REVIEW OF LITERATURE
The term menopause, climacteric, peri and post menopause are used interchangeably applied to different stages at the end of reproductive years in the human female. Menopause is derived from the Greek word men or month pause "To Stop" means cessation of menses, the climacteric or critical age is delivered from the Greek word "Klimacter" : Rung of the ladder and has been defined as transitory those in the life of human female between the age of reproductive and nonproductive ability (first : International congress on the menopause, 1976).

As the climacteric is regarded primarily as estrogen deficiency syndrome but typical complains. However those are which begin when estrogen production decline or stop. It occurs either spontaneously in the perimenopausal period or enforced after bilateral oophrectomy. These symptoms are likely caused directly or indirectly by estrogen withdrawal and they can be treated successfully with estrogen substitution called as hormone replacement therapy.

However replacement therapy is available in many formulation combination and routes. Oral route, various routes of H.R.T. are also available such as subcutaneous
implants, percutaneous gel, vaginal ring and pessaries and transdermal device. Since no single product or regimes can be prescribed to all women or aplpliciater of these option and explain the therapeutic choice of patience and physician.

Menopause occurs at a mean age of 51 years. The most significant symptom of menopausal transition in some women is menstrual irregularity (Mc kinley S.M. , Brambille 07 Posner JG - 1992

Cardivascular disease is a major cause of morbidity and death in modern society and leading cause of death in older women with a incidence that approaches that in men of comparable age. The risk factors include cigarette smoking, male sex, advancing age and elevated blood lipid contents, elevated blood pressure and alteration in lipoprotein metabolism are major contributors to cardiovascular disease in general and to coronary heart disease in particular.

**Age and Sex as Risk Factor For CVD**

Women develop CHD much less frequently than men however sex difference decreased with advancing age possibly due to menopause.

Oliver and Boyd (1955) showed that combined effects of cholesterol and blood pressure are powerful contributors of CHD both in men and women but at any level of risk factors
singly or in combination women were at low risk, that men of
same age group but this incidence decreased with advancing
age.

Sperry and Webb (1950) showed that age itself is a risk
factor for CVD due to associated increase in cholesterol and
triglycerides.

**Menopause and Cardiovascular Disease**

Snazzerdan and Oliver (1963) showed that premature
spontaneous menopause was associated with increased
incidence of ischaemic heart disease.

The Framingham's study by william B Kannel et al (1976)
showed that comparison of the incidence of cardiovascular
disease at specified ages showed upto 55 a two fold increase
among post menopausal versus pre-menopausal . The impact
was greater on younger ages than older both with surgical
natural menopause. Same was observed by Hjortland et al.

Castelli WP et al (1977) and Miller (1987) showed that the
levels of high density lipoprotein, were lower in persons with
CHD than in those without the disease. It was found in most
age , race , sex specific groups. The inverse HDL cholesterol
CHD association was not appreciably diminished when
adjusted for levels of low density lipoproteins and triglycerides.
LDL, total cholesterol and triglycerides were directly related to CHD prevalence.

Gordon et al (1978) showed that there was increased risk of CVD associated in women under 45 associated with natural or surgical menopause.

Rosenberg et al (1981) evaluated the relation between age at menopause and the risk of ischaemic heart disease. It showed that women oopherectomised before age of 35 years were at 7.2 times risk that of premenopausal women. Hysterectomy without oopherectomy was only weakly associated with increased risk.

Colditz et al (1987) showed that women who had undergone bilateral oopherectomy had increased risk of coronary heart disease as compared to premenopausal women.

Effect of Gonadal Steroids on Plasma Lipoproteins and Individual Phospholipids

The lower incidence of coronary heart disease has lead to many to believe that endocrine factors are of importance for the homeostasis of lipids in the plasma but also for the deposition and metabolism of lipid in the vessel wall.
Oliver and Boyd (1955) showed small but significant changes in the plasma lipid levels occur during menstrual cycle which is correlated with the varistions that occur in the hormonal secretion.

Kim and Kalkaff et al (1981) showed from menarche to menopause in a female there in 10-15% cycle suppression of plasma cholesterol, LDL, LDL alpha, beta during luteal phase while HDL cholesterol increases during other second half of the cycle.

