Guidelines on Use of HRT in the Management of Menopause

Introduction to Drug:

Hormone Replacement Therapy (HRT) is a combination of Oestrogen and Progesterone, mainly used to relieve vasomotor symptoms of menopause. It's use for cardiovascular and bone health in the post- menopausal woman has come under a lot of speculation. Benefit-risk assessment needs to be discussed and evaluated in individual patients prior to commencing of treatment. There are many different combinations of HRT in the market, to suit individual needs and lifestyle of the woman.

Pharmacology/ Metabolism/ Excretion Routes:

Oestrogens are hormones secreted principally by the ovarian follicles and also by the adrenals, corpus luteum, placenta, and testes, or are synthetic steroidal and non-steroidal compounds. At the menopause, ovarian secretion of oestrogens declines at varying rates.

Exogenous oestrogens elicit, to varying degrees, all the pharmacologic responses usually produced by endogenous oestrogens. Endogenous oestrogens are essential hormones that are responsible for the normal growth and development of the female sex organs and for maintenance of secondary sex characteristics, including the growth and maturation of the vagina, uterus, and fallopian tubes; enlargement of the breasts; maintenance of tone and elasticity of urogenital structures; growth of axillary and pubic hair; and pigmentation of the nipples and genitals.

Oestrogens have a weak anabolic effect and may cause sodium retention with associated fluid retention and oedema. Oestrogens also affect bone by increasing calcium deposition and accelerating epiphyseal closure, following initial growth stimulation.

Oestrogens have generally favourable effects on blood cholesterol and phospholipid concentrations however; use of progestins in conjunction with oestrogen (hormone replacement therapy, HRT) may blunt these favourable effects on the lipid profile.

Following oral administration, the natural, unconjugated oestrogens are inactivated in the GI tract and liver. Conjugated oestrogens and some synthetic derivatives of the natural oestrogens may be administered orally. Absorption and metabolism following oral administration of these drugs is rapid and daily doses are usually required. Oestrogens are readily absorbed through the skin and mucous membranes. Depending on the amount of oestrogen applied, systemic as well as local effects may occur following topical application.

The steroidal oestrogens are metabolized principally in the liver, although the kidneys, gonads, and muscle tissues may be involved to some extent. Oestrogens and their metabolites are excreted mainly in urine; however, small amounts are also present in faeces.

Progesterone is a progestinic hormone secreted mainly from the corpus luteum of the ovary during the latter half of the menstrual cycle. Progesterone is formed from steroid precursors in the ovary, testis, adrenal cortex, and placenta.

Progesterone shares the pharmacologic actions of the progestins. In women with adequate endogenous oestrogen, progesterone transforms a proliferative endometrium into a secretory one. The abrupt decline in the secretion of progesterone at the end of the menstrual cycle is principally responsible for the onset of menstruation. Progesterone also stimulates the growth of mammary alveolar tissue and relaxes uterine smooth muscle. Progesterone has minimal oestrogenic and androgenic activity.

Progesterone has a short plasma half-life of several minutes. The hormone is reduced to pregnanediol in the liver and conjugated with glucuronic acid, and then excreted mainly in urine.

Indications:

Oral conjugated oestrogens are used for the management of moderate to severe vasomotor symptoms associated with menopause and for the management of vulvar and vaginal atrophy (atrophic vaginitis).

If oestrogens are used solely for the management of vulvar and vaginal atrophy, use of topical vaginal preparations should be considered.

Oral conjugated oestrogen is also used for the management of female hypoestrogenism secondary to hypogonadism, castration, or primary ovarian failure.

Contraindications:

Progesterone is contraindicated in patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a history of these conditions.

The drug is also contraindicated in patients with undiagnosed vaginal bleeding or missed abortion, known sensitivity to the drug or any ingredient in the formulation, markedly impaired liver function or liver disease, or carcinoma of the breast.

Hormone therapy is not to be used to prevent heart disease in healthy women (primary prevention) or to protect women with pre-existing heart disease (secondary prevention).

C autions:

Progesterone should be used with caution, and only with careful monitoring, in patients with conditions that might be aggravated by fluid retention (e.g., asthma, seizure disorders, migraine, or cardiac or renal dysfunction).

The drug should also be used with caution in patients with a history of mental depression; progesterone should be discontinued if depression recurs to a serious degree during therapy with the drug.

