A PROSPECTIVE STUDY OF CENTCHROMAN USERS WITH SPECIAL REFERENCE TO ITS CONTRACEPTIVE BENEFIT
Hema Sreedharan Nair¹, Priyasree Jayasimhan²

¹Assistant Professor, Department of Obstetrics and Gynaecology, Government Medical College, Kollam.
²Assistant Professor, Department of Obstetrics and Gynaecology, Government Medical College, Thiruvananthapuram.

ABSTRACT

BACKGROUND
Centchroman is a novel nonsteroidal contraceptive that offers a unique combination of weak estrogenic and potent antiestrogenic properties. Centchroman inhibits the fertilised ovum from implantation and thus prevents pregnancy. The development of the steroidal contraceptive in the late 1950s was a big event in reproductive research. The pill has, however, some inherent logistic limitations such as the need for continuous administration and thus associated likelihood of side effects. This underscored the need for a safer alternative for preventing pregnancy such as postcoital contraceptives and those that interfere with events between ovulation and implantation. Hence, in this study, a clinical evaluation of centchroman for its contraceptive study was carried out on 153 women and the contraceptive benefit was evaluated at monthly intervals.

MATERIALS AND METHODS
It was a prospective study done in the family planning department of Sree Avittom Thirunal Hospital. Postnatal patients reporting to the family planning department at 6 weeks postpartum and also patients opting for medical termination of pregnancy or cases following spontaneous abortion were selected for the study. Contraceptive efficacy of centchroman was studied over a 12-month period.

RESULTS
153 subjects were studied. 63% of the subjects were in the age group of 20-24 years. 93% subjects used centchroman as a spacing method after first delivery and 6% after second delivery. 43% of acceptors were following MTP or abortion, 35% were postpartum cases and 22% were interval acceptors. 5.2% of subjects in the study group had rheumatic heart disease, 2% had hypertension and 2.6% had diabetes mellitus. Duration of use ranged from 3 months in 153 subjects to 12 months in 130 subjects. The main cause for discontinuation of centchroman was menstrual irregularity. Menstrual complaints were noted in 45% of the subjects. The major menstrual complaint was delayed cycle in 26% subjects and scanty flow in 12%. Pearl index calculated for centchroman was 2. This was slightly higher compared to the product specification of 1-1.8. Of the 153 patients in the study group, pregnancy occurred in 11 patients. 4 pregnancies were user failures and seven pregnancies were drug failures.

CONCLUSION
1. Centchroman is a safe nonsteroidal contraceptive for spacing of pregnancies.
2. Centchroman does not alter carbohydrate or lipid metabolism, coagulation factors or blood pressure and hence can be safely used in women in whom steroidal pills are contraindicated.
3. Menstrual irregularity is the major reason for discontinuation of centchroman.
4. Majority of menstrual disorders revert back to normal by 6-9 months of use.
5. Centchroman does not cause pathological ovarian enlargement.
6. Pearl index of centchroman was calculated to be 2.
7. Resumption of fertility following discontinuation was prompt.

KEYWORDS
Centchroman, Pearl Index, Menstrual Irregularity, Nonsteroidal Contraceptive.

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been estimated that by imparting effective control, we can reduce the colossal maternal mortality rate by at least 25%. The need for a safer alternative to progesterone-oestrogen combination pills has been felt since the sixties. Researchers all over the world have been designing and synthesising nonsteroidal oestrogen antagonists that would act by interfering with the delicate balance between oestrogen and progesterone at the uterine level without interfering with the synthesis or blood levels. After twenty two years of extensive research, scientists at the Central Drug Research Institute have developed a compound-centchroman in 1967. Centchroman, the world’s first nonsteroidal oral contraceptive agent has been launched for clinical use in 1991. It is a safe and reliable contraceptive agent ideally suited for spacing of birth in women who have no major medical contraindications.

Centchroman creates an imbalance between embryo development and uterine development. By its unique mode of action, centchroman accelerates embryo development and at the same time suppresses uterine development. Consequently, the implantation of the embryo in the uterine wall is prevented and pregnancy averted. This is a unique need oriented contraceptive agent included in the National Family Welfare Programme of India.

