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Causes and Long-Term Consequences of Premature and Early Menopause on the Women Health

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ABSTRACT
To review and summarize current affirmation on the women health consequences of premature and early menopause.We reviewed existing literature and combined results from cohort study of hysterectomy and primary ovarian insufficiency.Premature and early menopause may be either spontaneous or induced by other factors. Women who experience premature menopause (before age 40 years) or early menopause (between ages 40 and 45 years) experience an increased risk of overall mortality, cardiovascular diseases, neurological disease, psychiatric diseases, osteoporosis, and any other abnormality. The risk of adverse outcomes increases with earlier age at the time of menopause. Anyhow of the cause, women who experience hormonal menopause and estrogen deficiency before reaching the median age of natural menopause are at increased risk for morbidity and mortality. Estrogen treatment should be considered for these women, but may not eliminate all of the adverse outcomes.
Key Word- Premature and Early menopause, estrogen

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INTRODUCTION
Menopause is a normal part of aging. It refers to the time when ovaries reproductive function ends- when a woman`s ovaries stop producing eggs and the hormones estrogen and progesterone [1]. Menopause occurs when a woman has not had her period for 12 months or longer [2]. Most women reach menopause between the ages of 45 and 55, with the average age being around 51. However, about 1% of women experience menopause before the age of 40 years. This is known as premature menopause.Menopause between 41 and 45 years of age is called early menopause [3]. It is marked by amenorrhea, increased gonadotropin levels and estrogen deficiency [4].Premature menopause or early menopause can be spontaneous or induced by medical interventions such as chemotherapy or radiation treatment and surgical interventions like bilateral oophorectomy *i.e.* surgical removal of the ovaries. When menopause is surgically induced, it is associated with a rapid decline in ovarian hormone levels and consequently more severe menopausal symptoms. These symptoms include hot flashes, sleep disturbances, mood liability, and decreased energy [5,6].
The most commonly reported symptoms among women in high-income countries are vasomotor symptoms including hot flushes, vaginal dryness, insomnia, fatigue, and joint pain [7-9].Symptoms attributed to menopause vary between individuals and cultures, which has been attributed to general aging, menopausal fluctuations, or socially constructed phenomena [10]. Some of the adverse outcomes may be prevented or minimized by estrogen therapy started after the onset of premature and early menopause. However, estrogen alone does not prevent all log-term consequences and other hormonal mechanisms are probably involved[5,6].

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FEMALE REPRODUCTIVE CYCLE

The balance between estrogen and progesterone handles the development and maintenance of the female reproductive system. Cellular differentiation is regulated by progesterone while estrogen controls cell proliferation. Thus, uterine endometrium has 3 phases.

1. The follicular phase (estrogen dominant) is a growth phase where uterine glands grow and proliferate
2. During secretory (luteal) phase, [progesterone dominant] glands get tightly coiled, and secrete
3. During menses, spiral arteries constrict, and endometrium sloughs [11].

REGULATION OF REPRODUCTIVE HORMONES IN FEMALE

The hypothalamus is responsible for the secretion of gonadotropin-releasing pituitary to release follicle-stimulating hormones (FSH) and luteinizing hormones (LHs) FSH stimulates follicle growth, maturation of ovum leading to the release of estradiol from follicles. High levels of estradiol for a sufficient period stimulate sudden secretion of LHRH (GnRH-positive feedback), which induces a surge of LH (and FSH) secretes from the anterior pituitary. LH surge leads to ovulation and assists the development of corpus luteum. Corpus luteum then releases progesterone. Increased levels of estrogen and progesterone will signal anterior pituitary and hypothalamus to stop the secretion of FSH and LH. The resulting negative feedback leads to deterioration of corpus luteum, which further decreases the amount of estrogen and progesterone[12].

ETIOLOGY OF PREMATURE MENOPAUSE

The definite etiology of premature menopause cannot be determined but some causes are identifiable [13]. These include:

Non Pharmacological

A) Genetic Disorders: Genetic disorders are common in those cases that present early[14]. 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[13].