**Effect of Natural or Surgical Menopause on Lipoprotein Metabolism**

Lipid metabolism is an important aspect of liver function which is apparently influenced by oestrogen and progesterone. In circulation lipids, which are insoluble in water are transported within special carriers particles called lipoprotein. Lipoprotein contains hydrophobic glyceride and cholesterol esters molecules covered with a surface monolayer of phospolipids esterified cholesterol and specific proteins. The apolipoproteins, the lipo proteins are separated into density classes according to their relative amount of lipid and proteins. They are divided according to their density into low density lipoproteins, very low density lipoproteins and high density lipoproteins.
Low density lipoproteins and very low density lipoproteins particles can be described as carriers to peripheral tissue. The high density lipoproteins containing about 50% of proteins are at present regarded as cholesterol regulators which transfer cholesterol from peripheral tissues including vascular endothelium to the liver. Subsequent excretion of cholesterol through bils and biochemistry involved plasma enzymes lecithin cholesterol acyl transferase. HDL has also been suggested to block peripheral LDL receptors thereby reducing cholesterol uptake and storage in endothelial cells of vassals. The development of atherosclerosis is dependent on many factors excess storage of cholesterol in arterial wall is however of major importance in this event and an impairment of HDL levels might thus accelerate this process.

1- Serum Cholesterol

Oliver and Boyd (1959) showed that there was significant rise in serum cholesterol by ovariectomy.

Sznajderman and oliver (1963) showed a significant rise in serum cholesterol in women with premature menopause those compared with pre-menopausal women of same age group.

Arnold and Ritterband et al (1963) showed that levels of serum cholesterol was significantly higher in oopherectomised than those of hysterectomised women.
William and Kannel et al (1976) also showed increased serum cholesterol level menopausal women than pre-menopausal women.

Pansini et al (1984) showed that there was steady rise in serum cholesterol value in women with bilateral ovariectomy within 6 months of operation.

Farrish et al (1990) showed significant increase in cholesterol level ($p<0.05$) in 6 months of operation from a mean of 3.57m mol/l to 4.21m mol/l.

2. Serum triglyceride

Oliver and Boyd (1959) showed a significant elevation of serum triglycerides in bilateral oopherectomised women.

Sznajderman and Oliver (1963) showed that serum triglycerides were significantly raised ($p<0.01$) in study group of women with premature menopause as compared to healthy women of same age group but there was not significant fall in the level after menopause.

Aitken et al (1971) showed a significant rise in serum triglyceride with age. However, the levels of serum triglyceride in oopherectomised had slightly lower values but was statistically not significant.
Punnonen and Rauramo (1976) showed that the serum triglycerides level rose significantly ($p<0.01$) after 1 months of bilateral oopheractomy.

Pansini et al. (1984) showed no significant rise in triglyceride level within 3 months of bilateral oopheractomy.

Notaionitz et al. (1983) showed that serum triglyceride levels were higher in oopherectomised women (71%, $p<0.02$).

Farrish et al. (1990) showed no significant rise in serum triglyceride level in bilateral oopherectomised women.

3. **High Density Lipoprotein**

High density lipoprotein particles transport cholesterol from peripheral tissue including vascular endothelium to liver where it is metabolised and excreted through bile. An impairment of high density lipoprotein will accelerate excess storage of cholesterol in endothelium of arterial wall one of the factors leading to development of atherosclerosis.

The lower the high density lipoprotein level there is higher the risk of atherosclerotic manifestation HDL is heterogenous group and has got two main subfractions HDL$_2$ and HDL$_3$. Low levels of HDL$_2$ are clearly related to high risk of atherogenesity while total HDL and HDL$_3$ are not.
William and Kannel (1976) showed that serum HDL level is higher in women than men, but no discernable change in alpha fraction with menopause.

Punnonen and Rauramo (1980) showed that HDL cholesterol levels before and one month after castration did not differ significantly.

Notevitz et al (1981) showed that HDL levels in oopherectomised women were 27% lower than in intact women.

Pansini et al (1984) showed that HDL cholesterol has biphasic dependence on time with initial decrease and later significant increase during the later 3 months.

Farrish et al (1990) measured HDL subfraction to assess any change in relative amounts of cholesterol carried on HDL2, HDL3. No significant change was found in either fraction.

Low Density Lipoprotein and Very Density Low Density Lipoprotein

LDL and VLDL are directly related to atherogenesis of person and hence their elevated levels are also reported with conditions favouring atherogenesis. The values of LDL are calculated from standard formula. VLDL is 20% of the serum triglyceride. VLDL is supposed to carry triglycerides found in the liver or possibly in the intestine to body tissues where
triglycerides and fatty acids are hydrolysed by lipoprotein lipase enzyme. Metabolites are used for energy during the metabolic process and remanants left behind are taken by liver and converted to LDL. Accumulation of remanants favours atherogenesis and oestrogens reported to enhance the removal of remanants.