Diabetic patients should be carefully monitored during progesterone therapy, since decreased glucose tolerance has been observed in women receiving oestrogen-progestin combinations.

The clinician and the patient using progesterone/ HRT should be alert to the earliest signs and symptoms of myocardial infarction, cerebrovascular disorders, thromboembolism (e.g., venous thromboembolism, pulmonary embolism), thrombophlebitis, or retinal thrombosis. The drug should be discontinued immediately when any of these disorders occurs or is suspected.

Side- Effects:

Dizziness, breast pain, headache, abdominal pain, fatigue, viral infection, abdominal distention, musculoskeletal pain, emotional lability, irritability, and upper respiratory tract infection.

Breakthrough bleeding, spotting, changes in menstrual flow, amenorrhea, changes in cervical erosion and secretions, oedema, weight gain or loss, cholestatic jaundice, allergic rash with or without pruritus, breast tenderness, galactorrhoea, alopecia, hirsutism, pyrexia, sleep disturbances, nausea, and mental depression.

An association between pulmonary embolism and cerebral thrombosis and embolism and use of oestrogen-progestin combination preparations has been shown.

Safety in Pregnancy (if applicable):

Not Applicable

Safety during Breastfeeding (if applicable):

Not Applicable

Dosage & dose adjustment in hepatic/renal impairment:

Dosage of conjugated oestrogens /synthetic conjugated oestrogens must be individualized according to the condition being treated and the tolerance and therapeutic response of the patient. To minimize the risk of adverse effects, the lowest possible effective dosage should be used. Because of the potential increased risk of cardiovascular events, breast cancer, and venous thromboembolic events, oestrogen and oestrogen/progestin therapy should be limited to the lowest effective doses and shortest duration of therapy consistent with treatment goals and risks for the individual woman. Oestrogen and oestrogen/progestin therapy should be periodically re-evaluated.

Oestrogen therapy is administered in a continuous daily dosage regimen or, alternatively, in a cyclic regimen. When oestrogens are administered cyclically, the drugs usually are given once daily for 3 weeks followed by 1 week without the drugs or once daily for 25 days followed by 5 days off, and then the respective regimen is repeated as necessary.

While oestrogen therapy alone (oestrogen replacement therapy, ERT) may be appropriate in women who have undergone a hysterectomy, a progestin generally is added to oestrogen therapy (hormone replacement therapy, HRT) in women with an intact uterus. Addition of a progestin for 10 or more days of a cycle of oestrogen or daily with oestrogen in a continuous regimen reduces the incidence of endometrial hyperplasia and the attendant risk of endometrial carcinoma in women with an intact uterus.

When a progestin is used in conjunction with oestrogen therapy, the usual precautions associated with progestin therapy should be observed. Clinicians prescribing progestins should be aware of the risks associated with these drugs and the manufacturers' labelling should be consulted. Clinical studies indicate that addition of a progestin to oestrogen replacement therapy does not interfere with the efficacy of oestrogen therapy in the management of vasomotor symptoms associated with menopause, treatment of vulvar and vaginal atrophy, or prevention of osteoporosis. The choice and dosage of a progestin may be important factors in minimizing potential adverse effects.

Mode of administration:

Oral

Topical

Vaginal

Interactions:

Carbamazepine, phenobarbital, rifampin, St. John's wort [*Hypericum perforatum*]) may result in decreased plasma concentrations of oestrogen, resulting in decreased therapeutic effects and/or changes in uterine bleeding profile

Clarithromycin, erythromycin, grapefruit juice, itraconazole, ketoconazol may result in increased plasma concentrations of oestrogens and an increase in the incidence of adverse effects.

Oestrogens have been reported to enhance the anti-inflammatory effect of hydrocortisone in patients with chronic inflammatory skin diseases. It has been suggested that oestrogens may decrease the hepatic metabolism of corticosteroids and/or alter serum corticosteroid protein binding. Patients receiving concomitant oestrogen and corticosteroid therapy should be observed for signs of excessive corticosteroid effects, and alterations in corticosteroid dosage may be necessary when oestrogens are started or discontinued.

Oestrogens may decrease the action of oral anticoagulants. When oestrogen therapy is initiated in patients receiving anticoagulants, an increase in anticoagulant dosage may be required.

Who should prescribe?

Initiation by Specialist; continued repeat prescription by Medical officer and Senior Medical officer as per protocol.

Guidelines on Use of Carboprost

Introduction to Drug:

Carboprost (Haemabate®) is a prostaglandin analogue.