**Pharmacodynamics**

The chroman derivative is pharmacologically inert, biologically non-interfering and metabolically safe. Since carbohydrate, lipid and protein metabolisms are not interfered with and coagulation factors are not altered, centchroman is suited for contraception in high-risk subjects such as diabetics, hypertensives or cardiac patients. The only side effect noted is prolonged cycles due to long proliferative phase.

**Mechanism of Action**

Centchroman does not have any deleterious effect on gonadotropin release. It does not inhibit ovulation, but may delay it by prolonging the follicular phase. It does not inhibit corpus luteal function. Contraceptive effect is due to disorganised endometrial end-organ response to the reproductive steroids. The antifertility effect of centchroman could be due to;

1. By its potent antiestrogenic effect, it completely blocks mitosis in the uterine epithelial tissue. Thus, endometrial development is reduced leading to poor mitotic activity in the luminal glandular epithelium and stroma. The effect is achieved in a lower dose of 30-60 mg per week.
2. It has partial inhibitory effect on stromal mitosis reflecting a weak antiprogestational action. These strong antiestrogenic and weak antiprogestational actions prevent proper endometrial decidualisation.
3. Defective ovum transport is an added contraceptive effect. Tubal locking of embryos at the ampullary isthmal junction occurs either due to direct action of the compound on the preimplantation embryos or mediated through an alteration of tubal function.

4. Other mechanisms include delayed implantation and reduced rate of zonal shedding by preimplantation blastocyst.
5. By its potent antiestrogenic effect, it inhibits cervical mucus-sperm interaction and transport. In contraceptive efficacy, if user failure could be taken care of, centchroman is comparable to that of the best low dose oral contraceptive pill such as desogestrel 150 micrograms -ethinyl estradiol 30 micrograms combinations.

**Mechanism of Interception**

It is a very effective postcoital contraceptive agent with hardly 1% failure rate. The dosage is 60 mg (2 tablets) administered for 2 doses 12 hours apart within 24 hours of coital exposure. It is 100% effective when given between days 1 to 4 of exposure. Postcoital contraception is due to its effect on zygote, ovum transport and blastocyst development. The main side effect is delay in menstruation causing confusion. Adequate trials are yet to be conducted. The main advantages of centchroman over the other agents are:

1. Absence of side effects such as nausea, headache, depression, mood changes, mastalgia and poor libido.
2. No androgenic side effects such as acne and hirsutism.
3. Devoid of metabolic complications such as weight gain, hypertension, coagulation disorders, hyperglycaemia and abnormal lipid profile.

**Other Effects**

The antiestrogenic effect of centchroman varies with the concentration gradient of the drug.

1. At lower doses of 30-60 mg per week, by its potent antiestrogenic action, it blocks mitosis in the uterine epithelial tissue. This prevents endometrial decidualisation thus effecting implantation failure and contraception.
2. In a dose of 60-120 mg per week, it alters the cervical mucus-sperm transportation and thereby contraception.
3. At 120 mg per week dose, it has definite antiestrogenic effect on the neuroendocrine axis promoting stimulation of the axis and thus could induce gonadotropin synthesis, release and ovulation. At this concentration, the antiestrogenic effect is reflected by decreased maturation index in vaginal cytology.

**Non-Contraceptive Benefits**

Apart from the contraceptive and interceptive benefits of centchroman, this agent also exhibits certain other benefits to the patients as with the use of the low-dose oral contraceptive pills. Many of the non-contraceptive benefits of oral contraceptive pills are shared by centchroman. In addition, the latter does not exhibit alterations in endocrine, biochemical and metabolic milieu. These non-
contraceptive benefits are based on the selective estrogenic and the antiestrogenic properties of the drug. It exhibits oestrogen antagonistic effect on endometrium. Ormeloxifene efficiently inhibits the growth of cisplatin-resistant ovarian cancer cells. Centchroman has also been shown to decrease the incidence of epithelial ovarian cancer, pelvic inflammatory disease, ectopic pregnancy and iron-deficiency anaemia.

**Benefits Based on Estrogenic Action**

1. **Perimenopausal Symptoms.** By virtue of the mild estrogenic action, centchroman can be used to relieve the premenopausal symptoms such as hot flushes, fatigue, insomnia and headache. It could also be the contraceptive of choice in the premenopausal subject.

