

Early and Premature Menopause. Factors Impacting the Therapy Choice

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Abstract It is feasible to improve women's quality of life by identifying clinical and hormonal indicators of the onset of early or premature menopause and by developing a management and therapy algorithm. Several harmful health outcomes are linked to premature or early menopause. Hormone treatment research findings in timely menopausal women cannot be generalized to women with early menopause. Hormonal therapy is advised, barring major contraindications, to be used at least until the age of menopause naturally occurs. Depending on the severity of the symptoms, a longer course of treatment may be considered.

Keywords Early menopause, Premature menopause, Women's quality of life, Hormone replacement therapy

1. Actuality of the Topic

One of the lasting effects of early menopause is an increased risk of neurological illnesses, glaucoma, cardiovascular disease, osteoporosis, psychological disorders, and overall early mortality [6,7,8,9]. Early menopause is also an irreversible event. Some of the side symptoms of early menopause are lessened by hormone therapy (HT) [10,11]. To improve women's health, prediction and prevention through potential risk factor alteration will be essential. Early menopause is also linked to environmental and behavioral factors like obesity, ethnicity (African American or Hispanic), early smoking initiation, higher parity, and lower socioeconomic level [16,17]. In the European population, infertility was also linked to a higher risk of early menopause [5,21,22,23]. In the North Indian population, socioeconomic characteristics that have been linked to early menopause in European women [24,25] were not significant [26].

Loss of ovarian function before the age of 40, early between the ages of 40 and 44, and late after the age of 55 is considered premature menopause [31]. Infertility and menopausal symptoms are brought on by ovarian dysfunction, which also raises the risk of other illnesses like osteoporosis and eventual cardiovascular disease [32]. According to the literature, 1% of women have premature and early menopause [33,34]. Other risk factors include early menarche (before the age of 11) and infertility [36,37]. Low body mass index (BMI) and smoking are independent risk

factors [38]. Radiation therapy, chemotherapy, and surgery are examples of iatrogenic causes of premature and early menopause.

The cause is still unknown in the majority of cases, though. Many vegeto-vascular and psycho-emotional manifestations, including hot flashes, night sweats, emotional instability, vaginal dryness, low libido, and osteoporosis, are frequently made worse in women who experience premature and early menopause, which has a significant negative impact on their wellbeing [20]. Patients who go through an early or premature menopause may experience primary or secondary amenorrhea, menopausal symptoms, and decreased fertility because of a lack of sex hormones. It occurs in 10–28% of cases of primary amenorrhea and 4–18% of cases of secondary amenorrhea [38]. Additionally, patients seem to be more susceptible to long-term health issues such cardiovascular disease, osteoporosis, neurological disorders, and psychological issues that shorten life span [33].

Recent international recommendations, such as ESHRE and EMAS, have established the following criteria for premature menopause: women younger than 40 years of age with high FSH > 25 IU/L on two occasions > 4 weeks apart and at least 4 months of oligo/amenorrhea [2,13,40–42]. There is currently no radical treatment available for this illness. Hormone replacement therapy is the major treatment (HRT). Its objective is to reduce long-term health risks and menopausal symptoms. Anti-Müllerian hormone (AMH) plays an important role in the etiology and clinic of premature and early menopause, which is produced by growing ovarian follicles and is known as the best biological indicator of ovarian reserve and ovulatory potential [41].

The synthesis of this glycoprotein hormone starts to gradually decline from the age of 20 and its level becomes undetectable just before the onset of menopause [44]. This

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process occurs concurrently with the decline in the number of follicles brought on by aging [44]. The circulating AMH levels in women differ at the same chronological age despite the gradual loss in ovarian reserve and, as a result, the rate of its fall over time is very diverse, suggesting individual variances in the process of reproductive aging. The dynamic determination of AMH drop, as opposed to a single measurement, can be used to forecast the timing of menopause. It is the pace of steady depletion of the ovarian follicular reserve over time [42].

