Review Article

Premature Menopause

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Abstract

Premature menopause affects 1% of women under the age of 40 years. The women are at risk of premature death, neurological diseases, psychosexual dysfunction, mood disorders, osteoporosis, ischemic heart disease and infertility. There is need to use simplified protocols and improved techniques in oocyte donation to achieve pregnancy and mother a baby in those women at risk. Review of the pertinent literature on premature menopause, selected references, internet services using the PubMed and Medline databases were included in this review. In the past, pregnancy in women with premature menopause was rare but with recent advancement in oocyte donation, women with premature menopause now have hoped to mother a child. Hormone replacement therapy is beneficial to adverse consequences of premature menopause. Women with premature menopause are at risk of premature death, neurological diseases, psychosexual dysfunction, mood disorders, osteoporosis, ischemic heart disease and infertility. Public enlightenment and education is important tool to save those at risk.

Keywords: Bilateral oophorectomy, Induced menopause, Oestrogen, Ovarian failure, Premature menopause, Spontaneous menopause

Introduction

Premature Menopause is defined as premature ovarian failure before the age of 40 years[1,2] or ovarian failure occurring two standard deviations in years before the mean menopausal age of the study population.[1-3] The first definition is the most commonly accepted definition of premature menopause.[2] It is marked by amenorrhea, increased gonadotrophin levels and oestrogen deficiency. Premature menopause can be spontaneous or induced. Induced premature menopause could be as a result of medical interventions such as chemotherapy or surgical interventions such as bilateral oophorectomy. Regardless of cause, women who experience oestrogen deficiency at an early age before the natural menopause are now recognized to be at increased risk for premature morbidity and mortality.[4]

In the past, little was known about premature menopause until quite recently. It affects approximately 1% of women under the age of 40 years.[5] It is a relatively common condition. The diagnosis should always be considered in any woman presenting with a history of primary or secondary amenorrhea or oligomenorrhoea, vasomotor disturbances or other signs of oestrogen deficiency and may be confirmed by the detection of an elevated serum level of follicle stimulating hormone.

Cessation of menstruation and the development of climacteric symptoms can occur few years after menarche. The causes for premature ovarian failure are unknown. It is most frequently idiopathic but may be due to autoimmune disorders, genetic causes, infections, enzyme deficiencies or metabolic syndromes.[6,7]

In our environment, there is need to enlighten the public on premature menopause and the risk of osteoporosis, ischemic heart disease and associated infertility.

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Materials and Methods

We retrieved pertinent literature on premature menopause, selected references, internet services using the PubMed and Medline databases. We conducted a comprehensive literature search of publications related to premature menopause using the keywords 'premature menopause', 'induced menopause', 'spontaneous menopause' 'ovarian failure' and 'bilateral oophorectomy'.

Incidence

Premature menopause affects 1% of all women under the age of 40. It is seen in 10-28% of primary amenorrhea and 4-18% of secondary amenorrhea.[8,9] Premature menopause is however not a rare condition.[10]

Aetiology

The definite aetiology of premature menopause cannot be determined but some causes are identifiable.[3,10,11] These include:

Genetic disorders

Genetic disorders are commoner in those cases that present early.[12] Examples of genetic disorders are chromosomal abnormalities. Ovarian dysgenesis is a major cause of premature menopause. Ovarian dysgenesis is seen in 30% of the cases.[3] Sex chromosome anomalies predominate as a cause. The commonest abnormality is 45X0 (Turner's syndrome). Chromosomal abnormalities are reported in 10-20% of cases involving X sex chromosomes.[3]

Genetic causes of premature menopause:

- Examples of Chromosomal abnormalities
  - Turner's syndrome
  - Pure gonadal dysgenesis
  - Familial
  - Trisomy 18 and Trisomy 13