2. **Bone Metabolism** Desogestrel-containing oral contraceptive pills are recommended for premenopausal subjects for preventing increasing bone turnover and the decrease in bone density seen in women in this age group who experience an impaired ovarian function and a decrease in estradiol production. Since centchroman has estrogenic properties, it could support bone balance just as the oral contraceptive combined pill without affecting the coagulability of blood. Centchroman inhibits osteoclastic bone resorption by some in vitro studies. Regular and prolonged usage could also improve the pattern of menstrual cyclicity.

**AIMS AND OBJECTIVES**

1. To study the effectiveness of centchroman as a nonsteroidal oral contraceptive.
2. To study the possible causes for centchroman failure.
3. To study the incidence of other side effects of centchroman.

**MATERIALS AND METHODS**

The study was conducted in the Family Planning Department of Sree Avittom Thirunal Hospital. Postnatal patients reporting at 6 weeks postpartum and also patients opting for medical termination of pregnancy or cases following spontaneous abortion and those for interval contraception during a 12-month period.

**Inclusion Criteria**

1. Patients between 20-35 years.
2. Normal menstrual cycles.
3. Not on any other form of contraceptive.
4. Willing to come for follow up.
5. Medical illnesses where steroidal pills are contraindicated such as heart disease and diabetes mellitus.

**Exclusion Criteria**

1. History of jaundice or liver disease.
2. Cervical hyperplasia.
3. Irregular menstrual cycles.

In the study, no comparative group was selected as no other nonsteroidal pill is available. For all practical purposes, the claim put forward by the manufacturers was taken as standard. A detailed history of the patient including age, parity, educational status, systemic illness, medical termination of pregnancy, nature of last delivery, detailed menstrual history, previous use of contraceptives, reason for discontinuation and whether lactating or not was taken.

Examination of these patients consisted of a general examination, systemic examination and gynaecological examination. Each case was informed of the delay in the onset of menses. In gynaecological examination, the state of the cervix, position, mobility, size of uterus and any palpable adnexal masses were noted. A cervical smear was also taken. Haemoglobin estimation and urine examination was done. Centchroman is available as colourless, odourless tablets of 8 in a pack. It is supplied by Hindustan Latex. Patients are instructed to take one tablet on the first day of the menstrual period. Following MTP or abortion, the patient is instructed to take the tablet on the day of MTP or abortion. Postpartum patients are instructed to take the tablet on the day of the postnatal visit, i.e. at 6 weeks irrespective of whether cycles are resumed or not. For the first 3 months, centchroman should be taken twice a week. If the first tablet is taken on a Sunday, the second tablet should be taken on a Wednesday. Additional barrier contraception is advised for the first month. From the fourth month onwards, the patient is asked to take centchroman once a week, i.e. on the same day, the first pill was taken. When a tablet is missed, the patient is advised to take the missed tablet as soon as possible and normal schedule days adhered to. If a dose is missed for two or more days, but less than 7 days, the patient is asked to continue the normal schedule as well as an additional precaution such as condom till the next period. If missed for more than 7 days, the dosage is reinitiated as a new user twice a week for the first 3 months and weekly thereafter.

Patient is asked to report for monthly follow up. Any clinical complaint reported by the patient is noted. Menstrual history including cycle length, type of bleeding and vaginal discharge are noted. Breast and vaginal examinations and body weight are recorded every month. In case of delayed periods, pregnancy test is performed after 2 weeks of delay. If not pregnant, the patient is asked to continue centchroman as per schedule. In case of pregnancy, the drug is discontinued and patient given the option of termination. Patients reporting any side effect or poor compliance are discontinued. The contraceptive efficacy of the drug is determined from the number of pregnancies due to method failure during the study period. Any pregnancy due to noncompliance of the prescribed treatment schedule is classified as user failure.

