

Incidence and Risk Factors for Premature Menopause

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Abstract The review summarizes current data on the prevalence and etiology of premature menopause (PM). The key pathogenetic mechanisms of PM are genetic, autoimmune, metabolic, iatrogenic disorders, as well as the adverse effects of environmental factors. We analyzed the above aspects and came to our own conclusions. Based on these findings, we identified the main prognostic aspects of the disease.

Keywords Premature menopause, Early menopause, Epidemiology, Clinical features

1. Introduction

Premature menopause is characterized by accelerated loss of follicles during the fertile period and premature cessation of ovarian function [1,3]. This process has consequences for the entire female body, including because, in addition to physical changes, it is also characterized by psychological disorders (psychosocial discomfort), which together significantly reduces the quality of life of women with early menopause [2,4]. As is known, the duration of ovarian functioning is determined by the number of germ cells in the ovary and the factors initiating their apoptosis (programmed extinction) throughout a woman's life. In this case, the maximum number of germ cells in the ovary occurs at the 6th week of pregnancy (> 700 thousand eggs). Throughout a woman's life, germ cell apoptosis occurs at a rate of approximately 25–150 cells per day. So, by the time of menarche, the number of eggs decreases by 50%, and by the onset of menopause there are about 1000 of them [7,9]. PM is amenorrhea with elevated levels of follicle-stimulating hormone (FSH) in women under 40 years of age. In a recent large meta-analysis, which included data from 31 studies, the prevalence of PM and early menopause was 3.7% and 12.2%, respectively [5,6]. Regardless of the cause, women who experience estrogen deficiency well before the average age of natural menopause are now recognized to be at increased risk of premature morbidity and mortality [8,10]. Although the hormonal levels in women with spontaneous preterm ovarian failure are very different compared to women who have undergone induced menopause due to surgery, both conditions are associated with long-term health risks.

Purpose of the study: This review was aimed at studying the incidence rates of PM/RM, as well as identifying risk factors and prevalence in the world.

2. Materials and Research Methods

The search was carried out in the PubMed, Web of Science, Scopus and Cyberleninka databases, which were conducted in the world without time limits with a diagnosis of PM. The study included studies published in English on various aspects of PM including epidemiology and risk factors. A total of 22 articles were included in the study. The main criteria for the diagnosis of PM were: serum FSH level more than 25 IU/l, determined twice with a 4-week interval (according to the criteria of the European Society for Human Reproduction and Embryology (ESHRE, 2015), episodic or stable amenorrhea in women younger than 40 years, menstrual disorders (NMC) and clinical manifestations of estrogen deficiency.

The survey included a survey in accordance with the structure of the international PM registry with an assessment of sociodemographic data, family and reproductive history, duration and history of the disease, and the nature of therapy. During the study, the principles set forth in the Declaration of Helsinki of the World Medical Association (1961) were observed, the study was approved. Statistical analysis was performed using the STATISTICA 6.0 software package.

3. Research Results

According to published studies, the incidence of PM is highly dependent on race and ethnicity and is higher in developed countries. The results of this study show that mortality from breast cancer is higher in less developed regions. The results of this study showed that various risk factors, including demographic, reproductive, hormonal, hereditary, lifestyle-related, contribute to the incidence of PM. PM is the second most common pathology among menopausal manifestations among women of the late reproductive period. The lifetime risk of developing PM for every woman in the US is 12.4%, or one in eight women. In 2012, 1.67 million new cases of PM were detected

worldwide, which is 25% of all cases associated with the violation or absence of the menstrual cycle in women of the late reproductive period. Although PM exists throughout the world, its incidence is higher in developed countries, and the incidence is highly dependent on race and ethnicity. The incidence of PM/RM varies in different parts of the world²⁰, from 27 per 100,000 in Central Africa and East Asia to 92 per 100,000 in North America. It is estimated that by 2050 cases of PM will reach 3.2 million people. With an increase in the age of the population and influencing factors on the female body in developed countries, cases of PM increase. Almost 24% of all cases of PM occur in the Asia-Pacific region, with the highest rates observed in Central and Minor Asia, India, and Indonesia. In addition to these countries, the highest prevalence of PM/RM has marked its record in African countries and in many low-income countries.

