REVIEW OF LITERATURE
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As early as 1926 it has been observed that oestrogen prevent pregnancy in rats and mice when injected within a day or two after mating (Parkes, A.S. and Bellberg, C.W.).

In 1935, the same observation was again made (Burdick H.O. and Pincus G.).

In 1939, oral oestrogens too were shown to yield same results (Parkes, A.S., Dodds, E.C. and Noble, R.L.).

Not much attention was, however, devoted to this important discovery at that time, perhaps because the interest was not focussed sharply on the problem of population growth. By 1960, logistic difficulties in mass administration and side effects associated with 21 day regimen of progesterone oestrogen combined pill were getting known and this called for development of alternative contraceptive methods.
The designing of molecules possessing oestrogenic/anti-oestrogenic (atypical oestrogenic) and anti progestational properties which would possibly interfere with primarily intraovarian events appeared a possible approach to the problem.

Demonstration of oestrogenic activity of Diphenylethlenes (Dodds, B.C., Goldberg, L., Lawson, W. and Robinson, R., 1938) and oestrogenic/anti-oestrogenic activity of triphenylethlenes (Segal, S.J. and Nelson, W.O., 1958) made clear that oestrogenic activity is not highly structure specific. Incorporation of triarylethylene structure in a rigid framework appeared promising for design of pregnancy inhibiting agents and 1, 2-Diarylindenes, 1,2-Diaryldihydronaphthalenes have been reported to exhibit marked antifertility activity in experimental animal.

It was found that 2-phenyl-3 (p-(3-pyrrolidinethoxy) phenyl)-6-methoxyfuran and related compounds like 2-phenyl-3 (p-(3-pyrrolidinethoxy) phenyl)-naphto (2, 1-b) furan possess the property of preventing pregnancy in rhesus monkey when given within 24 hrs of coital act. Both these compound
were dropped from further study due to undesirable side effects in chronic toxicity studies.

Activity seen in 2,3-dephenylbenzofurans led to synthesis and screening of a variety of related structural types and significant antifertility activity has been observed in compounds like 3,4-dephenylchromones and 3,4 dephenyl chromans.

It was observed that in 3,4 dephenyl chromans, trans diastereomers were in general more active than the corresponding c-is compounds. Examination of Dreiding models of the isomeric chromans suggest that differential effect of 2 alkyl substituent on biological activity is due to change in confrontation of molecules, the trans isomers retain considerable planarity even when substituted at position 2, while same substitution induces considerable distortion in c-is compound. This would have important implication in receptor binding and this leads to the synthesis of trans-2, 2 dimethyl-3 phenyl-4-p-(3 pyrrolindonmethoxy) -phenyl)-7-methoxychroman (Conachroman).
Since than various actions of centehroman has been studied:

A - **Antifertility efficacy**:

Oral administration of centehroman at dose of 0.25 mg/kg and above (upto 4 mg/kg) on days 1-5 post coitum caused 100 percent prevention of pregnancy in rats and mice. In rats a single feeding of centehroman at dose of 1.25 and 2.5 mg/kg on any one of days 1-4 post coitum was 100 percent effective in preventing pregnancy. On day 5 the litter size was considerably reduced (55-62 percent) at both the doses. A slightly lower dose 1 mg/kg was fully effective (100 percent) in preventing pregnancy when administered on days 1, 2 or 3 and partially effective (60 percent) on day 4 and ineffective on day 5 post coitum. 0.5 mg/kg dose was virtually ineffective. Thus 1.25 mg/kg is minimum effective dose in single day post coitum regime. In mice a single feeding of centehroman (1.25 mg/kg) was 100 percent effective in preventing pregnancy in mice when given on days 1, 2 or 3 post coitum. In dogs when centehroman administered orally (2.5 and 5 mg/kg) or intramuscularly (1.5 and 2.5 mg/kg), 24 hours after mating caused 100
percent prevention of pregnancy. Oral administration of centchroman (2.5 mg/kg) on the day following the coital act caused cent percent prevention of pregnancy during a 8 month trial in rhesus monkey. This administration did not lead to permanent sterility in rats, since discontinuation of the treatment caused prompt return to normal fertility (V.P. Kamboj et al 1977).

