jul-21	NIL	PPH	APH / PPH	09-09-2021	YES	Nil	nil	twice weekly
106	Revathi	23	P1L1A1	Primi para	SPONTANEOUS EXPULSION	4-Aug-21	NIL	willing for chhaya	Willing for chhaya	18-09-2021	YES	Nil	nil	On weekly once regiment
107	Ashwini	25	P1L1	Primi para	LN	4-Aug-21	NIL	Not wiling for CuT	Patient not willing for CuT	18-09-2021	YES	Nil	Nausea	On weekly once regiment
108	Jamundheswari	32	P1L1	Primi para	LSCS	7-Aug-21	NIL	PPH	APH / PPH	21-09-2021	YES	Nil	nil	twice weekly
109	Nivetha	23	P1L1	Primi para	VACUUM	2-Sep-21	GHTN	Not wiling for CuT	Patient not willing for CuT	14-10-2021	Yes	Nil	Nil	On weekly once regiment

110	Rabithul	27	P1L1	Primi para	LN	6-Sep-21	NIL	Not wiling for CuT	Patient not willing for CuT	18-10-2021	YES	Oligomenorrhoea	Backache	twice weekly regimen
111	Repakka	20	P1L1	Primi para	LN	7-Sep-21	NIL	Not wiling for CuT	Patient not willing for CuT	19-10-2021	Yes	Nil	Nil	On weekly once regiment
112	Paarimalakumari	28	P1L1	Primi para	LSCS	8-Sep-21	NIL	Not wiling for CuT	Patient not willing for CuT	20-10-2021	Yes	Nil	Nausea	On weekly once regiment
113	Boomadevi	40	P1L1	Primi para	LN	9-Sep-21	NIL	Not wiling for CuT	Patient not willing for CuT	21-10-2021	yes	Nil	Nil	On weekly once regiment
114	Dharani Dasarathan	28	P2L2	MULTI PARA	LSCS	7-Oct-21	NIL	ABRUPTIO PLACENTA	APH / PPH	14-11-2021	YES	Nil	Nil	twice weekly
115	Jeevitha	27	P1L1	Primi para	LSCS	8-Oct-21	NIL	PPH	APH / PPH	15-11-2022	YES	Nil	Nil	On weekly once
116	Divya Lingeswaran	28	P2L2	MULTI PARA	LSCS	9-0ct-2021	GALL STONES	Bicornuate uterus	UITERINE ANOMALIES	16-11-2022	Yes	Nil	Nil	On weekly once regiment
117	Nivetha yogendran	27	P1L1	Primi para	LSCS	10-Oct-21	NIL	Atonic PPH	APH / PPH	17-11-2022	Yes	Nil	Nil	On weekly once
118	Bhuvaneshwari	29	P1L1	Primi para	LN	11-Oct-21	NIL	Not wiling for CuT	Patient not willing for CuT	18-11-2022	YES	Nil	Nil	On weekly once regiment