Arnold and Ritterband et al (1963) showed that mean serum cholesterol and percent of beta lipoprotein in oopherectomised women under 50 were higher then the hysterectomised women.

William and Kannel et al (1976) showed that cholesterol level in the prebeta fraction and beta fractions for women rises rapidly while remaining essentially unchanged for men older than that age range.

Pansini et al (1984) initial declined then increased in apoprotein B levels the main carriers of LDL and VLDL fractions a significant increase upto 12.5% of the pre-operative value.

The rise in LDL cholesterol value showed tendentious increase without variation the 5% level.

Farrish et al (1990) showed a significant rise in LDL cholesterol (p<0.05) in the 6 weeks after operation from a mean of 3.57 m mol to 4.21 m mol/l.
Effect of Hormone Replacement Therapy in Post Menopausal women on serum lipid

Increasing age has an influence upon circulating lipid levels. Both cholesterol and triglyceride concentration increases with age and there is augmented risk of atherosclerotic disease. Increased cholesterol level is associated with increased LDL and VLDL levels. HDL carrying 20% of cholesterol has a cardioprotective effect.

Of the two major subfractions of HDL cholesterol the HDL₂ is associated with reduced risk of cardiovascular disease diseases. The higher HDL concentration in females is due to higher HDL₂ concentration. Various studies have shown the blood lipid changes associated with oestrogen LDL cholesterol.

Experimental work by Imai et al (1980) indicated that it is not free cholesterol that causes intimal vessel damage but rather abnormal oxidation product of cholesterol then it can be assumed that young ovariectomised owmen are at greater risk of cardiovascular disease due to oestrogen deficiency.

Aitken (1971) showed that administration of 20-40 ug of mestronol daily in oopherectomised women was associated with significant fall in serum cholesterol and a significant rise in serum triglycerides.
Gustoson and Svanborg (1972) : an oestrogenic steroid was given for three weeks period to 6 oopherectomised women. There as significant rise in HDL and VLDL and decrease in LDL levels.

Punnonen and Rauramo (1976) showed that administration of 2 mg estradiol valerate in oopherectomised women showed significant rise in serum phospholipids but no significant effect on cholesterol and triglyceride levels.

Patterson et al (1980) showed that there was little alterations in the mean serum cholesterol concentration and triglycerides with cyclical oestrogen but sequential oestradiol valerate and norgestrel significantly reduced the mean serum cholesterol and significant rise in serum triglyceride in post menopausal women.

Punnonen and Rauramo (1980) showd that injections of both 10 mg of oestradiol valerate and 2.5 mg of estradiol benzoate plus 10 mg estradiol theryl propionate caused significant rise in HDL cholesterol level in bilateral oopherectomised women.

Notelovitz et al (1983) : different types and doses of oestrogen was administered in bilateral oopherectomised women. After 3 months serum cholesterol levels were unaffected by 1 and 2 mg of micronized 17 beta oestradiol or 0.625 and 1.25 mg of conjugated equine oestrogen.
Triglyceride levels were significantly elevated with conjugated oestrogen administration. A trend towards higher relative protein of high density lipoprotein and lower relative proportion of low density lipoproteins was observed in all.

The writing group for PEPI Trial (1995) It was demonstrated that there is a decreased in total cholesterol, an increasing in HDL level by about 10% , and decreased in LDL level also by about 10% on unopposed oestrogen for HRT.

Darling et al (1997) When HRT in pharma continuous conjugated equine estrogen with medroxyprogesteron acetate 5 Mg was compare with simvastatin , both caused a similar degree increase in HDL level.

**Menopausal Symptomatology**

According to Levgaten & Kraines (1966) Symptoms of menopause may begin in perimenopausal period, maximum of compleicts usually 2-3 years menopause and then slowly decreases.

The climacteric refers to the period before and after menopause during which Ovarian activity is diminished and gradually ceases. This period may manifest as short term syndrome and long term complications ,while short term syndrome must be treated and long term complications must be privented.
The climacteric syndrome includes early (Stage I early symptoms, intermediate (Stage II) and late symptoms (Stage III) and complication.

**Stage - I Early Symptoms :-**

Vasomotor Instability : Hot flushes, night sweating, vertigo palpitation and weakness.