Contraceptive efficacy trial of centchroman both in post coital (60 mg) and weekly schedules of 120, 60 mg dose in women of reproductive age (20-35 years) with parity of one or two plus and nonlactating has been evaluated for more than 6 months. Centchroman both at weekly and post coital schedule provided acceptable pregnancy. In weekly dose this comes to 4-5 pregnancies in 100 women years of use.

II- HORMONAL PROPERTIES :

(1) Oestrogenic activity :

Oral (0.1, 0.25, 0.5, 1.25 and 2.0 mg/kg) or subcutaneous (1, 5, 10, 50 and 100 µg/animal) administration of centchroman caused a significant increase in uterine weight in immature rats. The
uterotrophic potency was 40-50 percent of that of oestrone by oral route and about 23-44 percent parenterally. Although maximum increase in uterine weight was noticed at the highest dose, there was no indication of a dose response relationship. Doses of 1.25 and 2.0 mg/kg by oral route and 50 and 100 µg by subcutaneous route induced vaginal opening and smears presented proestrus and/or estrus condition. Uterotrophic activity reached its peak 2 days after administration of the compound or oestrogen and became virtually nil by 15 days. Oestrone induced vaginal cornification (Estrus smear) persisted between 2 and 7 days post treatment. Proestrus/estrus type smears were produced by cestchroman but not until 5 days and lasted till day 7 (V.P. Kamboj, et al 1977).

Oral administration of cestchroman from 5-20 µg (total dose) in mice produced a linear increase in uterine weight. Similar dose related increase is also seen with ethinyl estradiol and mestranol. An additional index of oestrogen like activity was vaginal opening. Oestrogenic effect as assessed by vaginal cornification in ovariectomized
mice after oral administration was 8 and 10 times less than that of mestranol and ethinyl estradiol respectively (Manshi, S.R., Nair, R.K. and Devi, P.K., 1977).

11. **Antiestrogenic property**: Injection or oral administration of oestrone (1 µg/animal) to immature female rats stimulated uterine weight and caused vaginal cornification at all doses. Simultaneous administration of oestrone and centehroman (0.125 mg/kg to 5 mg/kg) oral or parenteral also caused a significant increase in uterine weight but extent of uteroatrophic response was less than that produced by oestrone alone. The vaginal cornification was also suppressed. Histological features of uterus were similar to those compound alone group. Thus centehroman showed antiuteroatrophic activity. In delayed implantation test, there was no effect on number of implantation after concurrent administration of estradiol dipropionate and centehroman from days 9-12 of pregnancy. Thus centehroman did not show any antioestrogenic activity in this test (V.P. Kashi et al 1977).
Centchroman inhibits mitosis when given 1 or 2 days of pregnancy in mice (Manshi, S.R., Nair, R.K. and Devi, P.K., 1977).

Administration of centchroman to preweanling rats caused premature opening of vagina and an increase in ovarian weight, luteinization of follicular cells, ovulation and corpus luteum formation. These changes were brought about by premature release of follicle stimulating hormone with luteinizing hormone with resultant stimulation of ovary. Lack of proportionate increase in uterine weight in presence of ovarian stimulation in centchroman treated animals can probably be explained on the basis of antioestrogenic property of this drug. The presumed stimulation of secretion of gonadotrophins may be due to antioestrogenic action of compound and partly to its direct positive feedback action on luteinizing hormone secretion (J.K. Dutta and S. Roy 1980).

(iii) Progestational and antiprogestational effect:

Effect of centchroman on the uptake of
progesterone by different tissue of ovariectomized rats not showed increase uptake of centhromen by target tissue and any antiprogestational action could not be demonstrated (Kumari et al 1976).

In Clauserberg Assay when Morothisterone administered orally at different dose levels, produced a graded response on rabbit endometrium. Administration of centhromen failed to induced a similar proliferation reflecting absence of progestational activity. Same dose of centhromen when administered alongwith Morothisterone was able to inhibit partially proliferative endometrium suggesting a weak antiprogestational activity. Pregnancy maintenance in ovariectomized mice at dose of 25 μg/day of centhromen is not possible indicating absence of progestational activity. Antiprogestational activity was further reflected by its ability to inhibit decidua formation when administered alone or in combination of progesterone (Nair, R.K., Shyto, T.A. and Mamshi, S.R., 1977).

