Premature menopause

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PREMATURE MENOPAUSE

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Abbreviations

FSH- Follicle-Stimulating Hormone

LH- Luteinizing Hormone

POI- Primary Ovarian Insufficiency

POF – Primary Ovarian Failure

HCG – Human Chronic Gonadotropin

TS – Turner Syndrome

IVF – Invitro Fertilization

GALT- Galactose-1-Phosphate Uridylyltransferase

17OHD - Seventeen -Hydroxylase Deficiency

DGS - DiGeorge Syndrome

GU – Genitourinary

PCOS – Polycystic Ovarian Syndrome

EDCs – Endocrine Disruptive Chemicals

BPA - Bisphenol A

HIV -Human Immunodeficiency Virus

LD50- Median Lethal Dose

Gy- Gray

HT – Hormone Therapy

Content

Summary

Title: Premature Menopause

Author: Lee Shnaider

Menopause that starts before age 40 is referred to premature menopause.

Amenorrhea, elevated gonadotrophin levels, and a lack of estrogen are its hallmarks. Premature menopause can be either spontaneous or forced. It characterized by the triad of amenorrhea for at least 4 months, sex steroid deficiency, and two recordings of serum concentrations of FSH of more than 40 IU/L at least 1 month apart, in a woman aged less than 40 years. Although the exact reason of early menopause cannot be identified, there are certain potential causes – genetic, autoimmune, environmental, infectious, iatrogenic. For a woman, the diagnosis is a significant event. It is a condition which have an impacts for health, mental health, and reproduction. It results in irregular menstrual cycles and infertility. It is now known that women who experience estrogen deficiency at a young age -well before the median age of natural menopause -are at an elevated risk for early morbidity and mortality, regardless of the underlying etiology. Treatment of premature menopause usually includes hormone therapy replacement and various IVF treatments. The purpose of this article is to review and discuss various etiologies of premature menopause and ovarian insufficiency, and their consequences on women well-being.

Sažetak

Menopauzu koja nastupa prije 40.-te godine života nazivamo prijevremena menopauza. Obilježja prijevremene menopauze su amenoreja, porast razine gonadotropina i niska razina estrogena. Ona može biti prirodna ili inducirana. Karakterizirana je amenorejom kroz najmanje četiri mjeseca, porastom razine FSH uz uvjet uzastopnog određivanja FSH najmanje kroz dva ciklusa odnosno dva mjeseca, pri čemu je razina FSH veća od 40 IU/L u žene s prijevremenom menopauzaom mlađe od 40 godina. Iako se ne zna točna etiologija prijevremene menopauze, kao mogući etiološki čimbenici navode se genetski, autoimuni, okolišni, infektivni i jatrogeni uzroci. Dijagnoza prijevremene menopauze značajno utječe na ukupno zdravlje, mentalno zdravlje i reprodukciju. Vrlo često se manifestira nepravilnim menstruacijskim ciklusima i neplodnošću. Dokazano je da žene, u kojih nastupi estrogeni manjak daleko prije očekivane prirodne menopauze, imaju veći rizik ranog morbiditeta i mortaliteta, bez obzira na moguće etiološke čimbenike. Liječenje prijevremene menopauze uključuje primjenu hormonskog nadomjesnog liječenja i, u slučaju neplodnosti, metode pomognute oplodnje. Cilj ovog rada je prikazati i raspraviti etiološke faktore, dijagnostiku i mogućnosti liječenja prijevremene menopauze i prijevremene ovarijske insuficijencije koji značajno umanjuju kvalitetu života mlade žene.

1. Introduction

When a woman stops menstruation and reaches the end of her normal reproductive life, she enters the state of menopause. It occurs when a woman goes 12 months without having her period. The increase in gonadotropins (FSH and LH) is related to that. When the ovaries stop developing eggs and secreting estrogen and progesterone, menopause-related alterations take place. Long-term estrogen deficiency has detrimental effects on female health in general and in particular on bone density, cardiovascular and neurological systems, overall wellbeing, and sexual health(1).

Ovarian failure before the age of 40 is referred to as early menopause. Amenorrhea, elevated gonadotrophin levels, and a lack of estrogen are all hallmarks of early menopause . It is now known that women who experience estrogen insufficiency before the natural menopause are at an elevated risk for premature morbidity and mortality, regardless of the underlying etiology. One percent of women under the age of 40 are affected by it. 20% of cases of primary amenorrhea and 11% of cases of secondary amenorrhea are seen. The majority of the time, it is idiopathic, although it can also happen after radiation or surgery(2).

Following ovulation, monthly menstruation is crucial for female health and reproduction. The synthesis of sex steroids, which are essential for the genital tract's development, proper bone density, and general health, depends on healthy ovarian function. Because ovarian insufficiency can refer to a variety of ovarian functions that are impaired, it is more accurate than ovarian failure(3).

Primary ovarian insufficiency is characterized by the triad of amenorrhea for at least 4 months, sex steroid deficiency, and two recordings of serum concentrations of FSH of more than 40 IU/L at least 1 month apart, in a woman aged less than 40 years or two standard deviations in years before the mean menopausal age of the study population(3).

