



Indian Menopause Society

Guideline Number 3 : August 2010

Premature Menopause : Diagnosis and Management

Introduction : Premature menopause is a serious condition that affects young women and remains an enigma. The challenges posed by this important condition range from difficulties with nomenclature to the absence of standardized diagnostic criteria and management guidelines.

DEFINITION

Menopause is considered premature if it occurs before the age of 40 (i.e. two standard deviation below normal). Age 40 is an arbitrary cut off point designated by WHO.

Premature ovarian failure (POF) consists of the triad of amenorrhoea, hypergonadotropism, and hypoestrogenism in women under the age of 40.¹ In practice we often use the term Premature menopause & premature ovarian failure interchangeably. However, premature menopause is a permanent cessation of ovarian function while in some cases of premature ovarian failure there is potential for recovery of ovarian function.

INCIDENCE & PREVALENCE ²

Approximately 1% of women will experience ovarian failure before the age of 40 and 0.1% will have premature menopause below 30 years.

In women with primary amenorrhea, the prevalence is 18 to 28%, whereas in women with secondary amenorrhea, the prevalence is 4–18%.

Prevalence of familial POF varies widely between 4–31%.

Premature Menopause could be due to:

1. **Premature Ovarian Failure (POF)** Premature ovarian failure arises due either to follicle depletion (chromosomal defects or toxins), follicle dysfunction (autoimmune diseases) or can be idiopathic in most of the cases

2. **Induced Menopause** , as a result of bilateral oophorectomy or as a result of Ovarian damage secondary to medical causes such as Chemotherapy/Radiation.

DIAGNOSTIC CONSIDERATIONS

History: Symptoms can be variable depending on cause, and include absent or irregular menses, prolonged amenorrhoea, menstrual cycle-related mood changes, hot flushes, sleep difficulties, vaginal dryness or dyspareunia. The presence or absence of other endocrinopathies, including hypothyroidism, hypoadrenalism, hypoparathyroidism and diabetes mellitus should be enquired about. History of viral infections including mumps and cytomegalovirus and medication for example OCP, antipsychotics etc should be elicited.

A detailed gynaecological history of previous surgery for endometriosis, infertility, hysterectomy and / or bilateral salpingo-oophorectomy, cancer chemotherapy, and irradiation should be obtained to rule out iatrogenic causes of ovarian failure.

Family history suggestive of a genetic cause should also be elicited.

Physical examination:

- General and Systemic Examination
- Examination of genitalia and vaginal examination
- Assessment of secondary sex characteristics / pubertal development
- Phenotypical features of Turner's syndrome
- A careful search should be made for physical presentation of autoimmune disorders and thyroid dysfunction.
- Familial disorders of premature ovarian failure associated with unique physical manifestation as seen in Perrault's syndrome (congenital dysplasia of eyelids and deafness) and BEP (blepharophimosis, epicanthus inversus and ptosis) syndrome should be looked for.
- Finally, pituitary and neurological examination should be performed to rule out an intracranial tumor.

Laboratory investigations:

To establish the diagnosis

Serum FSH of > 40 mIU/ml & Serum estradiol of < 20 pg/ml performed twice with at least one month gap is diagnostic of Premature Menopause. The test should be performed in the absence of exogenous HT & if woman is on OC pill, it should be stopped for at least a month prior to test

To determine etiology

1. USG is done
 - to exclude outflow obstruction in cases of primary amenorrhea
 - to determine presence of follicles, to assess ET & ovarian volume in cases of secondary amenorrhea

2. Serum Prolactin, LH, DHEAS, Androstenedione, Free Testosterone, SHBG & Thyroid function tests are done to identify autoimmune diseases
3. Karyotyping & Fragile X assessment are done to identify genetic abnormality when suspected.

To rule out complications:

1. BMD by DEXA to rule out osteopenia / osteoporosis.

Progesterone withdrawal test is not helpful as some women in POF may produce enough estrogen to produce withdrawal bleeding

Ovarian biopsy adds little to the investigative process because the small samples obtained are not predictive of the natural history of the condition.

Various autoantibodies have been investigated as serological markers of ovarian autoimmunity. These include antibodies against steroidogenic enzymes (like 3 β -hydroxysteroid dehydrogenase), gonadotrophins and their receptors, the corpus luteum, zona pellucida and oocyte. However none of these antibody assays has been validated to confirm a clinical diagnosis of autoimmune premature ovarian failure.

At present there is no test able to predict premature menopause. However, prediction of premature menopause by assessing levels of Anti Mullerian Hormone may well be a reliable assay in the future.

