Current Status of Hormone Replacement Therapy

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Hormone replacement therapy is form of hormone therapy wherein the patient, in the course of medical treatment, receives hormones, either to supplement a lack of naturally occurring hormones, or to substitute other hormones for naturally occurring hormones.

The HRT is indicated in menopausal woman to overcome the short-term and long-term consequences of oestrogen deficiency.

INDICATIONS OF HORMONE REPLACEMENT THERAPY:

1. Commonest indication for HRT is natural menopause, is based on the idea that the treatment may prevent discomfort caused by diminished circulating oestrogen and other hormones, there by causing
    - Relief of menopausal symptoms
    - Prevention of osteoporosis
    - To maintain the quality of life in menopausal years.
2. Premature ovarian failure
3. Gonadal dysgenesis
4. Hormone replacement therapy for transgender and transsexual cases.

Surgical or radiation menopause

CONTRAINDICATIONS TO HRT

Absolute:

- Undiagnosed genital tract bleeding
- Hormone dependant neoplasm in the body
- Suspected Pregnancy
- History /Risk factor of venous thromboembolism
- Severe Active liver disease

Relative:

- Migraine headache
- Superficial thromboplebitis

- Strong family history of breast cancer
- Active endometriosis, large fibroid, or gall bladder disease

BENEFITS OF HORMONE REPLAEMENT THERAPY

- Improvement of vasomotor symptoms (70-80%)
- Improvement urogenital atrophy.
- Increase in bone mineral density (2-5%).
- Decreased risk in vertebral and hip fractures (25-50%).
- Reduction in colorectal cancer (20%).
- Possibly cardio protection.

Other possible benefits may be:

- Decrease chances of Alzheimer's Disease ,Osteoarthritis & Skin aging
- Favourable mood changes and improved sleep

HRT AND OSTEOPOROSIS:

The major cause of post menopausal osteoporosis appears to be an increase in bone resorption. HRT prevents bone loss and stimulate new bone formation. Oestrogen is found to play a direct role, as receptors have been found in the osteoblasts. Women receiving HRT should supplement their diet with an extra 500 mg of calcium daily.

HRT AND CARDIO-PROTECTION:

LDL on oxidation produces vascular endothelial injury and foam cell (macrophage) formation, which ultimately lead to intimal smooth muscle proliferation and atherosclerosis. Oestrogen prevents oxidation of LDL, as it has got antioxidant properties.

In postmenopausal women there is some amount of insulin resistance and hyperinsulinaemia. Hyperinsulinaemia induces atherogenesis. Oestrogen improve glucose metabolism.

RISKS OF HORMONE REPLACEMENT THERAPY

- Endometrial cancer: When oestrogen is given alone to a woman with intact uterus, it causes endometrial proliferation, hyperplasia and carcinoma. It is therefore advised to use progesterone to counter balance such risks.
- Breast cancer: Combined oestrogen and progestin replacement therapy, increases the risk of breast cancer slightly (R.R 1.26) which is does and duration related.
- Venous Thromboembolic (VTE) disease: has been found to be increased with use of combined oral oestrogen and progestin. Transdermal oestrogen use does not have the same risk compared to oral estrogen.
- Coronary Heart Disease (CHD): Combined HRT therapy shows a relative hazard (R.R, 1.29) of CHD. Hypertension has not been observed to be a risk of HRT.
- Lipid metabolism: An increased incidence of gallbladder disease has been observed following ERT due to rise in cholesterol (in bile).

AVAILABLE PREPARATIONS FOR HORMONE REPLACEMENT THERAPY

The principle hormone used in HRT is oestrogen. This is ideal for a women who had her uterus removed (hysterectomy) already. But a woman with an intact uterus, only oestrogen therapy leads to

endometrial hyperplasia and even endometrial carcinoma. Addition of progestins for last 12-14 days each month can prevent this problem. Commonly used oestrogens are conjugated oestrogen (0.625-1.25 mg/day) or micronized oestradiol (1.2 mg/day). Progestins used are medroxyprogesterone acetate (2.5-5 mg/day), micronized progesterone (100-300 mg/day) or dydrogesterone (5-10 mg/day).

Considering the risks, hormone therapy should be used with the lowest effective dose and for a short period of time. Low does oral conjugated oestrogen 0.3 mg daily is effective and has got minimal side effects. Dose interval may be modified as daily for initial 2-3 months then it may be changed to every other day for another 2-3 months and then every third day for the next 2-3 months. It may be stopped thereafter is symptoms are controlled.