Metabolic

- 17 alpha-hydroxylase deficiency
- Galactosaemia
- Myotonic dystrophy

Immunological

- Di George syndrome
- Ataxia telangiectasia
- Mucocutaneous fungal infections

Autoimmune diseases

This is reported in 30-60% of cases.[3] They are the more common causes in the later onset presentations.[11] Autoimmune causes of premature menopause are thyroid diseases, mumps, hyperparathyroidism and Addison's disease. The ovarian biopsy in these conditions show infiltration of the follicles with plasma cells and lymphocytes.[3] Women with autoimmune premature menopause are at increased risk for adrenal insufficiency, hypothyroidism, diabetes mellitus, myasthenia gravis, rheumatoid arthritis and systemic lupus erythematosis.[13,14]

Infections

Mumps is the commonest infection associated with premature menopause. Its effect is maximal during the fetal and pubertal periods when even subclinical infection can result in ovarian failure.[15] Pelvic tuberculosis can cause secondary amenorrhea and ovarian failure. Pelvic tuberculosis is seen in 3% of cases.[16] It is important to note that pelvic tuberculosis results in intrauterine synechiae with endometrial destruction more in women suffering from this infection and not ovarian failure.

Smoking

Is known to induce premature menopause. There is a dose-related effect of smoking on age of menopause.[3,17] The effect of smoking is believed to be caused through polycyclic hydrocarbons contained in cigarette smoke.[18] Apart from smoking, early menopause may be associated with poor health, poor nutrition and increased parity.[19]

Iatrogenic

Radiation and chemotherapy can cause premature menopause but the effect is reversible and the ovary may resume ovulation and menstruation after one year of amenorrhea.[3] Megavotlage irradiation (4500-5000 rads) is often associated with ovarian failure but irradiations less than 500 rads restores normal ovarian function by 50% after a period of one year or two and pregnancies have occurred.[3,10] There is no evidence that low dose irradiation (diagnostic or therapeutic doses of radio nuclides) or ultraviolet light or domestic microwave appliances cause significant loss of ovarian function.[20] The chemotherapeutic agents implicated in the aetiology of premature menopause are alkylating agents, methotrexate, 6 mercaptopurine, actimomycin and adriamycin. Ovarian damage from cancer therapy depends on the age at treatment and on the type of treatment. Women that are younger than 40 years are at lower risk for ovarian failure than older women. However, exposure to higher doses of alkylating agents and higher doses of radiation to the ovary are more likely to induce ovarian failure.[21]

Surgery

Ovarian failure following hysterectomy is seen in 15-50% of the cases.[3] This is caused by impairment of ovarian vascular supply or by the loss of some important endocrine contribution by the uterus to the ovary. At surgery, effort must be made to preserve all normal ovarian tissue and prevent damage to the ovarian blood supply.[10] The practice of prophylactic oophorectomy has increased overtime and more than doubled between 1965 and 1990.[22] Bilateral oophorectomy is carried out to prevent ovarian cancer.

Drugs

Prolonged GnRH therapy may lead to ovarian suppression and failure[3]. Others are chemotherapeutic drugs particularly alkylating agents.[23]

Pathophysiology

Lack of gonadotrophin receptors is the underlying cause of nonresponse of follicles and the main cause of this disorder.[3,10]

Clinical features

Premature menopause is associated with multiple symptoms such as vasomotor symptoms (Hot flushes and night sweats), vaginal symptoms (vaginal dryness and dyspareunia), urinary symptoms (frequency, urgency, incontinence and atrophic cystitis), sexual dysfunction, and sleep disturbances.[24] Other symptoms are headache, depression, anxiety, irritability, skin atrophy, joint pains, cancer phobia, pseudocyesis and lack of concentration.