Risk factors. PM is often a disease inherent only in women, it occurs mainly as a result of hormonal imbalance, radiation, stress, heavy physical exertion for a long time, and a family history of aggravated.

Reproductive factors. The correlation between reproductive factors and PM is associated with the action of ovarian hormones, which begin at puberty and continue during monthly cycles, and these hormones are also influenced by the number of pregnancies and, ultimately, their decrease at menopause [1,3].

Age of menarche. The results of a case-control study showed that younger age at menarche doubled the risk of PM (OR, 2.83; 95% CI, 1.02-7.86). This result has been confirmed by many other studies. Results from a large cohort study of 11,889 women in China showed that younger age at menarche is associated with an increased risk of PM (95% CI, 1.1–3.4). However, in other studies, younger age at menarche has not been associated with an increased risk of PM. A study in Italy found no association between PM and the onset of the menstrual cycle. As a result, it was found that early menarche in many cases leads to PM [5,7].

Abortion. The results of the study showed that a higher abortion rate was associated with an increased risk of developing PM (OR 6.26; 95% CI 4.16–9.41). However, this finding was not confirmed in another study. A reanalysis of the results of 53 epidemiological studies showed that spontaneous or natural abortion does not increase the risk of developing PM.

Hereditary factors. One of the most important aspects that has been confirmed in several studies conducted in the US and Canada. In women with a burdened gynecological history, 35.8% more cases of PM were reported [8,14].

Genetic disorders. Genetic disorders are more common in those cases that appear at an early stage [12]. Examples of genetic disorders are chromosomal abnormalities. Ovarian dysgenesis is the main cause of premature menopause. Ovarian dysgenesis is observed in 30% of cases [9] Anomalies of the sex chromosomes predominate as the cause. The most common anomaly is 45X0 (Turner's syndrome). Chromosomal abnormalities are recorded in 10-20% of cases involving X sex chromosomes [11].

Lifestyle factors. Obesity and overweight. The correlation between obesity and PM has been examined in several studies. Obesity is correlated with PM/RM due to a higher rate of conversion of androgen precursors to estrogen via peripheral aromatization in adipose tissue. On the other hand, high levels of insulin and insulin-like factors in response to obesity may stimulate the growth of cancer cells. According to a prospective observational study, among 74,177 women, 17% were associated with weight gain of more than 5 kg at age 18. The results of the study showed that obesity before pregnancy is an independent risk factor for PM (adjusted RR, 1.4; 95% CI, 1.1–1.9). Body mass index (BMI) also plays a role in patient survival and is an independent predictor of overall survival in patients with PM. The results of the study showed that obese women (BMI ≥ 30 kg/m²) at the time of diagnosis of PM had lower disease-free survival (RR 1.43; 95% CI 1.11-1.86) and overall survival (RR, 1.56; 95% CI, 1.14–2.14) compared with non-obese women. Researchers in a prospective cohort study reported that obesity mostly affects older people. The cohort study also showed a positive correlation between these pathologies.

Smoking. It is known to cause premature menopause. There is a dose-dependent effect of smoking on the age of menopause [10]. The effect of smoking is believed to be due to the polycyclic hydrocarbons found in cigarette smoke [12] In addition to smoking, early menopause may be associated with poor health, poor diet, and increased parity.

Alcohol consumption. Various studies have examined the role of alcoholic carcinogens and their correlation with PM. The results of the European Prospective Nutrition Study (EPIC) showed an association between alcohol consumption and PM, positive and negative for hormone receptors. The results of this study showed that the timing of drinking may influence the risk of developing PM, with the risk of developing PM being higher among those who drink alcohol before their first full-term pregnancy. In a case-control study after old age at first birth, alcohol consumption, with a 4.2-fold increase, was one of the main risk factors for PM. In a population-based case-control study, a correlation was found between alcohol consumption and PM.