Same observation had also been done by V.P. Kamboj et al in 1977.
When adult female rats were ovariectomized on the 3rd day of pregnancy and were treated with 2 or 6 mg progesterone daily for 15 days starting from day of operation. During last five days of progesterone therapy 1 mg/kg of centchroman was given daily. The results show that administration of centchroman did not counteract the increase in weight and total contents of biochemical constituent of uterus caused by progesterone therapy. On the contrary there have been evidence for additive effect. This supports the view that centchroman does not have any antiprostational property (S.N. Roy and J.K. Datta, 1977).

Centchroman given to rats at dose of 300 µg and 1.5 mg/kg body weight respectively in 2 ml aqueous solution. Both doses of centchroman caused a decrease in level of progesterone present in plasma. Centchroman did not cause any change in uterine weight. It did not prevent the uptake and retention of radioactive progesterone by uterus. Assuming that there is increased progesterone receptors at proestrus rats as it
was seen in guinea pigs by Milogram (1972). Censthorfan was given at dioestrus and uptake of progesterone was studied at proestrus. Results showed that censthorfan did not prevent uptake and retention of progesterone by uterus and thus supports that censthorfan per se had no anti progestational property (Kumari, G.L. et al 1977).

C- Endocrine pharmacology:

Effect on pituitary:

Censthorfan had no effect on weight and total gonadotrophin content of the young male rat pituitary (V.P. Kamboj et al 1977).


In man there is distinct rise in serum and urinary levels of luteinizing hormone after 7 days of censthorfan treatment (Sheth, A.R. et al 1977).
It had gonadotrophin modulating properties in female rats and women. It caused induction of ovulation in anovulatory women and stimulated luteinizing hormone secretion in gonadal dysgenesis patient with or without estrogen therapy. It had also been reported to stimulates luteinizing hormone secretion in normal male volunteers (Roy, S.N. et al, 1977).

**Effect on thyroid:**

Cenochromen (1.25 mg/kg for 5 days oral) had no significant effect on thyroid weight and I 131 uptake in immature female rhesus monkey (V.P. Kamboj et al 1977).

**Effect on adrenal:**

Cenochromen (1.25 mg/kg for 5 days oral) did not influence the excretion rate of 24 hours urinary 17-OH. EGS in immature female monkeys whereas estrone caused a slight increase (V.P. Kamboj et al 1977).
D- Effect on foetus and fertility of the offspring:

Oral administration of centchroman (1.25 mg/kg and 2 mg/kg) on days 5-7 of pregnancy to rats had no effect on developing blastocyst or newly implanted foetus, however 17-32 percent less blastocysts implanted as compared to controls. A single feeding (1.25 mg/kg) on day 8 of pregnancy caused 30 percent fetal loss as against 14 percent in control rats. No deleterious effect on genital organs of foetus or neonates were found on histological examination. No fetal masculinization or teratogenicity was noticed. The fertility performance of the offspring was studied for 2 generations and no detrimental effect was noticed (V.P. Kamboj, B.S., Setty Harish Chandra, S.K. Roy and A.B. Kar 1977).

E- Mechanism of action:

Centchroman inhibits pregnancy changes in uterine. It thus appears that interaction between centchroman and endogenous hormones might play a role in inhibition of decidual cell reaction. Lowering of lactic acid and glycogen concentration in uterine fluid of treated animals may be an
important factors in contraceptive action since
blastocysts is unlikely to survive in milieu depleted
of these things (V.P. Kamboj, M.M. Singh and A.B.
Kar 1973).

In another experiment done by V.P. Kamboj
et al in 1977, following observation was made :-

(1) **Effect on ova** :

Centchroman (1.25 mg/kg) administered
orally on day 1 of pregnancy did not impede transport
and fertilization of ova. There was arrest of
development in 30 percent of the ova when the
collection of ova from tubes and uterus was done
and examined.

(2) **Effect on decidua formation** :

A single oral administration of
centchroman prevented decidua formation in
tubectomized, ovariecetomized and traumatized rats
treated with progesterone (2 mg daily) for 3 days.
In controls, the traumatized horn was significantly
heavier than its contralateral horn and that of
centchroman treated animals and showed massive
decidual swellings.
(3) **Effect of oestrogen and progesterone on antifertility action:**

Centchroman interferes with action of both the oestrogen and progesterone since neither of these hormones per se could induce implantation in compound treated rats.

A study done over human female volunteers showed that centchroman may have its contraceptive effect mainly due to its action over cervical mucus and endometrium affecting sperm transport and implantation (Vaidya, R.A., Joshi, U., Meherji P., Rege, S., Betrabet, S., Joshi, L., Sheth, A. and Devi, P.K., 1977).