**Stage - II Intermediate Symptoms :-**

a. **Urogenital atrophy** :- Such as atrophy of vagina breast and urethra etc. Symptoms produced by this, are vaginal dryness, pruritis, discharge, dyspareunia and urethral syndrome such as stress incontinance, burning, frequency & urgency etc.

b. **Psychosomatic changes** :- Anxiety, Irritability, depression, insomnia, sexuality changes, diminished libido.

**Stage - III Long term Complications :-**

- **Osteoporosis** :- Presented as Bony pains and spontaneous fracture.
- Ischaemic Heart Disease.
- Cardiovascular changes.

**Stage I Vasomotor Instability :**

**Hot flushes** : Patients complains of Intense heat felt most commonly on the face the arms and the upper part of body. The hot flushes is inturn followed by profuse sweating and
often accompanied by palpitation, Dizziness, Anxiety and Insomnia or sleep disturbances.

It is often the earliest and most common climacteric symptom presents in 60-80% of perimenopausal and post-menopausal female, Average duration of hot flush is the minut. Frequency of the flush varies from few episode per week to several episodes per hour. Hot flush can occur at any time in day or night. Hot flushes are the Episode of inappropriate heat loss. During flush skin temperature may rise by 5°C these hot flushes are accompanied by vasodilatation and elevation of levels of leutenizing hormones.

Symptoms of vascular instability subside by itself within 2-3 years.

According to Novak typical climacteric symptoms in this series are only the vasomotor complains. It Namely hot flushes and profuse sweating often. accompanied by dizziness, palpitation and tingling in upper extremities.

According to Utian palpitation sometimes occurring at the same time at hot flushes age apprentally, not directly caused by oestrogen deficiency.

**Stage II - Intermediate Symptoms:**

- **Symptoms due to urogenital atrophy:**
  Atrophic changes occur with greater severity in tissues with a preponderance of estrogen receptors, which have been
detected in abundance in the human vagina and uterus, which are considered prime hormonal target organs. High concentration of estrogen receptors are also found in distal ureter and trigone of the bladder.

Recent studies have found hormone receptors in women in pelvis musculature like the levator ani and urogenital ligaments like round lagament (Smith et al 1990).

**Vaginal Symptoms:**

Low estrogen levels result in thinning of the vaginal epithelium, decreased vascularity and loss of elasticity. The epithelial cells remain immature, their glycogen content reduce and pH increases. The predominant symptoms resulting from these changes are senile vaginitis, vaginal dryness, itching and dyspareunia. Dyspareunia and vaginal dryness lead to decreased sexuality in females.

According to Raz R, Stamm M. (1993), vaginal symptoms include dryness, dyspareunia, and recurrent vaginal infections. Fortunately, these symptoms are reversible with estrogen therapy.

Urinary Complaints: -

Recurrent III, Burning, frequency, urgency, nocturia etc. genuine stress urinary incontinence may be related to estrogen deficiency.

Atrophy of distal urethra and stenosis ultimately causes outflow obstruction.

Stress incontinence - Estrogen receptors are found in distal part of urethra. Post menopausal changes lead to atrophy of mucosa, decreased vascularity and diminished tone of urethral muscles result in recurrent attack of UTI and stress incontinence. In stress incontinence patient complaining of passage of urine with coughing, snizzling and laughing. This is socially embarrassing situation (Reckess et al 1992).

b. Psychological Symptoms: -

Psychological symptoms such as anxiety, irritability, depression & insomnia are most common, just before the onset of menopause.

Falling estrogen level are directly related to mood changes and psychosomatic symptoms vasomotor symptoms often lead to sleep deprivation, chronic fatigue and hence related to psychological symptom such as depression, irritability and mood changes.
Social factors like breavement, departure of children from home and changing circumstances may contribute significantly to menopausal psychological effects.

**Stage III - Long Term Complication :-**

*a. Cardiovascular disorders :-*

Hypertension and atherosclerosis increase in women after menopause and leads to increase incidence of ischemic heart disease.

Menopause increased risk to coronary disease due to adverse changes in serum lipids and lipoprotein levels and the declining estrogen levels.

Although the risk of death from coronary artery disease is at least three times as great for men as for women before menopause the relative risk for women increases significantly after menopause.

*b. Osteoporosis :-*

A sudden decrease in the gonadal hormones estrogen and progesterone as seen after oophorectomy or with the onset of amenorrhea, is associated with dramatic changes in the remodeling of bone, resulting decrease in trabecular bone and predispose the person for spontaneous fracture.
Symptoms produced by these changes are body pain, backache loss of weight, kyphosis, wrist fracture after minor frame and spontaneous fracture of long bones.

