Chapter 3

Premature Ovarian Insufficiency (POI): A Current Overview of Diagnosis, Etiopathology, Epidemiology, Symptomatology, and Treatment Options

Oya Korkmaz[1]

Abstract

Premature Ovarian Insufficiency (POI) is a pathological condition characterized by the cessation of ovarian function prior to an individual attaining the age of 40 years. This syndrome is marked by elevated levels of gonadotropins and diminished levels of oestrogen, ultimately leading to infertility. According to guidelines provided by the European Society for Human Reproduction and Embryology (ESHRE), diagnostic criteria for this condition include increased follicle-stimulating hormone (FSH) levels exceeding 25 IU/l tested on two separate occasions with a four-week interval between each measurement, together with the presence of amenorrhea or oligomenorrhea for at least 4 months. The occurrence of POI has been associated with adverse effects such as reduced fertility, irregular menstrual cycles, failed pregnancies, and a reduction in overall health-related quality of life. The early decline in oestrogen puts women at increased risk of osteoporosis, hypertension, cardiovascular disease, weight gain, type 2 diabetes, cognitive disorders such as Parkinson's, depression, and Alzheimer's disease, and dementia. In this respect, it has important consequences that negatively affect women. However, genetic abnormalities, metabolic problems, autoimmunity, iatrogenic causes, infections, or environmental variables have been identified that contribute to the development of premature ovarian failure syndrome in some patients. The etiopathogenesis of the disease remains largely unknown in the majority of cases. This review aims to review the available literature, focusing on the diagnosis, clinical aspects, causes, symptoms, complications, and treatment of POI.

1 Department of Histology and Embryology, School of Medicine, Malatya Turgut Ozal University, Malatya, Turkey, e-mail: oya.korkmaz@ozal.edu.tr, Orcid: 0000-0003-2923-5869

https://doi.org/10.58830/ozgur.pub248.c1158

1. Introduction

Premature Ovarian Insufficiency (POI) is a medical condition characterized by the depletion of follicles in the ovary, resulting in the loss of both reproductive and endocrine functions in women who are younger than 40 years of age (Welt, 2008; Jankowska, 2017). The term 'primary' ovarian failure was initially coined by Fuller Albright in 1942 (Anastasi, 1998). The terminology used to describe this phenomenon has been a topic of continuous academic discussion, incorporating various designations such as premature menopause, premature ovarian failure, and hypogonadotropic hypogonadism. However, it is important to note that in Europe, the commonly used nomenclature is "premature ovarian failure," encompassing both spontaneous POI and secondary POI resulting from medical interventions such as chemotherapy, radiation, and surgery (ESHRE POI Guideline Development Group, 2015).

The condition is distinguished by a fast deterioration in ovarian function, an insufficiency of ovarian sex hormones that expedites the premature onset of menopause, and a reduction in ovarian reserve (Wesevich et al., 2020). These factors contribute to the occurrence of anomalies in the menstrual cycle, such as amenorrhoea and oligomenorrhea. Additionally, they result in elevated levels of gonadotropins, deficiencies in sex steroids, as well as complications in pregnancy and infertility among women (Ebrahimi & Akbari Asbagh, 2011). Over an extended duration, the phenomenon known as POI has been linked to the occurrence of cardiovascular problems, heightened susceptibility to osteoporosis, and cognitive impairment (Webber et al., 2016; Machura et al., 2018; Ishizuka, 2021) **(Figure 1)**. Additionally, it has been observed that POI is linked to premature death (Rocca et al., 2006).

POI has been found to result in psychological and physiological effects in women. In cases of POI, a decline in oestrogen production from the ovary leads to the manifestation of menopausal symptoms. These symptoms include vaginal symptoms, dyspareunia, vaginal dryness, hot flushes, night sweats, sleep disturbance, decreased libido, lack of energy, mood changes, reduced concentration, dry eyes, and altered urinary frequency (Lakhal et al., 2010). Not all women have these symptoms, and they are less prevalent in cases of primary amenorrhea. This indicates that the symptoms are likely a result of oestrogen deprivation rather than oestrogen insufficiency (Kovanci et al., 2015). The symptoms associated with POI might exhibit temporary or intermittent patterns and may exhibit varying degrees of severity. The

observed differences can be attributed to fluctuations in ovarian activity that transpire after the spontaneous onset of POI.