- **Oral oestrogen regime**
  - * Oestrogen: Conjugated equine oestrogen 0.3 mg or 0.625 mg is given daily for woman who had hysterectomy.
  - * Oestrogen and cyclic progestin: For a woman with intact uterus oestrogen is given continuously for 25 days and progestin is added for last 12-14 days.
  - * Continuous oestrogen and progrestin therapy: Continued combined therapy can prevent endometrial hyperplasia. There may be irregular bleeding with this regimen.
  - * Androgen: Rarely, young ophorectomised woman may require addition of androgen to boost libido.
- **Sub dermal implants:** Implants are inserted subcutaneously over the anterior abdominal wall using local anaesthesia. 17 β oestradiol implants containing 25 mg- 100 mg are available and can be kept for 6 months. This method is suitable in patients after hysterectomy. Implants maintain physiological E_2 to E_1 ratio. They avoid liver first pass effect & hence have lesser thrombo-embolic effect.
- **Percutaneous oestrogen gel:** 1 gm applicator of gel, delivering 1 mg of oestradiol daily, is to be applied onto the skin over the anterior abdominal wall or thighs. Effective blood level of oestradiol (90-120 pg/ml) can be maintained.
- **Transdermal patch:** It containing 17 β oestradiol, releasing about 25-50 μg of oestradiol in 24 hours. Physiological level of E_2 to E_1 is maintained. It should be applied below the waist line and changed twice a week. Now, **transdermal spray** ensuring slow & steady oestrogen level has been developed & is available.
- **Vaginal cream:** Conjugated equine vaginal estrogen cream 1.25 mg daily is very effective specially when associated with atrophic vaginitis. It also reduces urinary frequency, urgency and recurrent infection. Women with symptoms of urogenital atrophy and urinary symptoms and who do not like to have systemic HRT, are suitable for such treatment.
- **Progestins:** Patients not suitable for ET or with risk for endometrial carcinoma, only progesterone or progestins may be used. It may be effective in suppressing hot flushes and it prevents osteoporosis. MPA 2.5-5 mg/ day can be used.
- **LNG-IUS:** with daily release of 10 microgram of levonorgestrel per 24 hours, it protects the endometrium from hyperplasia and cancer. At the same time it has got no systemic progestin side effects. Oestrogen can be given by any route. it can serve as contraception and HRT when given in a perimenopausal women.
- **Tibolone:** Tibolone (2.5 mg/ day) is a steroid (19-nortesto-sterone derivative) having weak oestrogenic, progestogenic and androgenic properties. It prevents osteoporosis, atrophic changes of vagina and hot flushes. It increases libido. Endometrium becomes atrophic.

MONITORING PRIOR TO AND DURING HRT:

Annual check-up of following parameters is required for woman on HRT

- Blood pressure recording, Physical examination including pelvic examination.
- Breast examination and Mammography
- Cervical cytology & Pelvic ultrasonography (TVS) to measure endometrial thickness (normal < 5 mm). Any irregular bleeding should be investigated thoroughly

DURATION OF HRT USE:

Generally, use of HRT for a short period of 3-5 years has been advised. Tapering of dosage should be done as soon as possible. Menopausal women should maintain optimum nutrition, ideal body weight and perform regular exercise.

Individual woman should be given informed choice as regard the relative merits and possible risks of continuing HRT.

Women with premature ovarian failure, surgical menopause or with gonadal dysgenesis may require long term HRT, until normal age of menopause, with appropriate regular follow-up.

CURRENT PRACTISE IN HORMONE REPLACEMENT THERAPY:

Low Dose HRT – Women with intact uterus with 0.3 mg conjugated equine oestrogen (CEE)/ 1 mg of oestradiol and Medroxy Progresterone acetate (MPA) 1.5 mg/ norethisterone acetate 0.5 mg is found effective to control the vasomotor symptoms& increasing bone density. Oestrogen given in non-oral route ie. Patches, gel, vaginal cream & implants or tibolone have advantage of reducing risks. Progestogen is added in the HRT to minimize the adverse effects of unopposed oestrogen, in woman with intact uterus. Hormone therapy should be used with lowest effective dose and for as short period of time as possible. Dose interval may be modified before stopping the therapy. To minimise the systemic adverse effects of progestogen, Levonorgestrel intrauterine delivery system (LNG-IUS) is being used. It is primarily used as a contraceptive. Oestrogen component is delivered by oral or by transdermal route or as an implant. A small size LNG-IUS has been developed, suitable for the postmenopausal women that release 10 g LNG per day.

Also due to inherent risk involved with HT, focus is now shifting to alternative therapies like tibolone & phytoestrogens along with lifestyle modification, diet, nutritional supplementation & exercise to counter menopausal symptoms & effects of hormone depletion.

References

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2. Hickey M; Treatment of Menopausal symptoms: Lancet 2005;366:409-21