Numerous biochemical demonstration has shown that estrogen probably inhibit the activity of osteoclast and may render a negative calcium balance by inhibiting the loss of calcium via urine and feaces.

According to peck W.A. (1990). Bone loss after menopause in exaggerated to a rate of 3-5% per year.

This loss is most rapid during the first 5 years after menopause, when up to 201 of the expected lifeline loss from the femoral neck may occur (Hedlund LR, Gallagher, J.C.1989).

**Other Symptoms** :-

Skin changes Estrogen receptors are also found in skin and collagen tissues. In menopausal period, due to decrease in estrogen receptor, skin becomes dry and wrinkled. Due to increased production of melanin, complexion becomes dark usually patients of high class society or professional ladies present with this cosmetic problem.

**Changes in vaginal Smear following Menopause** :-

The most sensitive parameter of estrogen action on the vaginal epithelium is vaginal cytology. In post menopausal
female, apathic changes occur in vaginal epithelium. It is one of most practical, reliable and economical test available. The cytologic finding in menopausal patients may show a wide spectrum of changes ranging from persistent or elevated estrogenic pattern to one of complete atrophy.

Vaginal squamous epithelium consist of three layers superficial layer, Intermediate or parabasal and basal layer. Superficial layer is estrogen dependent. In menopause low estrogen levels result in thinning of the vaginal epithelium decreased vascularity and loss of elasticity. The epithelial cells do not undergo maturation, those glycogen contents reduce number of vaginal lactobacilli decrease and vaginal pH increases and predispose vagina to secondary infection. Vaginal smear consisting of Intermediate and parabasal cells with the Karyopyknotic index and low maturation index.

**Hormonal changes following menopause :**

In human ovary, there is a continuous and progressive decline in the number of follicles from total life onwards this loss can not be accounted for by ovulation alone, since the reproductive life in 30-35 yeas in women can only account for a loss of 350-450 follicles. All types of follicles small, medium and large show decline in number with age, continuously through a process of atresia also.
Progressive decline in the number of ovarian follicles is responsible for decreased production of ovarian inhibin (McLachlan et al 1988).

Ovarian inhibin is non-steroidal water soluble protein secreted by granules cells of graffian follicle under the influence of estrogen. It suppress the pituitary follicle stimulating hormones by negative feedback mechanism.

Reduce number of ovarian follicles leads to decreased estrogen production and ultimately decreased inhibin production so there is loss of negative feedback mechanism and ultimately FHS increases in blood.

In the menstruating women, FHS, on cycle days should be 5-10 IU/L with normally functioning ovaries, Elevated FHS levels (10-25 IU/L) suggest relative ovarian resistance consistent with menopausal transition FHS (levels > 40 IU/L are consistent with complete cessation of ovarian functions.

Prior to menopause, LH levels are usually in the range of 5-10 IU/L. LH levels increases in the menopausal transition in a manner similar to FHS.

So first detectable endocrine manifestation is a gradual increase in plasma follicle stimulating hormone. Sometimes after the rise in FHS, estradiol level decreases slightly and serum LH, increases Eventually as estradiol secretion falls to
very low level both FSH and LH rise to post menopausal level and remains elevated.

**Hormone Replacement Therapy :-**

Estrogen deficiency has been considered by many to be a physiological rather than pathological condition, probably because ovarian failure is genetically programmed. With the increased life deficiency becomes more significant. Hormonal changes induced by ovarian failure can influence health adversely, even in those who do not develop obvious menopausal symptoms, continuing changes even eventually lead to serious age related disorder such as osteoporosis.

In symptomatic menopausal female hormone replacement therapy provides certain relief. Beside this short term benefit, hormone replacement therapy now has an established role in prophylaxis against osteoporosis and cardiovascular disease, thereby lowering morbidity and mortality rates.

With increasing life expectancy and heightened health awareness, women now seek the prevention and cure of the problems and have expectations of long term good health. It is therefore, Imperative to understand and mean age the post menopausal period by giving them HRT, so as to allow her to enjoy optimum health during these years.

Although "Lilandwlar therapy" for various ailments may be traced back to Egyptian times, the first suggestion that
ovarian secretion could be used to treat symptoms of ovarian failure was made in 1885 by mariebra. The therapeutic preparation of that time included grass ovarian tissue, Ovarian Juice and powdard ovaries.