For the diagnosis of ovarian insufficiency, tests for predicting ovarian response to hormonal stimulation, measures of antral follicle count, concentrations of anti-

mullerian hormone (a novel endocrine marker produced by preantral and early antral follicles), early follicular phase FSH , inhibin B concentrations and the number of ovarian follicles were developed. Figure 1 illustrates how the size of the follicle pool affects the concentrations of endocrine hormones expressed during tests of ovarian reserve. Anti-Mullerian hormone appears to be the most direct and accurate test for ovarian insufficiency since its concentrations, unlike FSH, are unaffected by cyclic change(3).

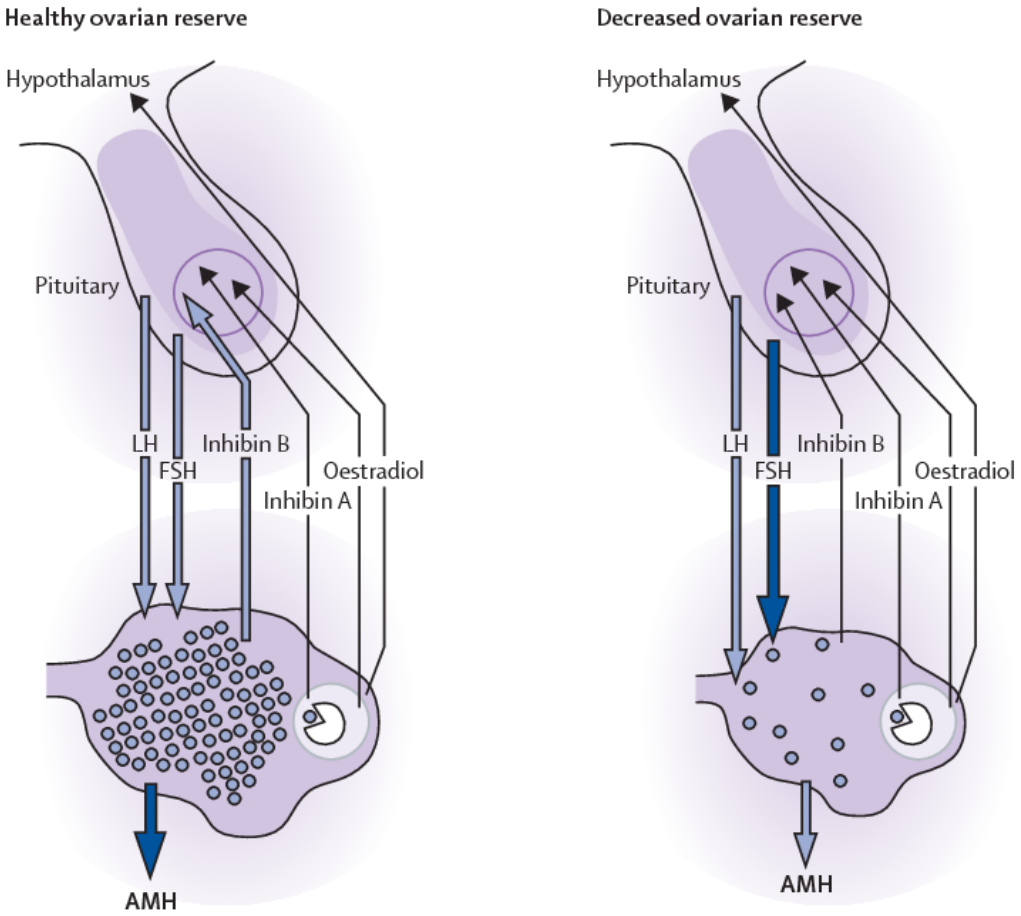

Figure 1. Healthy and decreased ovarian follicular reserve with increased age and changes in concentrations of ovarian and hypothalamic pituitary hormones - Primary ovarian insufficiency Michel De Vos, Paul Devroey, Bart C J M Fauser

The purpose of this article is to review and discuss various etiologies of premature menopause and ovarian insufficiency. This condition usually leads to sterility and has major effect on women in young age. This article will also review the different fertility preservation options that can be offered to different types of etiologies of premature menopause.

2. Etiologies

2.1 Genetic

2.1.1 Chromosomal

The most frequent cause of primary ovarian insufficiency has been attributed to genetic causes, though the effects of sex chromosome abnormalities (such turner syndrome or X structural abnormalities), autosomal, and X-linked mutations have also been widely documented. Although POI frequently occurs at random, there occasionally may be a family history. According to studies, X-linked inheritance with incomplete penetrance or autosomal dominant sex-limited transmission are the most likely causes of the condition in women with affected relatives(4).

X chromosome abnormalities, namely aneuploidies and rearrangements, represent about 13 % of POI, which makes them one of the commonest genetic causes. Turner syndrome or monosomy X (45,X), in which most women present by gonadal dysgenesis with primary amenorrhea, loss of ovarian reserve before puberty - as oocytes need two active X chromosomes. Women with TS usually need regular sex hormone treatment until the age of 50 years (4) .

Because there are other sources of androgens outside the ovaries in TS (also produced by the adrenal glands), pubic and axillary hair development is preserved. The goal of estrogen therapy in TS women is to promote breast and uterine development as well as growth spurt and peak bone mass. By beginning with low dose estrogen and evaluating clinical response by examining linear growth rate and breast development, normal pubertal development is produced (5) .

To protect the endometrium, progestogen is introduced. To prevent withdrawal bleeding, it can be applied successively but can also be applied sequentially. The sequential approach is advised, particularly if a future pregnancy is desired- by the European Society of Human Reproduction and Embryology. Women with POI who are TS patients have the following choices for parenthood: surrogacy, adoption, or donor egg IVF. The predicted rate of maternal death from aortic dissection in pregnancies of women with TS is 2%(5).