Pharmacology/ Metabolism/ Excretion Routes:

Carboprost tromethamine is an Oxytocic. It stimulates uterine smooth muscle and is a synthetic derivative of prostaglandin $F_{2\alpha}$. Elicits pharmacologic responses usually produced by endogenous prostaglandin $F_{2\alpha}$. It is more potent and has longer duration of activity on the uterus than prostaglandin $F_{2\alpha}$.

Rapidly absorbed following IM administration; peak plasma concentrations attained in 20–30 minutes.

Metabolized principally via ω-oxidation and to limited extent via ω-oxidation to a number of metabolites. Metabolized more slowly than naturally occurring prostaglandin $F_{2\alpha}$.

Excreted in urine (83%), mainly as metabolites.

Indications:

Post –partum haemorrhage due to uterine atony in patients unresponsive to Ergometrine and Oxytocin.

Can be used in termination of intrauterine pregnancy during the second trimester (weeks 13–20 of gestation, dated from the first day of the last menstrual period). Usually used after failure of another method.

Contraindications:

- **Most Significant** :
  Acute Renal Disease, Cardiac Disease, Inflammatory Disease of Female Pelvic Organs, Pulmonary Disease, Third Trimester of Pregnancy
- **Significant:**
  Bronchial Asthma, Disease of Liver, Renal Disease
- **Possibly Significant:**
  Anaemia, Diabetes Mellitus, Epilepsy, Gynaecological Surgery, Hyperbilirubinaemia, Hypertension, Hypotension, Mild Pre-Eclampsia, Severe Pre-Eclampsia, Stenosis of Cervix

Cautions:

History of glaucoma or raised intra-ocular pressure, asthma, hypertension, hypotension, anaemia, jaundice, diabetes, epilepsy, uterine scars. Excessive dosage may cause uterine rupture. Caution in patients with a compromised (scarred) uterus.

Side- Effects:

- **Most Frequent:**
  Diarrhea, Nausea, Vomiting

- **Less Frequent:**
  Abdominal Pain with Cramps, Chills, Dizziness, Fever, Flushing, Headache Disorder

- **Rare:**
  Allergic Dermatitis, Allergic Reactions, Anaphylaxis, Angioedema, Bradycardia, Bronchospastic Pulmonary Disease, Chest Pain, Dyspnea, Hypertension, Injection Site Sequelae, Paralytic Ileus, Peripheral Vasoconstriction, Skin Rash, Tachyarrhythmia, Urticaria, Wheezing

Safety in Pregnancy (if applicable):

Not to be used in normal gestation

Safety during Breastfeeding (if applicable):

No data available

Dosage & dose adjustment in hepatic/renal impairment:

Termination of Pregnancy.

IM: Initially, 250 mcg. Alternatively, initiate with test dose of 100 mcg.

Subsequently, 250 mcg at 1.5- to 3.5-hour intervals depending on uterine response. May increase dose to 500 mcg if uterine contractility is inadequate. Maximum total dose is 12 mg. Continuous administration for longer than 2 days *not* recommended.

Postpartum Hemorrhage.

IM: Initially, 250 mcg; repeat every 15–90 minutes up to a maximum total dose of 2 mg. Single dose usually adequate. Clinician should determine the need for additional doses and dosing interval based on clinical events.

Mode of administration:

By deep intra muscular injection or intramyometrial.

Interactions:

Prostaglandins can potentiate the uterotonic effect of oxytocin.

Enhanced hypotensive effects when given with some anti- hypertensives.

Who should prescribe?

Medical Officer / Senior Medical Officer after consultation with Specialist.

Guidelines on Use of Gemeprost

Introduction to Drug:

Gemeprost (Cervagem ®) is a prostaglandin used for the medical induction of late therapeutic abortion. Prostaglandin E_2, stimulates uterine smooth muscle and also produces cervical dilation and softening.

Pharmacology/ Metabolism/ Excretion Routes:

Although it is believed that the drug exerts its uterine effects via direct myometrial stimulation, the exact mode of this and other actions has not been fully elucidated.

Following vaginal insertion of Gemeprost suppositories, most of the drug slowly diffuses into the maternal blood; a small amount is absorbed directly by the uterus through the cervix or local lymphatic or vascular channels. Plasma concentrations of Gemeprost do not appear to be related to the uterine activity produced by the drug.