In 1923, Estrogen was first isolated from procaine follicular fluid by Allen and Doisy.

In 1931, they were discovered to be abundant in the urine of pregnant mares.

In 1938, the synthetic estrogen diethyl stiboestral and ethynyl estradiol were developed.

During 1930s, and 1940s estrogen although very expensive and minimally efficacious when administered orally, were used to suppress lactation after parturition and to treat severe menopausal symptoms. In long term clinical studies of estrogen use in men were being because of theoretical cardiovascular benefit.

In addition, in 1960s many advocate life long estrogen therapy for menopausal women to keep them feminine formen during this time oestrogen use increased tremendously, with little regard to adjustment of dose of selection and patient.

The fact remained, however, that many women had diabing symptoms, related to estrogen decline and demanded the only treatment that had been proved to be totally
efficacious the demand along with documentation in the 1980s that menopausal estrogen reduce the incidence of osteoprosis.

Hormone replacement therapy is available in many formulations and combination and can be given by various routes also.

**Oral Preparation** :-
- HRT using estrogen alone.
- Cyclic estrogen-progesterone preparation.
- Continuous Estrogen progesterone preparation.
- Estrogen-androgen HRT.

**Non Oral Preparation** :-
- Vaginal creams and pessaries
- Percutaneous gel
- Transdermal patch.

**Oral preparation - available are** -

A. **Conjugated steroidal estrogens.**
   
a. **Estrones**
   - Conjugated equine estrogen.
   - Esterified estrogen.
   - Peperazene estrone sulfate.

b. **Estradiol Cypiovate**
   - Estradiol Valerate
   - Micronised 17 beta estradiol
c. **Estriols**

- Estriol
- Estriol hemisuccinate.

B. **Unconjugated steroid analogues.**

- 17 Ethynyl estradiol
- 17 Ethynyl estradiol 3 methyl ether
- 17 Ethynyl estradiol 3 cyclo pentoether.

C. **Synthetic Estrogen analogues**

- Bengestrol
- Chlorotreonanene.
- Dinestrol.
- Diethylstilboestrol.
- Hexestrol.
- Promethestrol depropriovate.

II. **Non Oral Preparations**

- Earliest non oral routes of administration used:
  - Vaginal cream
  - Pessaries
  - Subcutaneous estradiol implant.

- More Recently
  - Percutaneous gel
  - Hormone containing vaginal rings
Most Recent
  - Transdermal therapeutic system.
  - Only estrogen containing
  - Oestrogen & progesterone

Oral HRT Using Estrogen Only:

This regimen is most frequently used in patients with surgical menopause, means postmenopausal women who have undergone hysterectomy. In these patients, the addition of progestrone is unnecessary since the need of endometrial protection does not exist.

Daily estrogen are the prefered method of HRT in these cases.

Only estrogen therapy can be given in non-hysterectomised women, with careful monitoring and annual screening endometrial biopsy. Method of therapy - cyclic administration of estrogen (3 weeks on and one week off) has been suggested to reduce the risk of hyperplasia.

Cyclic Estrogen-Progesterone HRT:

This regimen is frequently used in the post-menopausal patient with intact uterus.

The estrogen correlate the vasomotor disturbance and genitourinary atrophy and presents osteoporosis, progesterone is added exclusively to protect the endometrium from the development of hyperplasia and carcinoma endometrium.
Progesterone that have been clinically assessed for such protection are Norethisterone 5 mg. Medroxy progesterone acetate 10 mg. and dydrogesterone 10mg.

**Disadvantage of Progesterone :-**

❖ Vaginal bleeding

Hence long term complaint is poor side effect of progesterone include symptoms similar to premenstrual syndrome. It is also major factor leading to non-compliance.

**Continuous estrogen progesterone HRT :-**

Since withdrawal bleeding is unacceptable to most patients, combined continuous regimen may improve compliance, this regimen using conjugated estrogen 0.625 mg and medroxy progesterone acetate 2.5 mg and 5 mg.

**Only Progesterone HRT :-**

Progesterone may be used in perimenopausal HRT when cyclic disturbance predominate and in cases when estrogens are contraindicated progesterone is used as HRT.

**Non-Oral Routes :-**

Oral estrogen have been shown to be effective in terms of relieving menopausal symptoms (Camp bell and whitehead 1977) and may reduce the risk of ischemic heart disease (Loss et al 1981). However, oral estrogens may cause adverse effect d/t first pass metabolism in liver. To eliminate these adverse
effects, various new routes of hormone administration have been developed, which means estrogen and progesterone can be given non-ironally.