The primary ovarian insufficiency after TS is most frequently caused by the FMR1 premutation, which is a known congenital condition. Fragile X syndrome is caused by a CGG trinucleotide expansion to more than 200 repetitions. At 80 to 100 repeats, the risk of primary ovarian insufficiency is highest; however, with more than 100 repeats, the risk reduces(3).

Trisomy X or the triple X syndrome may be linked to POI (47,XXX). It does not always occur, although its prevalence is higher. The main cause of trisomy X syndrome is maternal nondisjunction mistakes during meiosis. Just 10% of people with trisomy X are thought to currently have a diagnosis. Most triple X syndrome sufferers do not seek for medical attention and have not had their chromosomes checked. It is common for the disorder to go untreated until maturity, when the genetic flaw is found due to other circumstances, such as infertility. According to earlier research, trisomy X women typically have higher amounts of the hormones estrogen and progesterone, which can lead to monthly irregularities and sexual precocity(6).

2.1.2 Metabolic

Galactosemia is an autosomal recessively inherited genetic condition brought on by a lack of galactose-1-phosphate. Many patients with typical galactosemia have hyper gonadotrophic hypogonadism and little to no GALT activity. Despite eating a diet low in galactose, most women with classic galactosemia develop primary ovarian insufficiency. It is unclear what the underlying pathophysiology of this issue is(7).

Kaufman et al. examined 18 female and 8 male galactosemia patients in 1981. (8) Males had normal gonadal function, whereas 12 out of 18 females showed symptoms of hypergonadotropic hypogonadism. During the onset of amenorrhea, blood FSH levels were found to be increased, ranging from 12.3 to 167 IU/L (FSH > 10 IU/L indicates decreased ovarian reserve, while FSH > 40 IU/L is typically seen in individuals with POI). Low serum estradiol levels were found, and pelvic ultrasonography revealed tiny or nonexistent ovaries(8) .

POI is typically detected in the second decade of life in galactosemic women. The ovaries have been linked to toxic damage caused by galactose and its metabolites. In addition, it has been proposed that POI may result from anomalies in FSH or its receptor and from disruptions in epigenetic pathways. Figure 2

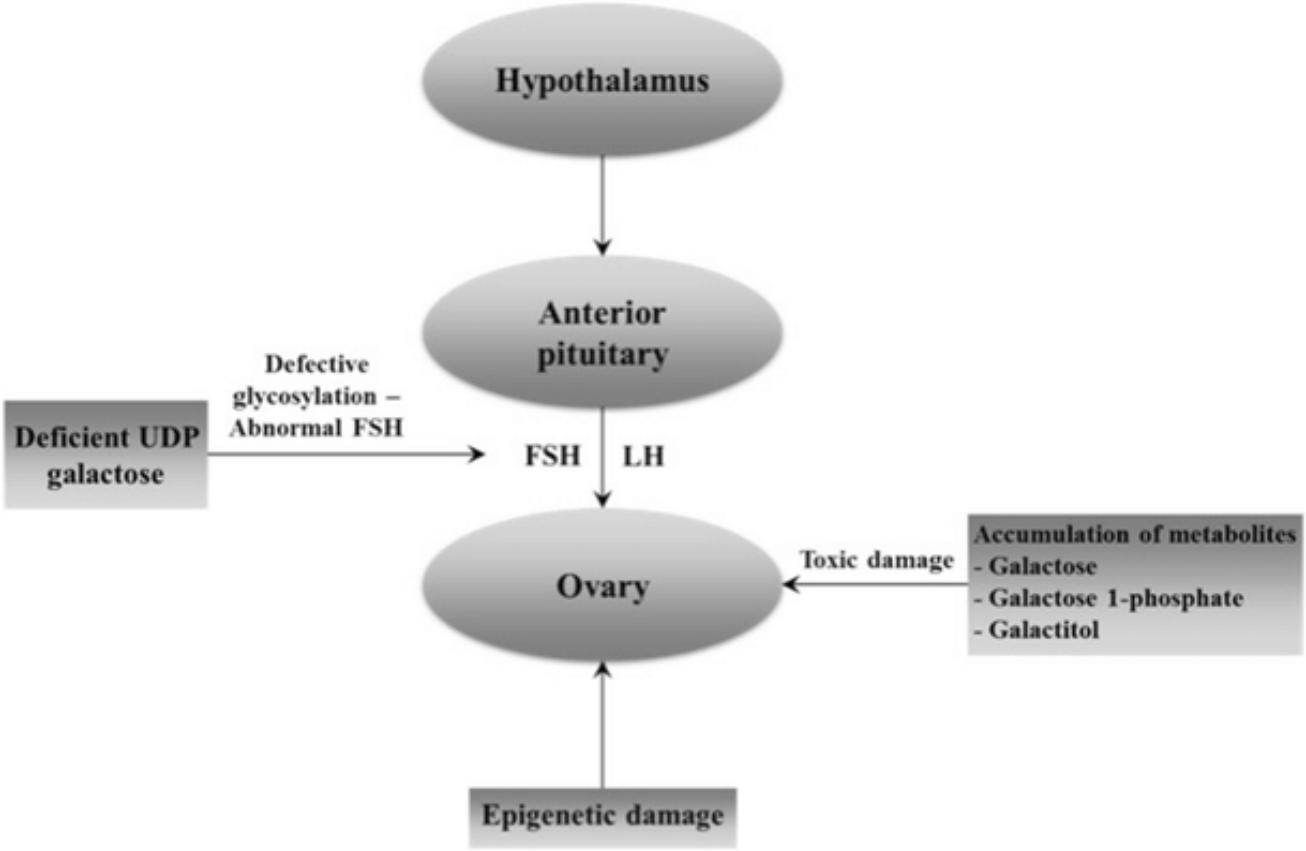

Figure 2 . Thakur, M., Feldman, G., & Puscheck, E. E. (2017). Primary ovarian insufficiency in classic galactosemia.

