REVIEW OF LITERATURE
RELATION OF LIPID LIPOPROTEIN PROFILE
WITH MENSTRUAL CYCLE

Menstruation is periodic discharge of blood, mucus
and cellular debris from the uterine mucosa and occurs at
more or less regular cyclical and predictable interval
from menarche to menopause except during pregnancy,
lactation, anovulation, or pharmacological intervention.

Hormonal changes of cycle affects function of
liver and so the lipid lipoprotein metabolism of body.
There is 10-15% cyclic suppression of plasma total choles-
terol, LDL and LDL apo beta during luteal phase while
HDL increases during luteal phase of menstrual cycle

RELATION OF LIPID LIPOPROTEIN PROFILE
DURING PREGNANCY

During pregnancy total plasma triglyceride and
cholesterol levels rise because of an increase in all
lipoprotein including LDL, VLDL and HDL enriched in
triglycerides. Increase of total apoprotein is caused by
higher levels of VLDL apoprotein B. This hyperlipidaemia
of pregnancy is attributed to derranged hepatic function
during pregnancy (Svanberg and Vikrot, 1955; Aurell and
EFFECT OF STEROIDAL CONTRACEPTIVES ON PITUITARY

Spellacy et al (1980) showed that oral contraceptives containing 50 microgram or more ethenyl estradiol suppress gonadotrophin release to a greater extent than the lower dose formulation. Mishell et al (1977) have provided evidence in humans that combined use of estrogens and progestins has a direct suppressive effect on pituitary gonadotrophins.

EFFECT OF CENTCHROMAN ON PITUITARY

Kamboj et al (1977) studied that centchroman (1.25 mg/kg for 7 days orally) had no effect on weight and total gonadotrophin content of the young male rat pituitary.

EFFECT OF STEROIDAL ORAL CONTRACEPTIVES ON OVARY

Maqueno et al (1972) studied that a large number of atretic follicles was seen when compared with ovaries from women not using contraceptives steroids. But this observation has not been confirmed in other studies by Starup et al, (1974).

EFFECT OF CENTCHROMAN ON OVARY

Kamboj et al (1977) studied that centchroman (0.25 mg/kg and 2.50 mg/kg) administered orally to immature female rats thrice daily for 3 days and there was no effect on their ovaries or their responsiveness
to exogenous gonadotrophins.

Singh et al (1982) gave centchroman even up to 10 times. The contraceptives dose to immature female rats and found no effect on ovaries or their responsiveness to exogenous gonadotrophins. In mated rats it has no effect on ovarian function even at 50 times the anti-implantation dose. Weekly doses of 120, 60 and 25 mg centchroman to women do not inhibit ovulation and show characteristic cyclic hormonal pattern. Thus, even at 4 times the contraceptive dose per week, centchroman does not suppress pituitary or ovarian function (Vaidya et al, 1977).

EFFECT OF ORAL STEROIDAL CONTRACEPTIVES ON UTERUS

Kar et al (1965) administered Enovid cyclically to prepubertal rhesus monkeys for period of 90 days to 3 years and observed an increase in uterine weight together with growth of serosa, muscularis and endometrium.

EFFECT OF CENTCHROMAN ON UTERUS

Oral administration of centchroman from 5-20 mg (total dose) in mice produced a linear increase in uterine weight. Similar dose related increase in uterine weight was also seen with ethynyl estradiol and mestranol. Simultaneous administration of oestrone and centchroman also cause in uterine weight but extent of uterotrophic response was less than that produced by oestrone alone (Kamboj et al, 1977).
EFFECT OF ORAL STEROIDAL CONTRACEPTIVES
AND CENTCHROMAN ON VAGINA

Oral administration of centchroman in ovariec-
tomized mice causes vaginal cornification which was 8
and 10 times less than that of mestranol and ethynyl
estradiol respectively (Munshi, Nair and Devi, 1977).