The terms hot flush, hot flash and vasomotor symptoms are often used to describe the same condition.[25] Hot flushes occur in 75%[3,25] of cases and tend to be more severe than in natural menopause. Hot flushes are the most common and distressing complaint for which women seeks advice from their physician. Hot flushes are unpredictable in onset, may present with recurrent periods of sudden, explosive, overwhelming uncomfortable sensation of intense heat or flushing that begins on the face or upper part of the neck and then to upper chest. Hot flushes may be associated with palpitations, a feeling of anxiety and red blotching of the skin. Hot flushes last for 2-5 minutes, varying in frequency with some women experiencing episodes multiple times in a day but decrease with the passage of time.[4] Hot flushes have a detrimental effect on a woman's functional ability and quality of life, however, they are not life threatening.[4,25]

Premature menopause may present with atrophic vagina which reduces the vaginal secretion, and dry vagina can cause dyspareunia. Loss of libido adds to sexual dysfunction. There is reduced libido in about 10-20% of the cases.[3] Premature menopause can cause urethral caruncle, dysuria, with or without infection, urge and stress incontinence.

There is characteristics loss of vaginal rugae, shortening and narrowing of the vagina. There is an overall loss of mucosal elasticity with reduced vaginal secretons and loss of vaginal transudate. The reduced vaginal secretions and the delayed timing of vaginal lubrication during sexual intercourse significantly contribute to dyspareunia in women with premature menopause. The reduced levels of oestrogens cause urogenital atrophy and urogenital diaphragm weakness. The atrophic changes in the female lower genital tract, leads to symptoms of dysuria, urethral discomfort and stress incontinence.

Sleep disturbances may be seen in women with severe hot flushes presenting with cognitive or affective disorders resulting from sleep deprivation.

Diagnostic criteria

There are no unique clinical features that establish the diagnosis of premature menopause. The diagnosis is based on a triad of amenorrhea, elevated gonadotrophin levels and signs and symptoms of oestrogen deficiency. The concentrations of gonadotrophins in the premature menopausal range are necessary to establish a diagnosis of ovarian failure but because of the intermittent presentation of the disease, repeated assays may be required at intervals of 2-4 weeks.[10] Women with FSH levels above 40 mIU/ml may not have viable ovarian follicles on biopsy and such women may be regarded as having undergone permanent ovarian failure.[26]

Investigations

1. FSH level >40 Miu/ml: E2 level <20 pg/ml.
2. Chromosomal study: Sex chromosomal analysis should be performed on all patients who present with primary amenorrhea or with early-onset ovarian failure. Buccal smears should be avoided as X and Y chromatin tests are often unreliable for diagnosing sex chromosome abnormalities.[10] The women that present with later onset ovarian failure should have their adrenal reserve checked.
3. Thyroid function: The women who present with later onset ovarian failure should be screened for high titres of anti-adrenal and anti-thyroid antibodies to rule out autoimmune adrenal or thyroid failure which may follow ovarian failure a year or more later.[10]
4. Blood Sugar: Blood sugar level should be checked.
5. X-ray of the pituitary gland to rule out tumor.
6. Blood calcium level.
7. Bone mineral density study.

Consequences of premature menopause

The consequences of premature menopause can be divided into short and long term consequences.

Short term consequences include vasomotor symptoms such as hot flushes, night sweats, palpitations and headaches, weight gain, vaginal dryness and dyspareunia, urgency and stress incontinence with psychological problems including irritability, forgetfulness, insomnia and poor concentration.[3,10,27,28]

The long term consequences of premature menopause include infertility, osteoporosis and an increased risk of premature death, cardiovascular diseases and stroke.[3,10,27,28]

Infertility

It is true that some authors have reported pregnancies in women with premature menopause,[29,30] but the reality is that it is rare. With recent advancement in oocyte donation, women with premature menopause now have hoped to mother a child. Currently, oocyte donation is widely used and it is a successful option in management of infertility due to ovarian failure. The possible theoretical reasons for high pregnancy rates in ovum donation programmes are:

1. Absence of the state of hypoestrogenism,
2. Absence of other causes of infertility,
3. Lack of endometrial hyperstimulation,
4. Absence of episodes of premature lutenization,
5. Better control of the window of receptivity.