Principles for the detection and treatment of POI in people with classic galactosemia who have completed puberty where developed by "International Clinical Guideline for the Management of Classical Galactosemia: Diagnosis, Treatment, and Follow-up, Guidelines" in 2017. They advise annual monitoring for menstrual irregularities, secondary amenorrhea, and POI symptoms (9).

The cornerstone of POI treatment is estrogen-based hormone replacement medication. Moreover, progesterone is administered to lower the likelihood of endometrial hyperplasia once full breast growth has been attained. Galactosemic patients frequently desire fertility preservation, usually before POI manifests itself because they have a high chance of developing POI(9).

A rare variant of congenital adrenal hyperplasia known as 17-Hydroxylase Deficiency causes excess mineralocorticoids, hypokalemic hypertension, and sexual abnormalities due to problems in the production of cortisol and sex steroids. The disorder has an autosomal recessive inheritance pattern (10).

In 46,XX people, the lack of sex hormone synthesis results in hypogonadism, which includes primary amenorrhea, no breast development, and axillary and pubic hair alopecia. If a post pubertal 46,XX patient displays hypogonadism, scant or missing sexual hair, infantile genitalia, some degree of spontaneous breast development, recurrent ovarian cysts, with or without hypertension and hypokalemia, the diagnosis of 46,XX partial 17OHD should be investigated(11).

The ineffective response to the ACTH and HCG stimulation tests may aid in the diagnosis. Patients with 17OHD 46,XX frequently seek obstetric or gynecological treatments due to primary or secondary amenorrhea, oligomenorrhea, or hypomenorrhea. When ovarian failure occurs before the age of 40, the patient often exhibits normal development of secondary female traits during adolescence and exhibits indications of estrogen shortage. Ovarian cystectomy is not necessary in patients with ovarian cysts because they frequently recur, with the exception of emergency situations (ovarian cyst rupture and torsion) . Some patients struggle with spontaneous fertility, and if necessary, assisted reproductive procedures may be considered(11).

2.1.3 Immunological

Ataxia telangiectasia is a rare hereditary type of autosomal recessive ataxia with early onset. The ataxia telangiectasia mutated (ATM) gene mutation, results in a clinical picture that combines neurological and systemic symptoms. Cerebellar atrophy with progressive ataxia, cutaneous telangiectasias, malignancy (especially lymphoid malignancy), and immunological insufficiency are some of the specific symptoms of the condition(12).

In national cohort study "Endocrine abnormalities in ataxia telangiectasia" published by Andreea Nissenjorn, Yael Levy-Shraga and Yonit banet-Levi in 2016 . It was found that of the female patients 13(out of 18) had increased levels of LH and FSH which indicated on ovarian insufficiency. The remaining five females had normal levels of gonadotropin but they were less then 10 years old – the age when there is natural suppression on the gonadotropin axis(13).

Only one of the clinically diagnosed female patients with increased gonadotropin levels attained complete sexual maturation and regular menstrual cycles. One of the other patients had full sexual maturity, regular periods, and secondary amenorrhea. Five patients were examined before the age of 13 and did not exhibit any signs of puberty, which was still considered normal for their age. But their elevated gonadotropin levels indicate ovarian failure, and it is expected that they may experience impaired pubertal development or amenorrhea (13).

The 22q11 deletion syndromes are a larger term that has previously been used to describe several syndromes, including DiGeorge Syndrome (DGS). DGS symptoms include a thymus that is missing or hypoplastic , cardiac problems, hypocalcemia, and parathyroid hypoplasia(14).

The 22q11.2 area may feature dosage sensitive genes because human sex development is susceptible to dosage gene effects. In fact, GU abnormalities are a recognized clinical trait shown in the 22q11.2 gene.

In a 2018 study by Sylvie J, Elena JT, Linda A, and Marion B describe four patients who had ovarian insufficiency and a 22q11.2 mutation. Ovarian shortage could be an uncommon symptom or go unreported. The increasing awareness of adults with 22q11.2 may be influenced by improvements in genetic diagnosis and treatment(15).

2.2 Autoimmune

A common autoimmune attack on the human ovary results in ovarian dysfunction, which can show up as POF, PCOS, unexplained infertility, or endometriosis(16). In the case of POF, the presence of lymphocytic oophoritis, its connection to other autoimmune diseases, and the presence of autoantibodies to ovarian antigens all support an autoimmune etiology(17). It has been associated with autoimmune reactions to ovarian tissue. Around 20% of POF patients have concurrent autoimmune disorders that were previously diagnosed. Thyroid, adrenal, and pancreatic problems are the most prevalent of these. 10% of Addison's disease-stricken women also present with POF. Addison's disease and adrenal immunity were present at the time that the first case of autoimmune lymphocytic oophoritis was identified (18,19).

