AUSTRALASIAN MENOPAUSE SOCIETY
EMPOWERING MENOPAUSAL WOMEN

Information Sheet

Early Menopause due to Chemotherapy and Radiotherapy

Key points

- Premature ovarian insufficiency (POI)/ failure (premature menopause) is loss of ovarian function before age 40 years. Early menopause is menopause before age 45 years.
- Chemotherapy/ radiotherapy causes POI due to impaired follicular maturation and/or direct primordial follicle loss.
- The extent of damage depends on the age and pre-treatment ovarian reserve of the patient, type of drug, radiation field/ type and cumulative dose.
- Amenorrhoea may be permanent or temporary with subsequent development of POI/ early menopause.
- Currently there is no reliable biochemical predictor of menopause.
- The most effective and established means of preserving fertility in young women are oocyte and embryo cryopreservation prior to starting treatment.

Chemotherapy is usually administered as part of cancer treatment but chemotherapy may also be given to women with severe connective tissue disorders such as systemic lupus erythematosus or kidney disease such as Wegener's granulomatosis. Total body radiotherapy is used in the treatment of lymphoma and bone marrow transplantation and abdominal pelvic radiotherapy is used in the treatment of gynaecological cancer. Chemotherapy and radiotherapy used to combat cancers carry a substantial risk for ovarian toxicity, and as survival rates for many cancers in women of reproductive age are increasing, more women are facing infertility and menopause as a consequence of their cancer treatment.

Menopause in women younger than 40 years of age is called *premature menopause or premature ovarian insufficiency (POI)/ failure*. Menopause occurring between 40-45 years of age is called *early menopause*. Diagnosis of premature or early menopause has long term physical and psychological consequences, so women may need emotional support and long-term medical follow-up.

The impact of chemotherapy and radiotherapy on the ovaries

- At birth, the ovaries contain approximately 1 million primordial follicles. With aging, this supply of oocytes naturally diminishes (atresia) until there are <1000 oocytes remaining at menopause[1]. However, chemotherapy or whole body/ pelvic radiotherapy damages ovaries, impairing follicular maturation or increasing the rate of oocyte loss with fewer remaining primordial follicles. This results in the development

of amenorrhoea which may be temporary (with a variable degree of recovery over the succeeding years but progressing to POI) or permanent (premature/early menopause)[2]. Return of menses does not necessarily mean return of fertility.

- The incidence of temporary amenorrhoea or early menopause after chemotherapy or radiotherapy varies according to the age of the person, her existing ovarian reserve, type of chemotherapy and the cumulative dose of chemotherapy or radiotherapy[3]. The risk of menopause increases with age, most likely because older women have decreased ovarian reserve compared to younger women. The incidence of premature menopause was reported as 8-50% in childhood cancer survivors[4,5]. The incidence of temporary/ permanent chemotherapy induced amenorrhoea in women with breast cancer ranges from 26-100%[6]. The incidence of cyclophosphamide–induced premature menopause in women with non- cancer diagnoses varies between 13-83%. Chemotherapy combined with radiotherapy is associated with an increased risk compared to chemotherapy alone.
- Chemotherapy with alkylating agents, such as cyclophosphamide, is associated with the greatest risk of amenorrhoea[7]. Paclitaxel (Taxol), also used in the treatment of breast cancer, affects ovarian function to a lesser degree. Chemotherapy with cyclophosphamide, methotrexate and 5 fluorouracil (CMF – commonly used for the treatment of breast cancer) will usually result in loss of ovarian function in 33% of women under age 30, 50% of women aged 30-35, 75% of women aged 35-40 and 95% of women over age 40[6]. Use of newer agents such as bevacizumab and tyrosine kinase inhibitors are also associated with an increased risk of POI.
- The ovarian radiation threshold for causing POI is considered to be 3 Gray; halving of the ovarian reserve is observed with doses of 2-4 Gray. Age, proximity of the radiation field to the ovaries, total dose, use of fractionation are important factors determining risk of POI[3,8]. Pelvic irradiation can also have adverse effects on the uterus contributing to infertility. Cranial irradiation may result in hypothalamic amenorrhoea.