The earliest non-oral routes of estrogen administration are vaginal cream, pessaries, subcutaneous estradiol implant, more recently, percutaneous skin gel and hormone containing vaginal ring have been developed. The transdermal therapeutic patches are the most recent development and have advantages over the older, delivery systems.

1. **Vaginal Cream**

In the late 1970s, it was realized that a significant amount of estrogen could be absorbed through the vaginal epithelium (Bigg et al, Schiff et al 1977). The efficiency with which estrogen absorbed are demonstrated by whithead et al 1978. It estrogen are given in adequate doses vaginally, the to will cause endometrial proliferation, so in these patients, cyclic progesterone is advisable. Fink et al (1985) have suggested the use of vaginal oestrial as a safe and effective alternative to CEE cream. Daily dose of 0.5mg improve both vasomotor and urogenital symptoms continuous 3 months administration caused proliferative changes in endometrium but not hyperplasia.

2. **Vaginal Ring/ Pessaries**

In 1970s, filicome ring 3 impregnated initially with progesterone (Mishell et al 1970) and subsequently a
combination of oestradiol and d-norgestrol (Mishell et al 1978) were shown to be effective method of contraception various attempts have been made at using them in post-menopausal female, and although effective, they are not particularly popular among patient.

Estradiol rings release 8 mg estradiol/24 hours at a constant rate. The ring is easy to insert and remove as it is soft and flexible. Each ring is to be used continuously for 90 days and is well tolerated, giving significant relief from vaginal dryness, itching, dyspareunia and dysuria.

3. **Subcutaneous oestradiol implants**:

This mode of therapy is not new, being initially pioneered by Greenblatt in the USA (Greenblatt and Suran 1949), Most recently there use has been encouraged in UK (Studd 1976). Small oestradiol pellets, of various doses, are inserted into the subcutaneous fat of the anterior abdominal wall using a trocar.

The implants consist of biodegradable crystalline steroid pellets in permeable silastic rods. They are cylindrical in shape and vary from 3-6 mm in length and 2.2-4.5 mm in diameter depending upon the dose. The implant contain 17-beta estradiol (25/50/100 mg) in a cholesterol base. Implantation is easy and is performed under local anaesthesia with specially designed trocar and cannula, into the subcutaneous fat of
either abdominal wall 5 cm. above and parallel to the inguinal ligament or over the buttocks taking care to avoid the sheath, muscle or any scar tissue, the oestradiol implants usually last for upto 6 month peak levels of oestradiol and oestrogen are achieved 1-2 month after implantation and begins to decline there after.

In women with intact uterus, cyclic progesterone therapy is indicated, hence hormone implants are preferred for HRT in women who have undergone a hysterectomy and may be inserted at the time of surgery.

Complication of Implants therapy are rare, bleeding at insertion site usually, responds to pressure. tachyphylaxis may be induced by frequent reinplantation and can be avoided by pretreatment counseling. Oestradiol implants appear to be effective in preventing post-menopausal bone loss (Magos and studd 1990 Maesseu 1993).

More Recently :-

1. Percutaneous gel - Oestradiol gel :-

17 Beta - Oestradiol, when applied to the skin in a hydroalcoholic base, can easily penetrate the outer stratum corneum. Some passes into the microvasculature beneath the epidermis and then into the systemic circulation, part of the estradiol is retained in the stratum corneum, to be absorbed
into the circulation over 24 hours, until the next application of gel.

About 10% of total dose of oestradiol is absorbed once the alcohol has evaporated from skin, no further absorption can take place. In place, where temperature are higher, evaporation of alcohol is quicker and less amount of drug is absorbed.

**Most Recently:**

Transdermal device first introduced in July 19, 1983. It is based on the theory that oestrones could be produced in oophorectomized mice by the application of oestrogen cream on the skin (1920s and 1930s).

Transdermal delivery of estradiol by a skin patch developed by Schenkel et al (1985) is now well established. Transdermal administration of estradiol appear to be at least as effective as oral Conjugated estrogen therapy on most of the end point which have been evaluated but allows a lower dose to be used. Thus avoiding some of the metabolic adverse effect experienced with oral treatment.

**Structure of System**

The transdermal therapeutic system is a cutaneous device which delivers estradiol into systemic circulation via the stratum corneum at a constant rate up to 4 days.
It is thin adhesive patch, consisting of a drug reservoir where estradiol is held in ethanol solution between an occlusive backing layer and a rate limiting microporous membrane.