EFFECT OF ORAL STEROIDAL CONTRACEPTIVES ON CERVIX

The sequential administration of estrogen and
progestin induces a predecidual reaction together with
considerable secretory activity of the cervical glands
(Dunkin et al, 1963).

In 1967, Taylor et al reported on 13 patients
who had a distinctive type of atypical polypoidal endo-
cervical hyperplasia, among those 13 patients, 12 were
taking oral steroidal contraceptives. Stern et al (1977)
reported a prospective study of 300 women who had cervical
dysplasia matched with 300 women who had normal cervical
smears. The combined oral contraceptive pills chosen for
the study contained 100 micro-gram mestranol and 1 mg
ethynodiol diacetate. The patient with dysplasia who were
taking oral contraceptives (compared with non users) showed
a significantly increased conversion of dysplasia to
carcinoma in situ after extended use (7-6 years).

EFFECT OF CENTCHROMAN ON CERVIX

Centchroman has no untoward effects on the
cervix and uterus in women with cervical erosion or
bulky uterus due to multiparity (Puri et al, 1988).
EFFECT OF STEROIDAL ORAL CONTRACEPTIVES ON BREASTS

Kahn et al (1965) postulated that norethymodral like other progestins stimulates the release of prolactin from pituitary.

The determination of deoxyribonucleic acid (DNA) has also been used as an index of mammary gland growth. Norethindrone did not increase the DNA content of the mammary gland and a combination of norethindrone with estradiol benzoate did not produce any effect greater than that of estradiol benzoate alone (Griffith et al, 1963).

The data from Royal College of General Practitioner study (1974) and the Walnut Creek contraceptive drug study (Ramcharan et al, 1974) suggested a slightly increased risk of breast cancer in women under 35 years of age with prolonged oral steroidal contraceptive use.

EFFECT OF CENTCHROMAN ON FOETUS

Oral administration of centchroman during the period of organogenesis to pregnant mice (25, 50, 100 mg/kg) and rabbits (20, 40, 80 mg/kg) did not have any deleterious effect either on mother or their litters. Histologically there was no evidence of any skeletal or visceral malformation in the foetuses (Sethi, 1977).
EFFECT OF STEROIDAL CONTRACEPTIVES ON FOETUS

Masculinization of female rats was obtained when the following progestins were administered during pregnancy: Norethindrone (Revesz et al., 1960), Norethynodral (Scholer et al., 1961), Medroxy progesterone acetate (Scholer et al., 1961).

ORAL HORMONAL CONTRACEPTIVES (COMBINED AND SEQUENTIAL) AND LIPID LIPOPROTEIN PROFILE

Lipoprotein metabolism is an important aspect of liver functions, which is apparently influenced by oestrogen progesterone treatment. Lipoproteins are classified according to their relative amount of lipid and proteins. LDL and VLDL can be described as carriers to peripheral tissues. HDL containing about 50% of protein are at present regarded as cholesterol regulators which transfer cholesterol from peripheral tissues including vascular epithelium to liver. HDL has also been suggested to block peripheral LDL receptors thereby reducing cholesterol uptake and storage in endothelial cells of vessels.

1. Serum Cholesterol

Wynn et al (1966) studied 102 women receiving oral contraceptive for more than 3 months and compared them with 75 normal females not taking any hormonal therapy. This study revealed an increase in serum cholesterol.

Faston et al (1970) studied effect of three
types of oral contraceptives having same constituents but in different amounts and found significant increase in group accepting high dose.

Wynn et al (1971) studied serum lipid levels in subjects using various combinations of contraceptive pills and found that sequential pills revealed least changes among the various pills studied.

Arora et al (1988) studied effect of sequential hormone on serum cholesterol in females of reproductive age group and found increase in serum cholesterol from 171.30 mg/dl to 192.34 mg/dl after 2 months of hormone use and to 213.45 mg/dl after 3 months of use.