Osteoporosis

This is a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in fragility of bone and susceptibility to risk of fracture.[23,31] Women with premature menopause are at increased risk for low bone density, earlier onset osteoporosis and fractures.[32] Maternal aging and oestrogen deficiency as a result of declining ovarian activity have been implicated in the aetiology of osteoporosis.[10,33] Albright, *et al.*[34] are the first to demonstrate the relationship between oestrogen deficiency, menopause and an increased incidence of fractures in women. Other studies later supported these findings and further demonstrated the beneficial effects of oestrogen replacement therapy.[35,36] Hormone replacement therapy is the corner stone in the prophylaxis and treatment of osteoporosis. The following oestrogen preparations are currently available for management of osteoporosis namely tablets for oral use, creams for percutaneous or vaginal use, vaginal rings, transdermal patches and subcutaneous implants. Subcutaneous implants provide a safe simple delivery system for hormone replacement therapy.[37] Implants have little or no adverse effect on clotting factors, blood pressure, or glucose tolerance.[37]

Cardiovascular consequences

Premature menopause is associated with an increased risk of ischemic heart disease and angina and the risk increases with an earlier age of ovarian failure.[10,38] It is also associated with increased cardiovascular mortality and total mortality.[39-41] Oestrogen deficiency increases the risk of ischemic heart disease and angina in a post-menopausal woman. Oestrogen is cardio protective in prevention of cardiovascular disease.[42] Oestrogen also increases HDL and decreases LDL, cholesterol and triglycerides. Oestrogen receptors have been found throughout the cardiovascular system.[43] A typical oestrogen effect is a relaxation in arterial tone and a decrease in resistance.[43]

Management of premature menopause

The most important approach in management of premature menopause is to identify the cause and institute treatment based on the cause. It is now possible to restore follicular maturation, ovulation and menstruation with treatment of identified cause of premature menopause.

With ovulation induction or oocyte donation in IVF programmes, it is possible to achieve pregnancy. Women with primed endometrium using oestrogen, can be followed with progestogen challenge test to demonstrate the possibility of induction of menstruation.

It is good practice to recommend oestrogen replacement therapy for women with premature menopause.[44-46] Women with hypo oestrogenaemia may require hormone replacement therapy (HRT) to avoid osteoporosis. There is some evidence that restoring normal oestrogen levels will reduce the later development of cardiovascular disease, osteoporosis and possibly dementia.[47] Thus, short term use of HRT is considered an option by many.[47-50] Treatment for each woman is considered virtually: Mandatory.[51] It is possible to treat autoimmune disease with corticosteroid therapy if antibodies to sex hormones are present in the blood.

Problems associated with premature menopause

Premature menopause is associated with long term health risks such as premature death, cardiovascular disease, neurologic disease, osteoporosis, and psychosexual dysfunction and mood disorders. Oestrogen mitigates some but not all of these consequences. The use of oestrogen is controversial and problematic because it is the most recognized effective treatment option which is often contraindicated. Premature menopause that result from cancer treatments such as chemotherapy and radiation or from bilateral oophorectomy has increased over time because of the improved success in the treatment of cancer in children, adolescents and reproductive-age women. Furthermore, the practice of prophylactic bilateral oophorectomy at the time of hysterectomy has increased overtime.[22] However, there is strong evidence that long term risks and adverse health outcomes following induced menopause is increasing.[22] Serious health consequences such as premature death, cardiovascular and neurologic disease, osteoporosis, psychiatric symptoms and impaired sexual function are linked with induced menopause.[22]

Women with premature menopause are at risk for low bone density, earlier onset osteoporosis and fractures,[32] earlier onset of coronary heart disease and increased cardiovascular mortality.[39] Women with premature ovarian failure have been reported to have diminished general and sexual well-being and are less satisfied with their sexual lives.[52] Furthermore, women with premature ovarian failure have more anxiety, depression, somatization, sensitivity, hostility and psychological distress than women with normal ovaries.[52]

Conclusion

Women with premature menopause are at risk of premature death, osteoporosis, ischemic heart disease, angina and infertility.[53] This condition is common in our environment affecting 1% of women under the age of 40 years. Public enlightenment and education is important tool to save those at risk. With simplified protocols and improved techniques the affected women may achieve pregnancy and mother a baby.

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