The administration of centchroman decreases significantly potassium concentration of uterine fluid on day 5 of pregnancy in rats. Anti implantation action of centchroman may be due to decrease in potassium concentration of uterine fluid on 5th day of pregnancy which thereafter may increase negative membrane potential on endometrium with the result a negative charged endometrium repels blastocyst bearing a similar charge and thus prevents implantation (Anand, G. Prakash and S.K. Roy, 1981).
F- General pharmacology and toxicity:

The effect of centchroman (doses ranging from contraceptive dose to 1/5 LD₅₀) on nictitating membrane, central nervous system, cardiovascular system, respiration, isolated tissues, diuretic and anti inflammatory activities was studied in different animals and compared with standard drugs.

The compound was found to have anti inflammatory activity, incomplete α-adrenergic blockade, non specific spasmylytic activity and a mild anorexigenic effect at high doses.

Acute toxicity:

This was determined by giving graded dose of compound to groups of mice and rats. LD₅₀ was determined by intraperitoneal route in mice and oral routes both in mice and rats. LD₅₀ was 400 mg/kg by intraperitoneal route. Oral contraceptive dose in mice and rats is 1.25 mg/kg. Since the oral LD₅₀ is more than 1600 mg/kg, the compound had a very high margin safety and at this dose mortality rate is 20 percent. It is devoid of any significant gross effects or CNS effects. The
smorexigenic activity observed at only high dose 

is unlikely to be a drawback in clinical dose 

range. The mild respiratory stimulation could be 
a reflex effect due to hypotension is again of not 
material consequence. The block of nictitating 
membrane and dose dependent hypotension is explainable 
by its adrenergic blockade action (I.M. Chak, 

Chronic toxicity :

Centchroman was administered orally at 
doses of 6.25, 12.5 and 25 mg/kg once daily for 
seven months to young adult male and female albino 
rats. It did not show any haematological, biochemical 
or histological evidence of toxicity. Similar study 
was also carried out in rhesus monkey with various 
doses. Haematology as well as biochemistry and 
histopathology of different organs did not reveal 
any adverse effect. Thus centchroman is devoid of 
any toxicity up to twenty times the contraceptive 
dose (Mukherjee, S.S., Sethi, N., Srivastava, G.N., 
In another study on effect of long term treatment with centchroman on reproductive organs of female rats showed no untoward effect on genital tracts of rats (P.K. Mehrotra 1980).

C. Clinical Pharmacology:

Centchroman was subjected to clinical pharmacological studies in healthy male and female volunteers as a double blind non cross over trial. In single dose study centchroman was given in doses gradually increasing from 5 to 320 mg in 17 male and 23 female in the age group of 19 to 37 years. Volunteers on placebo showed symptoms was 56 percent whereas volunteers receiving centchroman showed symptoms in 35 percent. No abnormal physical and laboratory finding was detected in any of groups following medication. In multiple dose study done over 20 female of 20 to 39 years of age, each volunteer received either 60 or 120 mg of centchroman once daily for 30 days. Control subjects received placebo. No side effect or abnormality in laboratory reports was detected. In 2 subjects (1 of each group)
showed delayed menstruation by 35 to 60 days and another 2 cases had scanty periods. (N. Chandra, R.C. Srimal, V.P. Kamboj, B.N. Dhawan and N.K. Gupta, 1977).

**M- Teratogenicity:**

As steroidal contraceptives do not produce congenital malformation but show other side effect like multiple birth, tubal pregnancies and abortion as high as 17 percent, a study was undertaken to evaluate the influence of centchroman on prenatal development of foetus in mice and rabbits. Oral administration of centchroman to pregnant mice and rabbits at doses of 20, 40 and 80 times of 100 percent anti-fertility dose (ED_{100}) during period of organogenesis. It did not cause any abortion or congenital anomalies. There were no defects in skeleton and different organs of foetus. The resorption rate in mice was within normal limits, only 50 mg/kg, the higher dose, showed a higher rate that was 26 percent. In rabbit it is 60 percent, as against 12-14 percent in controls of both the species. The litter size and weight in both species were comparable to
control. No abnormality developed in offspring during postnatal growth up to 6 weeks in both animals (N. Sethi, 1977).