Gemeprost is widely distributed in the mother and is rapidly metabolized in the maternal lungs, kidneys, spleen, and other tissues, primarily by oxidation of the side chains to at least 9 inactive metabolites. The drug and its metabolites are excreted principally in urine but small amounts are excreted in faeces.

Indications:

- Second trimester abortions;
- Second trimester intra-uterine death;
- Softening and dilatation of cervix to facilitate transcervical operative procedures in the first trimester.
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Contraindications:

Unexplained vaginal bleeding

Cautions:

Caution should be exercised when administering Gemeprost to patients with cervicitis, infected endocervical lesions, acute vaginitis, compromised (scarred) uterus, asthma or a history of asthma, hypertension or hypotension, seizure disorders, diabetes mellitus, glaucoma, increased intraocular pressure, anaemia, jaundice, or cardiovascular, renal, or hepatic disease.

Side- Effects:

Vaginal bleeding and uterine pain

Nausea, vomiting or diarrhoea

Headache, muscle weakness, dizziness, flushing, chills, backache, dyspnoea, chest pain, palpitation and mild pyrexia

Uterine rupture reported (most commonly in multiparas or if history of uterine surgery or if given with intravenous oxytocics)

Also reported severe hypotension, coronary artery spasm and myocardial infarction

Safety in Pregnancy (if applicable):

Not Applicable

Safety during Breastfeeding (if applicable):

Not Applicable

Dosage & dose adjustment in hepatic/renal impairment:

- **For termination of pregnancy**: 1mg, every 3 hours with a maximum of 5 administrations. A second course may be repeated after 24 hours of start of treatment in second trimester abortions. If treatment fails, other methods should be tried for termination of pregnancy.
- **In second trimester IUFD**: 1mg, every 3 hours with a maximum of 5 administrations only. Monitor for coagulopathy.
- **Cervical priming for surgery**: 1mg , 3 hrs prior to surgery;

Mode of administration:

Vaginally

Interactions:

Prostaglandins can potentiate the uterotonic effect of oxytocin.

Enhanced hypotensive effects when given with some anti- hypertensives.

Who should prescribe?

Medical Officer/ Senior Medical Officer after consultation with Specialist

Guidelines on Use of Goserelin Injection in Obstetrics & Gynaecology

Introduction to Drug:

Goserelin / Gonadotrophin Releasing Hormone Analogue (Zoladex®)

Goserelin acetate, a synthetic decapeptide analog of gonadotropin-releasing hormone (GnRH, luteinizing hormone-releasing hormone, gonadorelin), may be used as an antineoplastic agent and for its endocrine effects.

Pharmacology/ Metabolism/ Excretion Routes:

Goserelin is a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses and has greater activity than naturally occurring GnRH. After initial administration of goserelin, there is a transient surge in circulating levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and oestradiol. Following chronic and continuous administration of goserelin (generally, 2–4 weeks after initiation of therapy), a sustained decrease in LH and FSH secretion and a marked reduction of testicular and ovarian steroidogenesis are observed.

In most premenopausal women receiving goserelin, serum oestradiol concentrations are reduced to levels comparable to those observed after menopause within 3 weeks of initiating therapy. Consequently, physiologic functions and tissues dependent on gonadal steroids (oestrogen) for maintenance become quiescent. Serum oestradiol, FSH, and LH concentrations usually return to pretreatment levels within about 12 weeks after subcutaneous implantation of the last 3.6-mg dose of goserelin. In clinical trials, isolated elevations of oestradiol have been observed in about 10% of women. In addition, sustained decreases in LH and FSH secretion may not occur in some women receiving goserelin.

Well absorbed following sub-cutaneous administration.

The 3.6 mg dose: Peak plasma concentrations achieved within 12–15 days in men and 8–22 days in women.

It undergoes hydrolysis of the C-terminal amino acids and is eliminated predominantly in urine (90%) as metabolites and unchanged drug (20%).

Indications:

Endometriosis; Precocious puberty; Infertility; Anaemia due to uterine fibroids; Breast cancer; Prostate cancer

Before intrauterine surgery (reduces uterine volume/ fibroid size and associated bleeding)

Contraindications:

Not for use more than 6 months (do not repeat)

Undiagnosed vaginal bleeding

Known hypersensitivity to goserelin or any ingredient in the formulation, other GnRH agonists, or GnRH.