The fact that POF is an end-stage of the disease may substantially restrict an examination of anti-ovarian autoimmune responses and autoantibodies. By the time a woman receives a diagnosis, she has probably used up all her follicular supply and the target antigen that the autoimmune response on her ovaries that were attacked. Which is why, it may be challenging to determine autoimmunity as the cause of POI. In spite of that, there are several anti-ovarian antibodies(20).

Usually, physical examination is uneventful, although it may show signs of an underlying condition such hypotension, decreased pubic and axillary hair, or hyperpigmentation. Alopecia areata, vitiligo, early greying of the hair, malar rash, premature greying of the nails, and other symptoms that may be present in autoimmune conditions(21). Ultrasound has limited contribution in specific diagnosis of autoimmune cause but it is a good tool for ruling out other amenorrhea causes(22).

At the time of initial diagnosis, 14–27% of women have thyroid autoimmune disease, the most prevalent of which is Hashimoto's thyroiditis. It makes sense to check for thyroid peroxidase antibodies and evaluate thyrotropin levels(17). Between 1 and 10% of POF patients also have autoimmune diseases of the adrenal glands. POF may occur 8 to 14 years before Addison disease, according to some experts. In women with adrenal autoimmunity, there is a 50% chance of developing adrenal insufficiency. As signs of adrenal insufficiency emerge, all patients with primary ovarian insufficiency should be educated about them and have their adrenal function evaluated(23).

Estrogen and progestin-based cyclical hormonal therapy should be administered to all POF patients. However, some autoimmune disorders, such as SLE, may be made worse by estrogens and for this reason, all such patients should be carefully watched before starting hormone therapy(24). As gonadotropin medication may make autoimmune POF worse and promote follicle turnover, which has the consequence of diminishing follicular reserve, it is not recommended(25). For women dealing with this sad diagnosis, management should focus on symptom relief but most significantly, it should include mental support.

The following guidelines for the investigation of suspected POI were released by the European Society of Human Reproduction and Embryology (ESHRE); only those relevant to autoimmune diseases are mentioned below:
"-Screening for 21OH-Ab should be considered in women with POI of unknown cause or if an immune disorder is suspected .
-Refer POI patients with a positive 21OH-Ab/ACA test to an endocrinologist for testing of adrenal function and to rule out Addison’s disease.
-Screening for thyroid (TPO-Ab) antibodies should be performed in women with POI of unknown cause or if an immune disorder is suspected.

-In patients with a positive TPO-Ab test, thyroid stimulating hormone (TSH) should be measured every year" (26).

2.3 Environmental Hazards

Several pieces of data have been acquired over the last few decades that show specific chemical, physical, and biological elements in our environment that have a detrimental effects on human reproduction(27) .Any exogenic, non-human necessities that, when dispersed into the environment, have the potential to harm either human health or the environment are referred to as environmental pollutants(28) .The most common chemicals with a detrimental effect on ovarian function were phthalates, bisphenol A, pesticides, and tobacco, with higher follicular depletion causing menopause to begin earlier in age(29).

According to the Endocrine Society, endocrine disruptive substances are "exogenous compounds, or mixtures of chemicals, that interfere with any component of hormone action." EDCs can have temporary or permanent impacts on ovarian functioning, depending on the time of exposure relative to ovarian ontogenesis. They primarily act on estrogen receptors, which can have an impact on ovarian reserve(30).

One of the most frequently produced compounds in the world is bisphenol A. BPA production is currently estimated to be over 8 billion pounds per year, with an annual potential atmospheric release of about 100 tons(31). BPA is a known endocrine disrupter. BPA's application was discovered in the plastics sector in the 1940s. BPA is a component of polycarbonate plastics, which are frequently used to make infant bottles, food and beverage containers, and other plastics. BPA is also used in products that we regularly use at home and at work, such as the coating on CDs, DVDs, electrical and electronic equipment, cars, and sports safety gear(32) .Following early exposure to BPA, changes in gonadotropin release and hypothalamic/pituitary function have been described in females(33). Moreover, impacts on the developing ovary and changes in estrogen receptor levels in the brain and pituitary have been reported(33)(34). The reduced fertility observed over time in female mice exposed to BPA perinatally could be caused by the changes known to occur at each of these levels of the reproductive

axis and in reproductive tissues, according to a study published in 2011 by Nicole JC, Perinaz RW, and Ana MS(35).

Another common EDCs are the phthalates . Phthalates are pervasive environmental toxins to which people are regularly exposed. They are a class of synthetic compounds made up of phthalic acid alkyl diesters(36). They are often used as plasticizers and can be found in a variety of consumer and cosmetic items, from hairsprays and perfumes to insecticides and wood treatments, as well as in popular medical devices like tubing, blood and intravenous bags, dialysis equipment, and disposable and surgical gloves(37). Plastics are non-covalently bonded to phthalates, which means that they readily leak from them into the environment through sources like the atmosphere, soil, and natural water bodies(38).