What are the consequences of loss of ovarian function?

- Infertility, which for many women is devastating.
- Amenorrhoea/ oligo-menorrhoea may be the first indicator of POI.
- Symptoms of oestrogen deficiency. These include hot flushes, mood change, sleep disturbance, joint aches, dry vagina or poor lubrication during sexual arousal. These symptoms may occur even while the woman is still having menstrual periods. The onset of symptoms may occur gradually or suddenly.
- Psychological distress with increased rates of anxiety and depression. Women often feel confused, sad, jealous of other women's pregnancies or old before their time. Psychological counselling can ease this distress. Support from the woman's partner, family and friends is important.
- Long-term consequences include osteoporosis and cardiovascular disease.

- Women must also cope with the diagnosis of cancer or severe medical illness which has necessitated the use of chemotherapy/ radiotherapy and the related long-term consequences.

Diagnosis of Early Menopause

- At present, there is no specific predictor of early menopause although several biochemical markers, such as anti-mullerian hormone, are under investigation.
- The diagnosis of early menopause may take several months to confirm and can be stressful. Diagnostic criteria for POI includes > 4 months of amenorrhoea with a follicle stimulating hormone level in the menopausal range (>25IU) on two occasions at least 4-6 weeks apart.

Management of POI/ Early menopause

Fertility issues:

- For many young women, childbearing is only a distant possibility sometime in the future, so making decisions for fertility preservation can be overwhelming, especially after a recent diagnosis of cancer. Providing counselling and support is recommended.
- Giving chemotherapy at a particular stage of the menstrual cycle, administration of potentially "ovarian protective" drugs, such as the oral contraceptive pill or gonadotrophin-releasing hormone agonists (GnRHa), to women before chemotherapy have been tried with mixed results[9] and cannot be considered as reliable methods of fertility preservation. However, GnRHa may be the only option for women who need to start chemotherapy urgently (e.g. leukaemia or lymphoma).
- The most effective and established means of preserving fertility in young women are oocyte or embryo cryopreservation prior to starting treatment. Factors to consider include whether the patient has gone through puberty, whether the woman has 2-3 weeks before commencing chemo/radiation treatment when fertility treatment may be performed, and whether the cancer is hormone sensitive. Experimental options for fertility preservation include laparoscopic excision of ovarian cortex for cryopreservation and subsequent re-grafting, and harvesting of immature oocytes for in vitro maturation.
- Ovarian transposition (oophoropexy) outside the irradiation field can be considered prior to pelvic radiotherapy.
- The safety of becoming pregnant where a woman has had cancer or a severe medical illness is a decision she needs to consider after consultation with her treating doctors.
- For those women who have developed early menopause, some women decide to opt for a childfree life, others may want to adopt or foster children. Some women try IVF or drugs to stimulate egg production but these have a low chance of success.

Donor oocytes or embryos are the only reliable method of achieving a pregnancy for a woman with POI.

- Some women who have chemotherapy remain fertile, so if a pregnancy is not desired or is inadvisable, contraception should be used.

Hormone (replacement) therapy (HT/HRT):