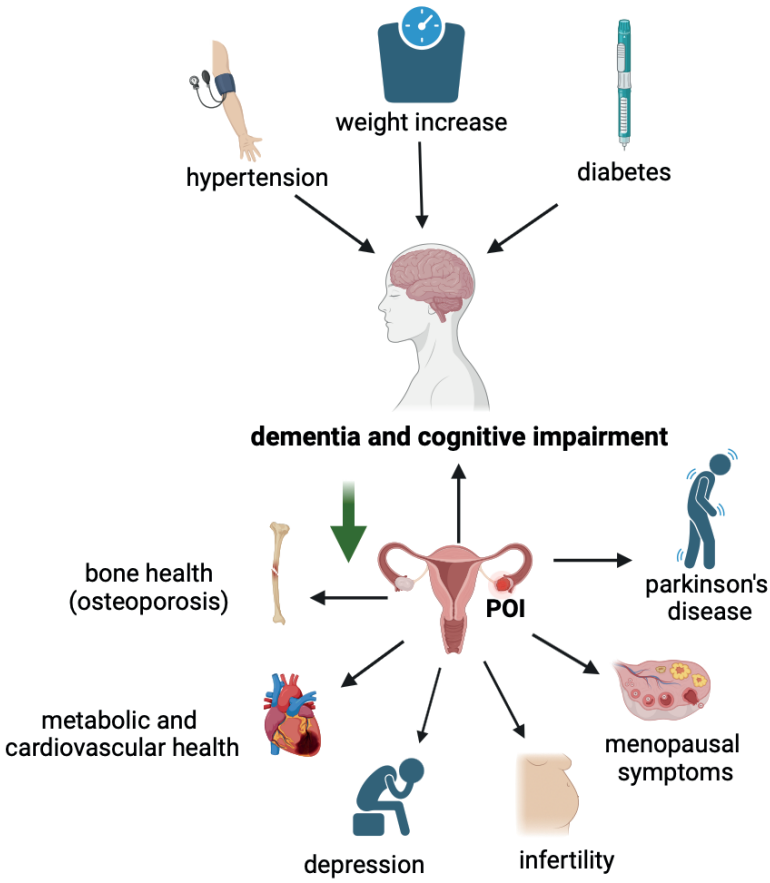

Figure 1. The potential hazards associated with the premature decrease in oestrogen levels

POI is distinguished by a diminished concentration of oestrogen, which manifests prior to the typical onset of menopause. The reduction of oestrogen levels is associated with an elevated susceptibility to several health conditions, including dementia, metabolic and cardiovascular problems, bone health (osteoporosis), depression, Parkinson's disease, Alzheimer's disease, and infertility. Cognitive deficits and dementia may also be precipitated by hypertension, weight gain, and midlife diabetes, conditions that frequently manifest in people experiencing menopause.

The presence of POI has been found to have a substantial negative impact on the health-related quality of life of affected patients. This is primarily

attributed to the heightened risk of cardiovascular complications, diminished bone mineral density resulting in the development of osteoporosis, atrophic alterations in the genitourinary system, as well as neurocognitive impairments such as dementia, Parkinson's, and Alzheimer's disease (Wesevich et al., 2020). The condition exerts a detrimental influence on the psychological well-being of patients, manifesting in adverse outcomes such as pregnancy failures and reduced pleasure in their sexual lives **(Figure 1)**. Regrettably, there exists a dearth of information regarding the fundamental causes and effective treatment approaches for POI, despite its ability to significantly impact individuals' lives. It is imperative to have a comprehensive understanding of the contributing factors and difficulties associated with POI in order to grasp the profound physical and emotional ramifications experienced by young women diagnosed with this disorder. Hence, it is imperative to conduct further research on the regulation and maintenance of follicular quality and quantity within the ovaries to effectively manage female fertility. This chapter aims to review and discuss the current knowledge in this field, focusing on the diagnosis, clinical aspects, causes, symptoms, complications, and treatment of POI.

2. Clinical Aspects of Premature Ovarian Insufficiency (POI)

2.1. Definition, Diagnosis and Prevalence

POI is typically identified by the presence of amenorrhoea in women under the age of 40. This condition is further characterized by elevated levels of FSH in the pituitary gland and diminished levels of estradiol (E2) in the bloodstream. In order to diagnose patients with POI, it is necessary to monitor estradiol (E2) and serum FSH levels on at least two different occasions, with a time interval of more than four weeks. A diagnosis of POI is made when patients consistently exhibit elevated FSH levels exceeding 25 IU/L (Wesevich et al., 2020). While formerly labeled as premature ovarian failure (POF), it has been observed that certain patients exhibit residual ovarian function, which never results in pregnancy. Hence, the European Society for Human Reproduction and Embryology (ESHRE) and the American Consensus meeting embraced the term POI (Welt, 2008). POI manifests in an estimated 1% of females who have not yet attained the age of 40. According to a research study conducted by the Study of Women's Health Across the Nation (SWAN), the prevalence of POI among women was found to be 1.1%. The investigation additionally assessed the frequency of POI within several ethnic cohorts, yielding the subsequent proportions: 1% for Caucasian females, 1.4% for African American individuals, 1.4% for

Hispanic individuals, 0.5% for Chinese individuals, and 0.1% for Japanese females. It is noteworthy to mention that the observed disparities in prevalence among different ethnic groups were determined to have statistical significance (Wesevich et al., 2020). According to Jankowska (2017), there is a higher prevalence of POI in nations characterized by a medium or poor human development index. Based on the findings of Allshouse et al. (2015), the occurrence rate of hyperandrogenism in women with secondary amenorrhoea is approximately 4-8%, but in cases of primary amenorrhoea, it ranges from 10-28%. The incidence rate exhibits variation according to age, with a rate of 1:100 cases observed at 40 years of age, 1:250 cases at 35 years of age, 1:1000 cases at 30 years of age, and 1:10,000 instances between the ages of 18 and 25. The incidence of POI has been found to be influenced by ethnicity, as indicated by epidemiological research conducted by Rebar (2009) and Rudnicka et al. (2018).