Phthalates may affect the ovary at any stage of development as well as in adulthood. Infertility, anovulation, early ovarian failure and reduced steroidogenesis are all possible consequences of these harmful effects(39). By specifically targeting follicles at various stages of follicular genesis, they can cause ovarian toxicity. They have the ability to either encourage faster development from that stage or induce atresia, which depletes the follicles in that stage(40). Phthalates can potentially hinder the ovarian steroidogenesis process directly. Depletion of the corpora lutea and/or antral follicles can both impact steroidogenesis, as these can interference with the steroidogenic units ability to operate(41). Normal menstrual cyclicity may change as a result of this interruption of hormone production. By suppressing the LH surge and/or changing FSH levels, a lack of ovarian-derived steroid hormones would upset the hypothalamus-pituitary-ovarian axis, resulting in infertile anovulatory cycles(41,42).

Depending on the period of exposure and the population of follicles the chemical targets, removing or reducing toxicant exposure may reduce the ovarian toxic consequences(40). Biomonitoring studies indicate that 75–100% of the population is

exposed to phthalates on a daily basis, based on high manufacturing quantities, broad use, and environmental pollution(43)(44). Given that the overall public is regularly exposed to phthalates, it is crucial to comprehend the effects of phthalate exposure on ovarian function(44).

2.4 Infections

Another suspected cause of POI has been identified as several occurrences of mumps oophoritis(45). It is commonly known that the mumps virus can affect organ systems besides the salivary glands. Involvement of the gonads is clinically evident in 20% of men and 5% of women. The presence of mumps orchitis can be quickly determined because the testicles are open to inspection and observation. Nonetheless, there aren't many cases of mumps oophoritis described because the ovaries are relatively inaccessible(46).

According to a multicenter study conducted in the United States with 1139 HIV-positive and 292 HIV negative women, HIV positive women were three times more likely to experience amenorrhea than HIV negative women (47). HIV-infected women experience the start of menopause earlier than HIV-uninfected women because they lose ovarian function earlier in life(48). Antral follicular count, FSH, inhibin B, and anti-mullerian hormone were among the indicators used in a prospective pilot study in France to assess the ovarian function of HIV-positive women . These findings suggest that HIV infection or the associated antiretroviral medication may affect ovarian functioning and fertility, leading to POI. Four indicators all exhibited high rates of aberrant values(49).

2.5 Smoking

Smoking has been shown as a significant factor of earlier menopause. In 1949, the first communication on how smoking causes the menopause to occur sooner, was published(50). The majority of research revealed an inverse relationship between smoking habit and menopause age, meaning that women who smoked more had the menopause at a younger age(51).

Many polycyclic aromatic hydrocarbons, such as benzopyrene, found in cigarette smoke have been linked to the dose-dependent destruction of primordial oocytes in tested animals(52). Also, it was hypothesized that smokers have lower levels of endogenous estrogens due to either decreased synthesis or greater hepatic conversion to 2-hydroxy estrogens, which may hasten menopause(53).

It has been discovered that current smokers experience a higher decline in menopause age than former smokers(54). The harmful effects of tobacco use on ovarian function are thought to be irreversible. If this is the case, smokers who stop during their reproductive years should have a similar risk of early menopause as smokers who do not stop. There has not yet been enough empirical studies on the impact of smoking cessation and the effect it might have on menopause age of onset(55).
In cohort study published by Mohammad R.H , Alexandra C, and Gali M.W, in 2012 it was noted that women who smoked during the 21-year follow-up or in earlier phases were shown to be more likely than non-smokers to develop early menopause(56).

2.6 Iatrogenic

2.6.1 Radiation

Ionization, a process where electrons are released into the cellular environment and interact with the cellular molecules, including DNA molecules, causes damage from radiation. The operation of the cell is disrupted as a result(57). By subjecting the tumor to ionizing radiation, radiotherapy works to either reduce the tumor mass or get rid of any remaining tumor cells. Radiation has an effect on both cancerous and healthy cells(58). The ovaries may be in the area of pelvic, abdominal, or spinal radiation, and the LD50 for the ovary is predicted to be 2 Gy (59).

POI can develop even at low radiation doses of around 0.01-0.99 Gy. A higher risk of POI development is linked to older age at treatment and higher radiation exposures(60). Radiation doses greater than 20 Gy to the ovary cause complete ovarian failure, follicle development suppression, and a significant drop in the quantity of oocytes(61). It is well recognized that ionizing radiation used in pelvic radiation therapy damages the ovarian reserve and leads to POI, especially in older premenopausal women whose primordial follicle pool is already constrained. This primarily depends on the patient's age at the time of radiation therapy and the amount of radiation that the ovaries received(62).

There is growing evidence that young cancer patients place a high value on conversations regarding fertility and fertility preservation. When pelvic radiation therapy is suggested for premenopausal women, the American Society of Clinical Oncology advises bringing up the possibility of ovarian transposition. The goal of ovarian transposition is to move the ovaries away from the radiation zones(63).

In study published by Lara H, Andrea C, and John N in 2022 they described POI in young women with locally advanced rectal cancer who were treated with pelvic radiation therapy. In their study they included women in their premenopausal years who underwent pelvic radiation therapy with the goal of curing rectal cancer were included. A portion of the individuals underwent ovarian transposition prior to pelvic radiation therapy. Reports of absent menses and menopausal symptoms were gathered from the patients' records to determine the preservation of ovarian function. Also, the levels of FSH, LH, and estradiol before and after radiotherapy were measured in an endocrine laboratory. From 75 patients who had at least 12 months of follow-up, 19 women (25%) had ovarian function preserved within 12 months after radiation therapy, and all were in the ovarian transposition group(64).