Three sizes of estradiol patches currently available as Estraderm TTS-25, Estraderm TTS-50 and Estraderm TTS-100 contain 2.4, and 8 mg of drug, respectively and desired to release estradiol at a rate of 0.21 µg/cm²/hour. Correspondingly to four days. These maintain blood level of 25 pg/ml, 40 pg/ml and 75 pg/ml respectively with small fluctuations.

**Site of application:**

Hairless skin of buttocks is most suitable site of application of patch, other sites are abdomen, lateral thorex, upper arm and breast.

**Proven Beneficial Effects of Estrogen Therapy on Menopausal Symptoms**

The beneficial effects of estrogen therapy on menopausal symptoms are certainly better known and understood than those of many drugs.

1. The Hot flushes are appearing the most typical and most sensitive indicator of the effectiveness of estrogen.
Hot flushes and profuse sweating are quickly and significantly reduced by estrogen treatment (Greenblatt et al 1950; Lauritzen 1973, Utian 1975, Coope 1976).

2. Atrophic cystitis and urethritis with corresponding symptoms can certainly be ameliorated by estrogen medication as shown by urinary cytology and disappearance of complaints (Hoffmann 1950 a,b, Lauritzen 1968, Jonsson 1973, Smith 1977).

3. Estrogen also improve the readiness for social contact and psychic alertness in aged women (Caldwell 1952, Caidwell and wetson 1954, Dueker 1957, Evans and Marmorston 1963).

4. Estrogen medication also abolishes dizziness and tingling sensation and the concomitant rise of blood pressure which occurs with hot flushes (Lauritzen and Velizese 1961).

5. Vulval atrophy and vulvitis based on atrophy are consistently and safely improved by estrogen administration either locally or parenterally (Lauritzen 1970, Rauromo 1976).

6. Estriol, Ethinyl estradiol and estradiol valvate have been reported to reduce first and even second degree stress

7. The beneficial effect of estrogen on dermal thickness, skin appearance, wrinkles, elasticity and blood perfusion have been studied by Aertgeerts (1972).

8. The atrophic changes which occurs in the skin following oophrectomy can be prevailed by and even reversed by administration of estrogen (Rauramo and Punnonen 1973).

9. A consistent and favourable effects is also obtained by local and parenteral estrogen administration in atrophic changes when painful intercourse is the problem (Joswig prieve et al 1973, Lauritzen and Muweller 1977).

10. Estriol increases alertness and attention and there is also improvement of memory (Vanhulle and Drumol 1976).

11. Estrogen replacement therapy is necessary for patients of premature menopause as it helps to reduce cardiovascular and cerebrovascular disease mortality (Cust & Whited head 1980).

12. Prospective cohort studies have also shown beneficial effects of HRT in reducing the risk of non spinal fracture
and this was marked in women who began therapy within five year of the menopause and it was unaffected by age or concomitant progestin therapy (Canlay JA, Seeley D.G., Ensured K, Black D-1995).

13. Psychological symptom of a wide variety including fatigue, irritability tension, anxiety, mood fluctuations, Headache, insomnia, altered libido etc. are extremely, in post menopausal women, (Mittal S. 1996).

14. A four years randomized study from the university of Taxes showed for the first time on the additive effect of intermittent cyclical etidronate and HRT on the bone mineral density in both vertebral and the hip (Jha U.P. 1997).

Despite the proven efficacy of the oral route for oestrogen replacement dose related adverse effects are a major drawback 60-90% of an oral estrogen dose is converted into estrone, in the liver, which is pharmacologically inactive substance.

These substance causes harmful effects on body so the member of non oral forms of estrogen delivery, which avoid first pass metabolism have been found to be effective in treating menopausal symptoms, but precise control of dosage is difficult with these method.
Recently, a transdermal preparation which delivers estradiol at a constant rate has become available, various studies have also proven the beneficial effects of transdermal route of estrogen as hormone replacement therapy.

In the initial prospective study of the efficacy of the transdermal therapeutic system in post menopausal women, Laufer and coworkers (1983) showed that transdermal estradiol delivered from a patch, significantly reduces the incidence of hot flushes, they also reported beneficial effects on vaginal cytology.

Padwick and colleagues (1985) used a graphic rating scale to compare menopause symptoms score before and during the treatment cycles in 12-menopausal women.