Genetic Causes of Premature Menopause:

- *Chromosomal abnormalities*–

(a) *Turner's syndrome* -Sex chromosome anomalies predominate as a major cause. The common abnormality is 45X0 (Turner's syndrome). Chromosomal abnormalities are reported in 10-20% of cases involving X sex chromosomes[14].Turner`s syndrome has a phenotype associated with complete or partial monosomy X and affects about 1 in 2,500 females, is the most common genetic condition resulting in POI [15]. The most frequent chromosome constitution is 45 XO, or complete absence of one X chromosome. Women with 45XO have gonadal dysgenesis, and most cases have only streak ovaries composed of fibrous stromal tissue containing few or no ovum [16]. About half of patients with Turner syndrome are mosaic, of which the most common chromosome composition is 45X/46XX (15%) while 46XXq or 46XXp deletions account for about 6% [17,18]. In patients with partial monosomy X, the exact karyotypic abnormality is relevant to determining the phenotype. Deletions on the short arm (p) of the X chromosome are associated with dysmorphic features such as short stature and congenital malformations, whereas partial or complete deletion of the q arm often manifesting gonadal dysfunction [18].

(b)*Pure gonadal dysgenesis*-46,XX gonadal dysgenesis is characteristic of female hypogonadism with a karyotype of 46,XX.[19]Streak ovaries are present with non-functional tissues unable to produce the required sex steroid estrogen. Low levels of estrogen effect

the HPG axis with no feedback to the anterior pituitary to inhibit the secretion of FSH and LH[20].

(c)*Familial*- The fragile X mental retardation 1 (*FMR1*) gene that is located on the q arm of the X chromosome is of particular relevance in the context of POI [21]. Fragile X syndrome, the most common cause of familial mental retardation, results from an inherited triplet repeat mutation in the *FMR1* gene. The normal number of CGG repeats in the untranslated region of the *FMR1* gene is less than 40. Repeat length between 55 and 200 is termed a premutation, and a length of greater than 200 repeats represents the full mutation[22]. Interestingly, only those women with a permutation in the *FMR1* gene are at risk for developing POI, whereas those with either normal or full mutation are at no higher risk than the general population. Premutations of the *FMR1* gene are present in as many as 14% to 20% of women with familial POI. And are found in up to 2% to 5% of women with isolated POI [23-27].

(d)*Trisomy 18 and Trisomy 13* -X trisomy seems to be related to ovarian dysfunction as 47,XXX women might experience oligomenorrhea, secondary amenorrhea, and early menopause [28].

(A) Metabolic Disorder :

- *17-alpha-hydroxylase deficiency*: Defects in the sex steroid biosynthetic pathway can lead to predictable consequences depending on the enzyme deficiency. When 17 α-hydroxylase/17,20-lyase is deficient, pregnenolone cannot be converted to 17 α-hydroxypregnenolone. This leads to a reduced ability to produce cortisol, androstenedione, testosterone, and estrogens. This condition in XX genetic females will be associated with normal appearing external genitalia, but affected individuals fail to undergo secondary sexual development at puberty. The ovaries do respond to exogenous gonadotropins. The disorder is a result of an autosomal recessive mutation isolated to a single gene, *i.e.*, *CYP17* located on 10q24–25 [29].
- *Galactosaemia:*A number of inherited enzymatic pathway disorders have been associated with ovarian follicular dysfunction leading to POI. Galactose 1-phosphate uridylyltransferase deficiency (galactosemia) was one of the first to be characterized.The gene encoding this enzyme is located on 9p and the pathogenesis is believed to involve toxic accumulation of galactose during infancy. Phenotypic features of this disorder involve defects in the ocular, renal, and hepatic systems. Because galactosemia requires treatment in childhood to prevent mental retardation, it is unlikely to be diagnosed in an otherwise healthy adult presenting only with POI [30].
- *Myotonic dystrophy*:is associated with hypotonia of striated and smooth muscle, ophthalmological lesions such as cataracts, cardiac muscle conduction defects and endocrinological disorders. Moreover, hypogonadism is frequently described and MD is associated with decreased fertility. In women, the relationship between MD and infertility remains unclear and publications on the subject are controversial. Some investigators have associated MD with an increased risk of ovarian dysfunction [31].