2.6.2 Chemotherapy

The types of cancer drugs used and the patient's age at diagnoses are both factors that influence ovarian damage. In particular, alkylating drugs, cisplatin, and the nitrosoureas are harmful to immature ovaries when administered in large doses of chemotherapy(65). Young women being treated with alkylating drugs for acute

leukemia, brain tumors, and hodgkin disease are been found to have higher FSH plasma concentrations. Nevertheless, a majority of these young women show gradual normalization of FSH levels, and only a small proportion appears to have irreversible ovarian failure(66)(67).

In study published by Himelstein Brow in 1977 which examined ovarian tissue after cancer treatment, histological and ultrasound tests have shown that there are fewer ovarian follicles and follicular growth is inhibited when compared to age-matched controls. Figure 3 (68).

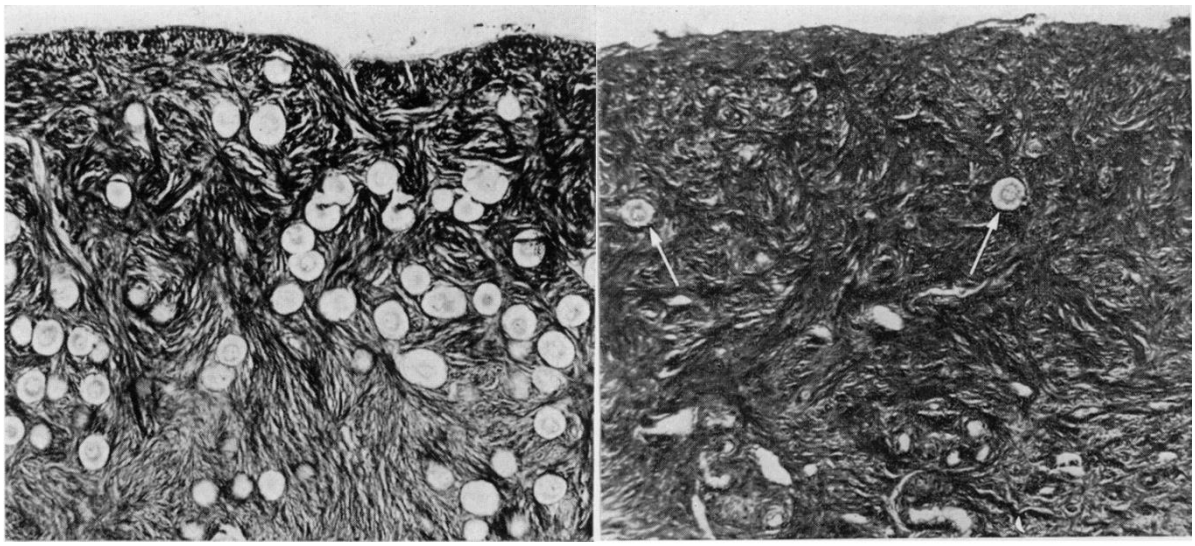

Figure 3 – LEFT-cortex of ovary of a 4-year-old girl who died in an accident. many small non growing follicles are present. RIGHT – cortex of ovary of a 3-year-old girl who died of neuroblastoma who received chemotherapy. only few small non growing follicles. Himelstein-Braw, R., Peters, H., & Faber, M. (1977). Influence of irradiation and chemotherapy on the ovaries of children with abdominal tumors. British Journal of Cancer.

Menopause appears to begin when the number of ovarian follicles falls below a certain threshold, therefore it makes sense that cancer treatment would cause the population of follicles to decrease and cause menopause to begin sooner(69).

2.6.3 Surgery

Prior to menopause, women who undergo bilateral oophorectomy develop surgical primary ovarian insufficiency. More than half of all hysterectomies are performed on women who are 45 years old or younger, and the majority of bilateral oophorectomies occur at the same time as the hysterectomies (70). Although it can also be brought on by ovarian vascular dysfunction or by the uterus that no longer providing some crucial endocrine support to the ovary(2).

Hormone deficiency-related symptoms, an increased chance of contracting certain diseases and a rise in morbidity and death are all side consequences of prophylactic oophorectomy. These outcomes resemble those of females who acquire POI through other methods. But, with surgical POI, symptoms appear more quickly and the results can be more serious.(71). One element of the solution to the issue of millions of women having surgical POI and losing the protective effects of estrogen at a young age is to reduce the incidence of bilateral oophorectomy at the time of hysterectomy in premenopausal women with low risk for ovarian cancer(72).

3.Diagnosis

Subfertility, secondary amenorrhea or oligomenorrhea, and symptoms of estrogen insufficiency are the typical presentations of POI. Aside from varying degrees of amenorrhea, the spontaneous POI phenotype can be incredibly varied, with some women presenting with little or no symptoms(73). Low ovarian reserve found in association with amenorrhea or oligomenorrhea is a constant trait, despite the fact that these symptoms can vary due to intermittent ovarian hormone production(74).

Most recommendations to date have suggested that this be verified by two elevated FSH tests, spaced 4-6 weeks apart. Although the National Institute for Health and Care Excellence guideline recommends >30 IU/l, the most commonly used diagnostic limit is >40 IU/l(75).