**RESULTS**

During the study period, 153 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 status at acceptance, failure rate, e.t.c. The salient features are summarised as follows:

1. The age pattern ranged from 20-35 years with maximum number in the age group of 20-24 years, i.e. 60.1%.
2. 93% of patients in the study group had one living child, 6% had 2 living children and 1% had no living children.
3. The maximum number of acceptors were following MTP or abortion- 43%, 35% were postpartum cases and 22% were interval acceptance.
4. Eight patients in the study group had rheumatic heart disease, 3 had hypertension and one was a case of perforated typhoid ulcer, which had been operated upon.
5. All patients in the study group used centchroman for 3 months, 97% for 6 months, 93% used the contraceptive for 9 months and 85% for one year.
6. The major cause for discontinuation was menstrual irregularity seen in 6 cases. Other causes were inability to come for follow up in 1% and desire to conceive in 2%.
7. The drug-related systemic side effects were very few and included headache, giddiness and vomiting in less than 0.5% of acceptors. Menstrual complaints were noted in 45% of the users. Delayed cycles were noted in 26%, decreased flow in 12%, amenorrhea in 7% and heavy flow in 0.6%.
8. The frequency of menstrual complaints decreased as the duration of use increased. Maximum number of patients with menstrual complaints was seen during the first 3 months of use. Sonographic study of ovarian morphology was done in 28% acceptors. Corpus luteal cysts were detected in 17.8%, follicular cysts in 17% and normal ovaries in 71.4%.

Failures
Of the 153 patients screened, 11 became pregnant. 4 pregnancies were due to user failure. The patients had either missed the tablets or had not used an additional method of contraception for the first month. 7 cases were method failures.

Pearl index
The Pearl index of centchroman was calculated using the formula, Pearl index = Number of accidental pregnancies + 1200/cycles of use and this was found to be 2. In computing the Pearl index, only the method failure cases were taken.

Failure and Duration of Use
Of the method failures, 2 cases occurred after 4 months of use, 2 cases after 5 months of use, one case at 6 months, one case at 7 months and one case at 9 months. No failures were seen at 10, 11 and 12 months of use. From the graph, it can be seen that the failure rate decreases as the duration of use increases and stabilises at 10 months of use. 10 patients opted for medical termination of pregnancy.

Association between Age of the Patient and Failure Rate
Using the chi-square test, it was found that there was no reason to assume dependence of the 2 factors in this group of patients.

Association between Obstetric Status and Failure Rate
A higher failure rate was observed in patients taking centchroman after MTP or abortion compared to interval or postpartum cases. A chi-square test applied to note the association found that there is no reason to suppose dependence of the 2 factors in the present sample that has been subjected to the study.

Return of Fertility After Discontinuation of Centchroman
Of the 3 patients who discontinued centchroman, one patient conceived 4 months after discontinuation, one patient after 6 months and one patient was lost to follow up.

DISCUSSION
Centchroman 3, 4 trans 22 dimethyl 3 phenyl 4 pyrrolidone ethoxyphenyl 7 methoxy chroman is a nonsteroidal antifertility agent synthesised at the Central Drug Research Institute, Lucknow. It is devoid of gross pharmacological effects seen with steroidal oral contraceptives and has excellent therapeutic index. It provides acceptable pregnancy protection in the postcoital and weekly schedule in women.

Age of the Subjects
Of the 153 acceptors, 92 patients, i.e. 60% were in the age group of 20-24 years. According to the National Family Health Survey done in Kerala, the mean age for marriage for females is 22 years. This correlates with the present study since the majority of acceptors were in the age group of 20-24 years. Patients above 35 years were excluded from the study.
Parity
93% of patients in the study group had one child, 6% had 2 living children and 1% were nullipara. In Kerala, temporary methods of contraception are accepted mainly by women with one living child while permanent methods are accepted mainly by women with 2 or more living children. In the present study too, majority of the acceptors were women with one living child. 1% of the acceptors were post vesicular mole evacuation cases and they were nulliparae.

<table>
<thead>
<tr>
<th>Parity</th>
<th>Numbers</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>One living child</td>
<td>142</td>
<td>63</td>
</tr>
<tr>
<td>2 living children</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2. Distribution According to Parity

Use in Systemic Illnesses
Centchroman was used in 8 patients with rheumatic heart disease, 3 patients with hypertension and 4 patients with diabetes mellitus. Unlike steroidal pills, which are relatively contraindicated in the above situations, none of the patients developed any complications with centchroman. Thus, it can be safely used in patients with organic diseases in whom steroidal pills are contraindicated.