(B) Autoimmune Diseases-They are the more common causes in the later onset presentations [32]. Autoimmune causes of premature menopause are thyroid diseases, hyperparathyroidism and Addison's disease. This is reported in 30-60% of cases. The ovarian biopsy in these conditions show infiltration of the follicles with plasma cells and lymphocytes[14]. Women with autoimmune premature menopause are at increased risk for adrenal insufficiency, hypothyroidism, diabetes mellitus, myasthenia gravis, rheumatoid arthritis and systemic lupus erythematosis[33-34].

(C) 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 [35]. Pelvic tuberculosis can cause secondary amenorrhea and ovarian failure. Pelvic tuberculosis is seen in 3% of cases. It is important to note that pelvic tuberculosis results in intrauterine synechiae with endometrial destruction more in women suffering from this infection[36].

(D) Smoking - Is known to induce premature menopause. There is a dose-related effect of smoking on age of menopause[37]. The effect of smoking is believed to be caused through polycyclic hydrocarbons contained in cigarette smoke [38].Apart from smoking, early menopause may be associated with poor health, poor nutrition and increased parity [39].

(E) Iatrogenic- Radiation can cause premature menopause but the effect is reversible and the ovary may resume ovulation and menstruation after one year of amenorrhea [13].Megavoltage irradiation (4500-5000 rads) is often associated with ovarian failure but irradiations less than 500 radiations restores normal ovarian function by 50% after a period of one year or two and pregnancies have occurred [40]. 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[41].
In patients developing malignant diseases, radiotherapy can lead to premature ovarian insufficiency. The effect of radiotherapy is dependent on dose and type of therapy and also depend on the age of the patient. Complete ovarian failure occurs with a dose of 20 gray(Gy) in women under 40 years of age and with only 6 Gy in older women[42]. The prepubertal ovary is relatively resistant to gonadotoxicity due to radiotherapy[43]. There is little risk of premature menopause in women treated with radiation fields that exclude the pelvis [44].Ovariopexy which involves transposition of the ovary away from the radiation field preserves ovarian function in 60–100% of patients [45].

(F) Surgery - Ovarian failure following hysterectomy is seen in 15-50% of the cases [13]. 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 [46]. The practice of prophylactic oophorectomy has increased overtime and more than doubled between 1965 and 1990.Bilateral oophorectomy is carried out to prevent ovarian cancer [47].

Pharmacological

(A) Drugs- Prolonged gonadotropin-releasing hormone therapy may lead to ovarian suppression and failure. Others are chemotherapeutic drugs particularly alkylating agents[48]. The chemotherapeutic agents implicated in the etiology 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 [49].
Teenagers receiving chemotherapy have a 4 times increased risk of POF. This risk is increased among women aged 21–25 years [50].Approximately 25% of breast cancer cases occur in premenopausal women, and breast cancer accounts for one third of cancers in reproductive-age women[51].Adjuvant chemotherapy and endocrine therapies are now standard, resulting in ovarian insufficiency and sex steroid suppression among many women with a history of breast cancer. Approximately two-thirds of premenopausal women become amenorrheic after starting the chemotherapy regimen most commonly used for breast cancer [52].However, the overall risk of inducing menopause depends on the type and dose of

chemotherapy and on the age of the woman. Consequences of induced ovarian failure include premature menopause, infertility, vasomotor symptoms, vaginal dryness, dyspareunia, weight gain, and osteoporosis [53,54].

PREMATURE OVARIAN INSUFFICIENCY

Primary ovarian insufficiency, also known as premature menopause or premature ovarian failure, is defined by the presence of menopausal-level serum gonadotropins in association with irregular menses in a woman younger than 40 years [55-57]. It is defined by a triad of signs: amenorrhea for at least 4 months, decreased estradiol serum concentrations, and elevated follicle-stimulating hormone (FSH) serum concentrations [more than 40 IU/l in at least two samples a few weeks apart [58.59].The prevalence of menopause varies according to age, and it is 1: 10,000 at the age of 18-25 years, 1 : 1000 in women aged 25-30 years, and 1 : 100 in the age range 35-40 years. POI is related with familiar occurrence in about 15% of cases, which suggests a genetic etiological background [60-62].Three potential mechanisms can be associated with POI, *i.e.,* a congenital decrease in primordial follicles, accelerated follicular atresia, and an inability to recruit primordial follicles [63].In women younger than 40, at least two menopausal FSH levels (>40 IU/L) will be sufficient for the diagnosis of POF. The first tests to be made in these patients to distinguish other hormonal reasons are FSH, estradiol, prolactin, and TSH measurement [64].