Diet. The relationship between diet, unbalanced nutrition and PM has been the focus of many researchers and has been examined in various studies. In a case-control study, an association was established between a non-vegetarian diet and PM. The results of the case-control study showed that a diet low in polyunsaturated and saturated fatty acids in PM. The results of another study showed that the risk of developing PM increases with total consumption of meat (HR, 1.20; 95% CI, 0.86–1.68) and unprocessed meat (HR, 1.20; 95% CI, 0.86–1.68).

The results of a European prospective study of PM and nutrition showed a significant association between saturated fat intake and the risk of developing PM (HR, 1.13; 95% CI, 1.00–1.27; P for trend, 0.038). The result of the study showed that the low concentration of vitamins was a decisive factor in the development of PM. According to the results of

the study, there is an inverse relationship between the serum content of 25-OH vitamin D and PM. The result of a case-control study showed that women with vitamin D deficiency have a 27% increased risk of developing PM compared with women with a normal status. In a cohort study, serum vitamin D levels above 25 OH and regular vitamin D supplementation were associated with reduced incidence of PM [13].

Physical activity. Results from a prospective cohort study of 74,171 women aged 50–79 years showed that increased physical activity was associated with a reduced risk of developing PM. In this study, more physical activity was associated with greater benefit (RR 0.86; 95% CI 0.78–0.95). Researchers in an observational study stated that physical activity after the diagnosis of PM can improve the quality of life of patients. They stated that the greatest benefit from exercise was seen among people who walked 3–5 hours a week at a moderate pace.

Sleep duration. There is a relationship between sleep duration and PM. Compared to women with normal sleep duration, women with longer sleep duration may be at increased risk of PM. However, in this study, this association was not seen in women with shorter sleep times. Another study found that various aspects of sleep, such as sleep duration and quality, are associated with an increased risk of wasting, which can lead to PM (HR, 1.20; 95% CI, 0.86–1.68).

Socioeconomic status. One issue that has been discussed in more detail in recent studies is the role of socioeconomic status in the incidence of PM. Various studies have found an association between high socioeconomic status and PM, it is more common in women with lower socioeconomic status, which may be due to direct exposure to important risk factors. In addition, the sedentary lifestyle and high carbohydrate diet in this social class can directly or indirectly affect the menstrual cycle of women. At the same time, they can detect lower levels of vitamin C, retinol and beta-carotene, as well as changes in the levels of the hormones estrogen and FSH [14].

Radiation. A large population-based case-control study showed that the risk of developing PM in women exposed to radiation is higher due to iatrogenic effects on the ovaries, induced menopause may occur (OR 3.55; 95% CI 1.47–8.54).

Autoimmune diseases. This is reported in 30-60% of cases [3]. They are more common causes of late manifestations [11] Autoimmune causes of premature menopause are thyroid disease, mumps, hyperparathyroidism, and Addison's disease. Ovarian biopsy under these conditions shows infiltration of the follicles by plasma cells and lymphocytes. Women with autoimmune premature menopause are at increased risk of adrenal insufficiency, hypothyroidism, diabetes mellitus, myasthenia gravis, rheumatoid arthritis, and systemic lupus erythematosus (HR, 1.22; 96% CI, 0.9–1.98).

Infections. Mumps is the most common infection associated with premature menopause. Its effect is greatest

during prenatal and pubertal periods, when even subclinical infection can lead to ovarian failure. [15] Pelvic TB can cause secondary amenorrhea and ovarian failure. Pelvic tuberculosis is observed in 3% of cases [6]. It is important to note that pelvic TB is more likely to result in intrauterine synechia with endometrial destruction in women with this infection than in ovarian failure.