AMH levels are thought to influence a number of health outcomes in premenopausal women in addition to reproductive function, such as lipid disorders, cardiometabolic risk, cardiovascular disease, and breast cancer risk [32,42]. A greater rate of AMH decline is regarded as a risk factor for coronary heart disease and cardiovascular disease in women regardless of menopausal status and metabolic risk factors.

These inter-individual variations in the annual rate of AMH reduction have underlying mechanisms that are mainly unknown. The age-related loss of ovarian follicles is primarily caused by age and genetics, while environmental and lifestyle variables can also affect this process. While the particular environmental factors that contribute to ovarian aging and their underlying developmental mechanisms are unknown, there are encouraging results on the impact of smoking and diet on menopausal age and the rate of AMH loss [45,46]. According to long-term cohort studies, women with rapid ovarian aging, as determined by the annual rate of AMH reduction, had significantly different metabolic features from those of the study's participants with slow ovarian aging.

It will be possible to create recommendations for the elimination and correction of these problems based on the results of the hormonal exams, depending on whether the menopause started early or prematurely. The physiological replacement of ovarian steroid hormones, or HRT, until the beginning of natural menopause, is a standard therapy for women with premature menopause (up to 50 years). HRT's major objective is to maintain an adequate level of estradiol, which will shield premature or early menopausal women from the development of serious side effects and early death caused by persistent estrogen insufficiency [1,2,7,9].

The basic idea behind utilizing menopausal hormone therapy (MHT) in older women, whose major treatment objective is to maintain quality of life, differs only slightly from the basic idea behind using HRT in young women. It is possible that younger women need more estrogen than older ones do. Additionally, these women can have higher expectations for sexual performance, which typically calls for the use of testosterone replacement therapy and vaginal estrogen (estriol) [1,29,30]. In situations where fatigue and libido loss persist despite the use of HRT, androgen replacement therapy can be helpful. Transdermal testosterone and dehydroepiandrosterone treatment are options for androgen replacement [1]. It is recommended to utilize combined oral contraceptives (COCs), which include

high steroid hormone concentrations, as HRT in women who have premature or early menopause. However, using COCs raises the possibility of adverse side effects such as dyslipidemia and thromboembolic diseases [2].

The reduction in endogenous estrogen and consequent termination of ovarian function are the most major physiological changes that occur after menopause [1]. It has been demonstrated that HT therapy can reduce the negative effects of early menopause on a variety of outcomes [1,16]. Women with early and premature menopause may benefit from HRT not only for symptomatic relief but also for maintaining bone mineral density and lowering the cardiovascular and neurocognitive effects of estrogen deficiency [10,12,14,19]. This is in contrast to women with natural menopause, in whom the main reason for starting MHT is moderate to severe vasomotor symptoms. Prematurely menopausal women have a 5–10% probability of spontaneous pregnancy, albeit this is uncommon [8].

The current guidelines for women who experience early or premature menopause advocate using HRT at least until the age of menopause naturally. The Endocrine Society, European Menopause and Andropause Society, American Society for Reproductive Medicine, and International Menopause Society all support it (IMS). British Medical Society, North American Menopause Society, and International Osteoporosis Foundation [48,49]. If necessary, longer-term therapy may be considered [50]. The ideal estrogen dosage for women experiencing premature or early menopause has not yet been studied, and greater dosages are frequently required to manage symptoms. It is frequently advised to use a dosage that is at least 100 micrograms of transdermal estradiol. Due to the fact that this dose can produce blood estradiol concentrations that are close to those of menstrual women [31,48].

For women who have early ovarian failure, individualized therapy is extremely crucial. Recent studies on the route, dosage, and makeup of estrogen therapy for girls with hypogonadism and Turner syndrome have demonstrated that the highest levels of physiological estrogen are produced by transdermal estradiol doses that approach the blood concentrations of estradiol and estrone found in adolescent girls with regular menstrual cycles. [51]. Estrogen has been demonstrated to be cardioprotective, despite controversies, and its decline may raise the risk of cardiovascular disease in postmenopausal women [8,37]. The information gathered will aid in the delivery of logical and successful therapy that raises the standard of living for young women.

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