HYSTERECTOMY

Hysterectomy, the surgical removal of uterus, is the second most frequently performed non-obstetric surgery after cesarean section in many parts of the world [65-69]. Moreover, to reduce the future risk of ovarian cancer, prophylactic oophorectomy which involves removal of ovaries is often recommended simultaneously with hysterectomy [70].Common medical indications of hysterectomy include gynecological ailments such as fibroids, dysfunctional uterine bleeding, and uterine prolapse [71].An earlier onset of menopause can be spontaneous or the result of medical interventions such as surgical removal of the ovaries or be due to chemotherapy or radiation treatment with subsequent ovarian damage. When menopause is surgically induced, it is associated with a rapid decline in ovarian hormone levels and consequently more severe menopausal symptoms. These symptoms include hot flashes, sleep disturbances, mood liability, and decreased energy.Research also shows several adverse effects of hysterectomy such as urinary incontinence, sexual dysfunction, late medical problems such as backache and weakness and earlier onset of menopause[72-77].

HYSTERECTOMY RISKS & COMPLICATIONS

Most women experience no complications during or following a hysterectomy. In fact, the relief of painful symptoms often results in a positive post-surgery experience. In some cases, the surgeon must change from a vaginal incision to an abdominal incision during surgery.
Following hysterectomy, long-term complications can include the following:

- Decrease in sexual desire (if both ovaries have been removed).
- Feelings of loss or diminished femininity.
- Increased risk for osteoporosis in women under age 45.
- Pain during sex (if vagina has been partially removed).
- Pelvic weakness.
- Vaginal dryness (caused by low estrogen levels if ovaries are removed) [78].

After a hysterectomy, if the ovaries were also removed, a woman will entermenopause. If the ovaries were not removed, a woman may enter menopause at an earlier age[79].

CONCLUSION

Premature menopause and early menopause, whether spontaneous or induced, are associated with long-term health risks which may include premature death, cardiovascular disease, neurologic disease, osteoporosis, psychosexual dysfunction, and mood disorders. Estrogen mitigates some but not all of these consequences. The most common interpretation of these findings is that premature or early menopause is the first step in a chain of causality leading to tissue or organ dysfunctions and lesions via hormonal mechanisms [80]. However, before discussing this interpretation more extensively, we also mention the alternative hypothesis that premature or early menopause is the result of an accelerated aging process determined by genetic or non-genetic causes and involving all tissues and organs throughout the body, including the ovaries [81]. Under this hypothesis, the hormonal changes following premature or early menopause have no causal role in the development of premature death, cardiovascular disease, neurologic disease, osteoporosis, psychosexual dysfunction, and mood disorders. The evidence in support of this hypothesis is limited. Whether different types of premature menopause or early menopause result in different long-term health consequences remains unknown. Their hormonal milieus differ because the postmenopausal ovary is hormonally active, producing small amounts of estradiol and estrone, as well as androgens including testosterone, androstenedione anddehydroepiandrosterone[82].Following bilateral oophorectomy in premenopausal women, estradiol levels drop,testosterone levels drop by 40–50%, and follicle-stimulating hormone levels rise abruptly. Women undergoing bilateral oophorectomy continue to have lower levels of androgens than naturally menopausal women even beyond 65 years of age [83]. With Premature ovarian insufficiency, follicle-stimulating hormone levels are elevated and estradiol levels are low, but sporadic increases in estradiol may occur [84]. Ovarian androgens remain age-appropriate in these women [85]. Ovarian failure caused by cancer therapy, when permanent, is associated with elevated follicle-stimulating hormone levels and reduced estradiol levels similar to natural menopause; androgen function has not been well-characterized. Overall, different consequences from the different types of menopause may relate to the extent of disruption of the hypothalamic-pituitary-ovarian axis as much as to the reduced levels of circulating sex steroid hormones [80].

CONFLICTS OF INTEREST

There are no conflicts of interest.

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