Iatrogenic. Radiation and chemotherapy can cause premature menopause, but the effect is reversible and the ovaries can resume ovulation and menstruation after one year of amenorrhea [3]. Megavolt exposure (4500-5000 rad) is often associated with ovarian failure, but exposure less than 500 rad restores normal ovarian function by 50% after a year or two and pregnancy occurs [3,13]. There is no evidence that low doses of radiation (diagnostic or therapeutic doses of radionuclides), ultraviolet radiation or household microwave devices cause significant loss of ovarian function [10]. Chemotherapeutic agents involved in the etiology of premature menopause are alkylating agents, methotrexate, 6-mercaptopurine, actinomycin, and adriamycin. Damage to the ovaries as a result of cancer therapy depends on the age at which treatment is given and on the type of treatment. Women younger than 40 have a lower risk of ovarian failure than older women. However, exposure to higher doses of alkylating agents and higher doses of ovarian radiation is more likely to cause ovarian failure [11].

Operation. Ovarian failure after hysterectomy is observed in 15-50% of cases [3]. This is caused by a disruption in the blood supply to the ovaries or the loss of some important endocrine contribution from the uterus to the ovary. During surgery, efforts must be made to preserve all normal ovarian tissue and prevent damage to the blood supply to the ovary to prevent ovarian cancer.

Clinical features. Premature menopause is associated with numerous symptoms such as vasomotor symptoms (hot flashes and night sweats), vaginal symptoms (vaginal dryness and dyspareunia), urinary symptoms (frequent urination, urgency, urinary incontinence, and atrophic cystitis), sexual dysfunction, and sleep disturbances [2,4]. Other symptoms are headache, depression, anxiety, irritability, skin atrophy, joint pain, fear of cancer, lack of concentration.

The terms hot flashes, hot flashes, and vasomotor symptoms are often used to describe the same condition. Hot flashes occur in 75% of cases and tend to be more severe than with natural menopause. Hot flashes are the most common and distressing complaint for which women seek the advice of their doctor. Hot flashes are unpredictable at first, and may present with recurring periods of sudden, explosive, overpowering, intense heat or flushing that begins in the face or upper neck and then progresses to the upper chest. Hot flashes may be associated with increased heart rate, restlessness, and redness of the skin. Hot flashes last from 2 to 5 minutes, with varying frequency: some women have attacks several times a day, but their number decreases over time [8] However, hot flashes adversely affect the functional abilities and quality of life of a woman, they are not

life-threatening [4,5].

Premature menopause may present with vaginal atrophy, which reduces vaginal secretions, and vaginal dryness may cause dyspareunia. Loss of libido exacerbates sexual dysfunction. In about 10-20% of cases, there is a decrease in libido [2]. Premature menopause can cause urethral caruncle formation, dysuria with or without infection, urgency, and stress incontinence. Characterized by prolapse of the folds of the vagina, shortening and narrowing of the vagina. There is a general loss of mucosal elasticity with decreased vaginal secretion and loss of vaginal transudate. Decreased vaginal discharge and delayed release of vaginal lubrication during intercourse greatly contribute to the development of dyspareunia in women with premature menopause. A decrease in estrogen levels causes urogenital atrophy and weakness of the urogenital diaphragm. Atrophic changes in the lower genital tract in women lead to symptoms of dysuria, urethral discomfort and stress incontinence. Sleep disturbances can be observed in women with severe hot flashes, manifested by cognitive or affective disorders as a result of lack of sleep.

4. Conclusions

The PM places a huge burden on most women around the world. This study examined the epidemiological aspects and risk factors associated with this condition. Although this pathology is not directly related to the mortality of women, it significantly reduces the quality of life and leads to disability. The results of this study showed that the incidence of PM is influenced by various factors, of which the most important are genetic factors, environmental factors and lifestyle, as well as many factors such as iatrogenic interventions, hormonal imbalance, stress, physical inactivity, low social status, unbalanced nutrition. By eliminating these factors, the incidence of the disease can be exponentially reduced.

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