2. **Serum Triglycerides**

Faston (1970) studied effect of dependent dose regimen of oral contraceptives on serum lipid levels and found significant rise in serum triglyceride levels in females using combined pills but no change with progestin only pills. In combined pills there was continuous rise but with progestin only pills there was a decrease after 3 months of oral contraceptive use in triglyceride levels and remain static for 2 years.

Wynn et al (1979) studied effect of various oral contraceptive pills containing doses of ethynyl oestradiol from 30 microgram to 150 microgram and revealed a dose related rise in triglyceride which was greatest in high dose oestrogen.
Krause et al (1983) found significant change in triglyceride levels 55 and 65 mg/dl for control and test groups respectively taking EE/NG (30 microgram/0.3 mg).

Arora et al (1988) found a significant rise in serum triglycerides levels in females using sequential hormones for 3 months.

3. **High Density Lipoproteins (HDL)**

Aurell and Cramer (1966) found a significant fall in serum HDL levels with use of oral contraceptives. Values fell from 60 to 46 mg/dl in test group.

Krause et al (1977) found that change in HDL depends upon relative amount of oestrogen and progestin. Progestin component is known to counter the effect of oestrogen on HDL level.

Krause et al (1983) compared two low dose oral pills in relation to lipid subclasses and found no change with norgestral group while significant change with norethindrone group.

Arora et al (1988) found that there was significant fall in levels of serum HDL in women using sequential hormones.

Estrogen usage alone increased the mean HDL levels approximately 10–20 mg/dl with EE₂, 20 microgram or 50 microgram increased HDL to a greater extent than daily conjugated estrogen 0.625 mg or 1.25 mg. Progestrogen only preparations, decrease mean HDL cholesterol concentration approximately 7–15 mg/dl and this occurs with both
17-acetoxy progesterone derivatives as well as the 19-nortestosterone products. There is direct relationship between the dose of progestin and the reduction of HDL cholesterol (Bradley, Wingard and Petitti et al, 1978).

Briggs (1979) found almost all combinations products to decrease HDL cholesterol somewhat with 30 microgram EE₂ product, those pills with 0.5 mg norethindrone had minimal effect on mean HDL cholesterol while doubling the dose of protestogen to 1 mg norethindrone decreased mean HDL by 7 mg/dl (Levy and Feinleib, 1975).

The estrogen in a combined pill appears to decrease the serum concentration of low density lipoprotein, to increase high density lipoprotein but some progestine cause the reverse (Stadel, 1981). Almost certainly, the adverse changes noted in HDL; LDL ratios are the consequences of the 19-nortesto-sterone progestins and these changes are likely related to the specific progestin and its dose (Kauppinen-Makelin and colleagues, 1992). Importantly progestins can change the relative amount of total HDL, HDL₂ and HDL₃ (Tikanen and associates, 1981; 1982). It is believed that the HDL₂ fraction provides cardiovascular protection (Miller and cc-workers, 1982). Therefore the estrogen and progestin effects the specific HDL₂ fraction are of special importance because oral contraceptive may alter a women's cardiovascular risk even though total HDL cholesterol values are unchanged. Briggs (1982) reported no change in total
HDL with levonorgestrel use, but Hatcher and colleagues (1990) found that it decreased HDL$_2$ and increased HDL$_3$. Apparently norethindrone containing oral contraceptives do not alter HDL$_2$ fractions (Hatches and associates, 1990; Krause and colleagues, 1983). More recently, however, Patsch and co-workers (1989) reported that two triphasic formulations containing norethindrone and one containing levonorgestrel, all had similar effects on total HDL, HDL$_2$ and LDL.

4. **Serum LDL and VLDL**

Krause et al (1983) found that VLDL increased with only noregestrel. LDL was significantly lower in norethisterone group.

Arora et al (1988) observed significant rise in serum LDL and VLDL levels in females of reproductive age group using sequential pills for 3 months.

5. **Centchroman and its effect on lipid levels**

Nityanand et al (1988) studied 122 women taking centchroman for more than one year, there was no change in serum lipid profile as compared to control subjects.