Diagnose perimenopause based on vasomotor symptoms and irregular periods, menopause in women who have not had a period for at least 12 months and are not using hormonal contraception. Diagnosis based on symptoms in women without a uterus and without the use of laboratory tests in otherwise healthy women over 45 with menopausal symptoms(75).

The production of anti-mullerian hormone by growing antral follicles in the ovaries is presently believed to be the most accurate indicator of reduced ovarian reserve, especially in light of the increased accessibility of ultra-sensitive standardized assays. It could be possible to do an anti-mullerian hormone test to confirm the POI diagnosis(75). In addition to looking for anatomical anomalies, a transvaginal ultrasound scan can be useful in determining ovarian volume. They are typically correlated with anti-mullerian hormone levels which are low in POI, as would be anticipated(76).

Evaluation of the karyotype and the FMR1 gene premutation should be provided if the diagnosis of spontaneous POI is likely. Although all women with POI should ideally be offered genetic testing - women with very early POI, those with learning challenges and those with a family history of POI can be given priority. Autoantibody testing should be carried out due to the higher prevalence of autoimmune diseases in POI. The tests conducted will in part be influenced by one's personal and family history(77).

4.Treatment/ Preservation

Women with POI are not emotionally ready for the diagnosis, and many specialists and working groups believe that a structured intervention is necessary to deal with the myriad effects(78). Further investigation is needed into the psychosexual and psychosocial symptoms of POI in order to comprehend the complexity of the contributing variables to the burden of the disorder and to develop a long-term treatment plan using hormonal and non-hormonal techniques(79).

Hormone replacement therapy is crucial for POI for a variety of reasons. First, in prepubertal girls with primary amenorrhea, it promotes the development of secondary sexual traits. It is successfully reduces common vasomotor symptoms like hot flushes, sweating, and urogenital issues brought on by bladder and vulvovaginal atrophy. Also it have a beneficial effect on other symptoms like mood problems, energy levels, and musculoskeletal aches and pains(80).

To treat the symptoms of estrogen insufficiency, all women with POI/POF should take cyclical HT with estrogens and progestins. Some women might use HT to treat menopausal symptoms even before amenorrhea appears. Estrogens can be given continuously or cyclically, orally, or transdermal. In fact, estrogen medication may increase the likelihood of getting pregnant by theoretically bringing the LH level down to normal range and preventing the premature luteinization of the remaining follicles in these patients. Estrogen therapy does not hinder ovulation and conception in these individuals. To avoid the endometrial hyperplasia that unopposed estrogen may bring on, progestins should be given cyclically, 10–14 days each month. Contrary to postmenopausal women, young women with POI/POF have a 5–10% chance of spontaneous pregnancy (81).

An estrogen regimen can include three to four metered 0.75 mg doses of estrogen gel or estradiol patches ranging from 75 to 100 g. Non obese women can safely utilize oral estradiol (2-4 mg/day), as they are not known to have an elevated risk of thrombosis. Even though there aren't many dose-response studies of HT in POI, there seems to be a dose-response relationship when it comes to cardiovascular and bone advantages. Low-dose vaginal estrogen or progesterone can be added to the regimen without worry of overdosing and negative side effects if genitourinary symptoms continue (81).
With appropriate androgenic progestogen dosages and durations, endometrial protection appears to be guaranteed. 200 mg of micronized progesterone can be given orally or vaginally for 12 days every cycle as an endometrial protection regimen.
Women with POI can start a no bleed continuous combination regimens right away if they have more then one year amenorrhea or switch to it after a few years if they like. Sequential HT may be linked to a decreased risk of breast cancer even though continuous combined HT is related with improved endometrial safety(82). There is still a 5 to 10% probability of spontaneous pregnancy because POI can vary. Yet, there are no rules that would specify the best course of action or method for treating infertility. Clomiphene, gonadotrophins, GnRH agonists and antagonists, glucocorticoids, and menopausal hormone therapy have all been the subject of studies(83).

Freezing of eggs or embryos is the best fertility preservation options for women of reproductive age who are going to undergo gonadotoxic chemotherapy or pelvic radiation that produces acute POI. IVF with an autologous or donor embryo transfer to a gestational carrier or surrogate carrier, respectively, can help women with POI(84).

Conclusion

1% of women under the age of 40 experience premature menopause . Missed periods are usually the first sign, later symptoms may be similar to those of natural menopause. Three groups of tests should be performed when ovarian failure is suspected or has been diagnosed. They include tests that establish the diagnosis of POF, tests that help clarify the etiology, and screening tests for other diseases known to have higher prevalence among women with POF. Measuring serum FSH level is the core study to establish the diagnosis of POF after pregnancy has been ruled out, serum LH and estradiol are also important. Medical treatment of patients usually includes hormone replacement and psychological support. In our days, adoption, ovum donation, or embryo donation are alternatives for resolving infertility. All women with POF should receive cyclical HT with estrogens and progestins to relieve the symptoms of estrogen deficiency and to maintain bone density. A few women may need HT even before amenorrhea develops to alleviate menopausal symptoms. women may be able to become pregnant and receive early therapy to lower health and psychological risks with increased awareness and improved techniques. If implemented as soon as possible, preventive measures and hormone therapy will have the most impact on maintaining fertility.

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Biography

Lee Shnaider, daughter of Sveta and Oleg Shnaider, was born in Nahariya, Israel, in 1995. Graduated from The Hebrew Reali School in Haifa. Completed two years of service in the IDF prior to starting medical school in Zagreb.

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