The implant containing 10.8 mg of goserelin should not be used in women, since there are insufficient data available to date to determine whether this preparation is associated with reliable suppression of serum oestradiol.

Known or suspected pregnancy or lactation.

Cautions:

Fetal/Neonatal Morbidity and Mortality:

May cause fetal harm; embryotoxicity and fetotoxicity demonstrated in animals. Before initiating goserelin therapy in women, pregnancy must be excluded. Women of childbearing potential should be advised to avoid pregnancy while receiving the drug and use an effective nonhormonal method of contraception during goserelin therapy and continue contraception until the return of menses or for at least 12 weeks following subcutaneous implantation of the last 3.6-mg dose of goserelin. No adequate and well-controlled studies to date in humans.

If a patient with endometriosis or undergoing endometrial thinning becomes pregnant during goserelin therapy, the drug should be discontinued and the patient should be advised about potential fetal hazard.

In addition, if used during pregnancy (i.e., in women with advanced breast cancer), apprise of potential fetal hazard. Although continuous use of goserelin usually inhibits ovulation and stops menstruation, contraception is not ensured.

Non-hormonal, barrier methods of contraception should be used during entire treatment period.

Use with caution in patients with metabolic bone disease as it can cause decrease in bone mineral density.

Polycystic Ovarian Disease

Side- Effects:

Effects of inhibition of oestrogen production- menopausal-like symptoms (hot flushes, increased sweating, vaginal dryness, dyspareunia, loss of libido), loss of trabecular bone density.

When treating fibroids, bleeding associated with fibroid degeneration can occur.

Irritation of nasal mucosa with spray formulation; irritation at injection site.

Most Frequent:
Acneiform Eruption, Alopecia, Angina, Arthralgia, Cough, Diabetes Mellitus, Dry Eye, Dry Skin, Dyspnea, Dysuria, Erectile Dysfunction, Flu-Like Symptoms, Herpes Simplex Infection, Hyperglycemia, Injection Site Sequelae, Lethargy, Libido Changes, Malaise, Myalgia, Palpitations, Paresthesia, Pneumonia, Pruritus of Skin, Urinary Incontinence, Urinary Retention, Urinary Tract Infections, Vasomotor Symptoms associated with Menopause

Less Frequent:
Abdominal Pain with Cramps, Anaemia, Anorexia, Anxiety, Bone Pain, Cerebrovascular Accident, Chronic Heart Failure, Conduction Disorder of the Heart, Constipation, Cramps in Legs, Depression, Diarrhoea, Dizziness, Edema, Fatigue, General Weakness, Gout, Gynaecomastia, Headache Disorder, Hypertension, Hypertonia, Hypotension, Insomnia, Mastalgia, Myocardial Infarction, Nausea, Osteoporosis, Pain, Peripheral Vascular Disease, Severe Chronic Obstructive Pulmonary Disease, Skin Rash, Upper Respiratory Infection, Vomiting, Weight Gain

Rare:
Anaphylaxis, Pituitary Apoplexy, Pituitary Neoplasm, Psychotic Disorder, Pulmonary Thromboembolism, Urticaria

Safety in Pregnancy (if applicable):

Exclude pregnancy, give first injection during menstruation or soon after, or use barrier contraception for 1 month before.

Safety during Breastfeeding (if applicable):

Avoid during Breastfeeding. Goserelin is distributed into milk in animals. Discontinue nursing prior to initiating goserelin therapy.

Dosage & dose adjustment in hepatic/renal impairment:

Endometriosis: 3.6 mg monthly for a maximum duration of 6 months.

Preoperative: 3.6 mg every 28 days (minimum 2 doses)

Pituitary desensitisation prior to Ovulation induction: 3.6 mg

Not associated with accumulation after long term administration in patients with renal/liver impairment.

Decreases in bone mineral density have occurred in women receiving goserelin; concurrent use of hormone replacement therapy or bisphosphonates (e.g., alendronate) may minimize bone mineral loss associated with GnRH agonist therapy without compromising efficacy of these drugs in the management of endometriosis.

Mode of administration:

Goserelin acetate is administered as a biodegradable implant subcutaneously into the anterior abdominal wall, under the supervision of a clinician.

A local anaesthetic may be given prior to implantation of goserelin. In the event that the implant needs to be removed, it may be located by ultrasound.

Interactions:

No formal drug interaction has been reported/studied.

Who should prescribe?

SMO after consultation with Specialist.