MANAGEMENT OF PREMATURE MENOPAUSE

It can best be managed by following measures

- Education and counseling
- Diet and lifestyle
- Psychological issues
- Symptom control
- Management of infertility
- Prevention of Long-term Sequelae

EDUCATION AND COUNSELLING

Education about the condition, including its long term consequences should be done. Counseling or patients support group should be offered to all women. All management options should be discussed and the woman should be encouraged to participate in the decision making process.

DIET AND LIFESTYLE

A well-balanced diet and exercise are essential to alleviate the long term effects of oestrogen deficiency.

Calcium in the diet should be increased. Some foods may interfere with absorption of calcium, such as tea, coffee and alcohol and should be avoided. Vitamin supplements may be required.

Weight-bearing exercise is the best type of exercise to maintain bone strength.

SYMPTOM CONTROL

As such there is no treatment to restore ovarian function hence treatment is directed towards substitution of ovarian function with HRT.

Hormone replacement therapy remains the cornerstone of treatment. Physiological replacement of ovarian steroid hormones until the age of normal menopause at 50 is generally accepted as routine.

The principle of HRT use in young women differs only slightly from that in older women with the main treatment goal being optimal quality of life. Young women may require a higher oestrogen dose than that used in an older age group. Women presenting with primary amenorrhoea require oestrogen replacement in order to optimise breast and uterine development. Risk/benefit data for this young population is scant.

HRT regimen should be individualized for each patient. Sexual dysfunction requires vaginal oestrogen and androgen replacement.

Among oral oestrogen choices, conjugated equine oestrogen and 17 β -oestradiol have consistent and comparable effects on hot flushes and may have similar short-term adverse effects.³

Some young women with premature menopause find the combined oral contraceptive pills a more acceptable option for oestrogen replacement. However the pill-free week amounts to 3 months of oestrogen deficiency each year which may correlate with symptoms of oestrogen deficiency or bone loss.

Transdermal oestrogen avoids first-pass liver metabolism, has rapid onset and termination of action, involves non-invasive self-administration and attainment of therapeutic hormone levels with low daily doses.⁴ This route of oestrogen administration also appears to be free of an excess risk of thrombosis.⁵ However neither the patches nor the implants are easily available in India.

Topical vaginal oestrogen may be used for vaginal dryness or dyspareunia.

Women with an intact uterus should be prescribed Progesterone.

Progestogens: There is a wide range of choice and the most commonly used oral agent is Medroxy Progesterone Acetate.

A sequential regimen ensures a monthly menstrual bleed.

A continuous regimen avoids menstrual flow but breakthrough bleeding may be more common in young women compared to an older age group in whom there is greater uterine atrophy.

Levonogestrel intrauterine system has the advantage of avoiding the adverse effects of oral progestins.

(Details of HRT are in Guideline No 1 on Management of Vasomotor Symptoms)

Androgen replacement is useful in some instances when fatigue and loss of libido persist despite optimised oestrogen replacement.⁶ Transdermal testosterone administration and dehydroepiandrosterone treatment are two of the options for androgen replacement in these women.⁷

HT should be started as early as possible & continued till the usual age of menopause after which woman should be managed according to guidelines for postmenopausal women

It has been observed that after bilateral oophorectomy, estrogen level falls by 50% in 1st 24 hour, hence HT should be started in immediate postoperative period & continued till the usual age of menopause. In such cases androgen may also be considered along with estrogen.

Pre HT Evaluation in the form of comprehensive history taking, physical evaluation, pap smear, pelvic USG, Mammography should be done prior to HT initiation

Regular follow ups are mandatory for women on HT. Initially after 1-3 months to confirm adequacy of therapy, then annually or more frequently if required.

MANAGEMENT OF INFERTILITY

Women with POF have a 5% chance of spontaneous conception at some time after diagnosis

Several medical therapies have been tried to induce ovulation in women with POF; however, in a systematic review all were reported to be equally ineffective.⁸

Assisted conception with donor oocytes has been used to achieve pregnancy in women with POF since 1987.⁹ Presently it remains the only means of fertility treatment that carries high success rate in POF.

About 3% to 5% of women with premature menopause also suffer from Adrenal insufficiency and should be investigated before starting infertility work up

THE FUTURE

Increasing survival rates in young cancer patients, new reproductive techniques and the growing interest in quality of life after gonadotoxic cancer therapies have made fertility preservation an

important issue. Cryopreservation and auto transplantation of human ovarian tissue prior to cytotoxic therapy may offer treatment options in the future.

CONCLUSION

An understanding of basic ovarian embryology and physiology will allow clinicians to apply current treatments and develop new innovative therapies for their patients with Premature Menopause. The three critical issues of management in these women are the effect of the diagnosis on the psychological health of the woman, the consequent infertility and the long- and short-term effects of estrogen deficiency arising from ovarian decline.

Numerous questions relating to this condition remain unanswered, and several important management issues are yet to be addressed.

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