- Young women with early menopause may elect to take oestrogen therapy to relieve the symptoms of oestrogen deficiency, and often higher doses may be required compared with older women. The decision to use HRT (also known as menopausal hormone therapy (MHT)) should be undertaken following discussion with her doctors as the presence of certain illnesses or cancers prevents the use of oestrogen therapy. After breast or endometrial cancer most women are advised to avoid medication containing oestrogen. In this setting, non-hormonal treatments of hot flushes or vaginal dryness may be useful (see AMS Information Sheet *NonHormonal Treatments for Menopausal symptoms*). Where HRT/MHT is used then current advice is to continue this until the age of average menopause at 50-51 years[1]. Decision to continue thereafter is similar to the decision with menopause at the normal age.
- Options include oestrogen tablets, patches, or gels. Oestrogen combined with a progestogen is required if a women has not had a hysterectomy (see AMS Information Sheet *Combined Menopausal Hormone Therapy*) otherwise oestrogen alone can be used in women who have had a hysterectomy (see AMS Information Sheet *Oestrogen Only Menopausal Hormone Therapy*). In addition, regular vaginal oestrogen can be used to improve comfort during sexual activity.
- The combined oral contraceptive pill (OCP) can be used as a replacement hormone up to the age of 50 if the woman has no significant risk factors (such as a clotting tendency, past clots or is a current smoker). The decision to use the OCP should be undertaken following discussion with her doctors as the presence of certain illnesses or cancers prevents the use of oestrogen therapy. For example, the OCP should usually be avoided after breast cancer.
- If contraception is required, hormonal options include the OCP or the Mirena IUD plus oestrogen (usually as a patch or gel). Non-hormonal contraceptive options are the copper IUD or barrier methods.

Prevention of bone loss:

- Osteoporosis/ bone loss due to oestrogen deficiency is common in women with POI. As well as the known osteoporosis risk factors including smoking, inadequate calcium intake and lack of exercise, chemotherapy itself, high dose corticosteroids, aromatase inhibitors and GnRHa therapy also contribute to bone loss. Measurement of bone density is an important part of managing POI. It is important to check bone mineral density every one to two years, depending on baseline bone density, particularly if the woman is not taking HT/HRT. Oestrogen therapy is effective at

maintaining bone density. The WHI study demonstrated fracture reduction with oestrogen therapy in postmenopausal women. Limited evidence suggests that the OCP containing ethinyl oestradiol may have a lesser effect on bone density[10].

- A healthy lifestyle is important to maintain bone health. Women with early menopause should avoid smoking, engage in regular weight-bearing exercise, and ensure adequate dietary intake of calcium and vitamin D.
- If a woman suffers a minimal trauma fracture, there are several proven therapies other than oestrogen available to reduce her risk of further fractures. Specialist referral is recommended.

Prevention of cardiovascular disease:

- POI is associated with an increased risk and earlier onset of cardiovascular disease, cardiac failure and mortality[3] with endothelial dysfunction, coagulation changes and dyslipidaemia implicated in the pathogenesis
- HRT/MHT has beneficial effects on endothelial function, insulin resistance and lipid profile. Early institution of HRT/MHT and continuation to at least until the age of natural menopause is recommended to assist cardiovascular risk reduction[3].
- Screening for and appropriately managing cardiovascular risk factors (e.g. hypertension, weight, smoking, diabetes mellitus, hyperlipidaemia) is recommended.

Cognitive function:

- Memory disturbance associated with chemotherapy is well recognised; however, the effect of long term oestrogen deficiency on cognitive function is unclear at present. Increased risk of cognitive dysfunction, Parkinson's disease and Alzheimer's disease was observed in some but not all observational studies of women with surgical premature menopause[3]. Studies have shown impairment of verbal memory after bilateral oophorectomy or administration of a GnRHa which is reversed by oestrogen treatment[3]. Oestrogen therapy in women with POI until the age of natural menopause may have benefits related to cognitive/ neurological function.
- Lifestyle measures (exercise, stop smoking, maintain healthy weight, safe alcohol intake) to reduce the risk of cognitive impairment is indicated.

Support Groups:

- ACCESS: Australia's National Infertility Network: www.access.org.au
- Cancer Australia: www.cancer.org.au
- American Cancer Society: www.cancer.org
- The Daisy Network Premature Menopause Support Group: www.daisynetwork.org.uk ;
- American Society of Clinical Oncology: www.peoplelivingwithcancer.org

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