<table>
<thead>
<tr>
<th>Systemic Illness</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>8</td>
<td>5.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
<td>2.6</td>
</tr>
<tr>
<td>Intestinal perforation operated</td>
<td>1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Table 4. Acceptance Rate in Patients with Systemic Illness

Duration of use
All patients in the study group used centchroman for the first 3 months. 4 patients in the study group became pregnant in the first 3 months. This was mainly user failure where the patient had either missed the tablet or had not used an additional protection for the first month. Rest of the 149 patients continued in the study for 6 months, but at the end of one year, 19 patients withdrew from the study. The major cause for discontinuation of centchroman was menstrual irregularity mainly delayed cycles. Other causes included inability to come for follow up, desire to conceive or adoption of an alternate method.

<table>
<thead>
<tr>
<th>Duration (Months)</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>153</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>149</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>142</td>
<td>93</td>
</tr>
<tr>
<td>12</td>
<td>130</td>
<td>85</td>
</tr>
</tbody>
</table>

Table 5. Duration of Use
Complaints
Systemic side effects were very few ranging from giddiness (2 cases), headache (1 case) and vomiting (1 case). This may represent the normal incidence of such happening in the population. This is in contrast to steroidal oral contraceptive pills, which have an incidence of headache of 2.8%, nausea (1.2%) and breast tenderness of 8% (Rajan 1986).

Menstrual Complaints
Were noted in 45% of the acceptors. This was found to be higher compared to the standard claimed by the manufacturers of 8-10%. The major menstrual complaint was delayed cycles seen in 26% of the acceptors. 12% of the acceptors experienced infrequent cycles and 7% experienced amenorrhea. One patient experienced heavy flow. The frequency of menstrual complaints decreased with time and by the first year of use, only 12% had menstrual complaints. In case of delay, a pregnancy test was done after 2 weeks of delay.

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed cycles</td>
<td>40</td>
<td>26</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Table 6a. Menstrual Complaints

Ovarian Morphology
Sonographic evaluation of the ovaries was done in 28 patients. 20 patients had sonographically normal-looking ovaries. Follicular cysts were seen in 4 patients and corpus luteal cysts were seen in 4 patients. None of the cysts were larger than 2.5-3 cm, so the incidence of ovarian enlargement following centchroman use cannot be considered significant.

<table>
<thead>
<tr>
<th>Duration of Use (Months)</th>
<th>Complaints</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>69</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>12</td>
<td>18</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 6b. Menstrual Complaints

Failures
Centchroman marketed as Saheli has a failure rate of only 1.63%, which is not higher than oral contraceptive pills. Of the 153 acceptors, 11 cases of pregnancies were recorded in the study. Of the 11 cases, four cases occurred in the first 3 months of use. All the four were user failures.

Rest of the 7 cases of pregnancies were method failures. The number of pregnancies decreased with increasing duration of use. By the 4th month of use, 2 patients were pregnant, 2 patients by 5 months, one patient by 6 months, one patient by 7 months and one patient by 9 months.

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients screened</td>
<td>153</td>
<td>--</td>
</tr>
<tr>
<td>Pregnanies</td>
<td>11</td>
<td>7.18</td>
</tr>
<tr>
<td>User failure</td>
<td>4</td>
<td>2.6</td>
</tr>
<tr>
<td>Method of failure</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 8. Failures

Pearl Index
Was calculated taking into account the method failures only. This was found to be two. This was found to be slightly higher than the claims put forward by the company - Failure rate of 1.8/HWY. There was a higher failure rate in patients taking centchroman after MTP or abortion, but the association was not statistically significant.

Reversibility of Fertility
Of the 3 women who withdrew from the study because they wanted to conceive, one patient conceived within 4 months, another within 6 months and the other patient was lost to follow up. This shows that reversal of fertility is prompt following discontinuation of centchroman.
CONCLUSION

1. Centchroman is a safe nonsteroidal contraceptive for spacing of pregnancies.
2. Centchroman does not alter carbohydrate or lipid metabolism, coagulation factors or blood pressure and hence can be safely used in women in whom steroidal pills are contraindicated.
3. Menstrual irregularity is the major reason for discontinuation of centchroman.
4. Majority of menstrual disorders revert to normal by 6-9 months of use.
5. Centchroman does not cause pathological ovarian enlargement.
6. The Pearl index of centchroman in this study is 2, which is higher than that laid out by the product manufacturers of 1-1.8.
7. Resumption of fertility following discontinuation of centchroman was prompt.

REFERENCES