2.2. Clinical Presentation of POI

The clinical presentations observed in women diagnosed with POI exhibit significant variability, with symptoms that closely resemble those commonly linked with menopause. These factors encompass challenges in achieving pregnancy and the emergence of irregularities in the menstrual cycle following childbirth or the cessation of contraceptive methods. Additional investigation is merited in the event that a woman in good health encounters the cessation of menstrual cycles for a continuous duration of three months, since POI may be considered a plausible alternative diagnosis (Torrealday et al., 2017). Several often observed symptoms, including dyspareunia, hot flushes, night sweats, dry eyes, and reduced sexual desire, bear resemblance to those experienced during menopause or insufficient levels of oestrogen. Nevertheless, it is possible that women who are affected by primary amenorrhoea may not exhibit any symptoms related to hypoestrogenism. In some instances, females diagnosed with POI may exhibit certain physical characteristics commonly associated with Turner syndrome. These manifestations include diminished height, a neck with excess skin folds, shortened fourth and fifth metacarpal bones, a chest resembling a shield shape, an elbow with an increased carrying angle, ears positioned lower than average, and a hairline that is positioned lower than typical. Torrealday et al. (2017) have reported that Turner syndrome is the predominant hereditary cause of POI, characterized by clinical symptoms that are commonly encountered before the initiation of menarche.

Occasionally, familial disorders exhibiting atypical characteristics have been shown to be related to POI. Various phenotypic expressions can be

observed, encompassing dwarfism, auditory impairment, and neoplastic growths on the eyelids (Torrealday et al., 2017). POI has been found to be related to the clinical outcomes of several autoimmune illnesses, including thyroid and adrenal autoimmunity (Kovanci & Schutt, 2015). The aforementioned manifestations encompass irregular depigmentation of the skin, premature onset of grey hair, localized hair loss, candidiasis, and dystrophy of the nails. Additionally, it is possible for these women to exhibit symptoms associated with adrenal insufficiency, including orthostatic hypotension, salt cravings, hyperpigmentation, abdominal pain, anorexia, and alopecia in the axillary and groin regions. Significantly, there are indications of thyroid sickness, including exophthalmos, goiter, and alterations in heart rate. In the context of pelvic examination, it is frequently noticed that the ovaries cannot be palpated, accompanied by indications of atrophic vaginitis. However, it has also been shown that women who possess enough levels of oestrogen to sustain a healthy vaginal mucosa may exhibit this condition as well (Torrealday et al., 2017). Enlargement of the ovaries may be noted in some instances.

2.3. Histology of the Ovaries in POI

The differentiation between ovarian morphology and histology in individuals with POI and those with gonadal dysgenesis is possible. Gonadal dysgenesis is characterized by the depletion of ovarian follicles during embryogenesis or within the early years of postnatal development, resulting in the absence of follicles in the ovaries. Instead, the ovaries exhibit stroma that manifests as fibrous lines (Taylor et al., 2019). Conversely, women diagnosed with POI exhibit follicles within their ovaries; nevertheless, these follicles demonstrate resistance to elevated levels of gonadotropins. The histology of the ovaries exhibits variations based on the phenotypic manifestations of POI. Nevertheless, it is worth noting that the majority of antral follicles have histological abnormalities. These abnormalities manifest as atretic follicles, which can range from partial sloughing to the full lack of granulosa cells, as observed in the study conducted by Meduri et al. in 2007. A significant association has been seen between the presence of 15 or more follicles in the ovaries of people diagnosed with POI and the detectability of serum anti-Müllerian hormone (AMH) (Meduri et al., 2007; Yoon et al., 2013; Alvaro Mercadal et al., 2015). Although the sample numbers in each group were statistically inadequate, the findings revealed that women with 15 or more follicles exhibited a mean serum AMH level of 2.16 ng/ml. In contrast, women with no follicles and five or fewer follicles displayed mean serum AMH levels of 0.42 ng/ml and 0.33 ng/ml, respectively. The

utilisation of ultrasonography does not allow for the direct visualisation of ovarian follicles. However, the evaluation of serum AMH levels can serve as a means of identifying individuals with POI who may possess follicles with the potential for future growth (Yoon et al., 2013; Alvaro Mercadal et al., 2015). Massin et al. (2004) show that the assessment of ovarian histology in people with POI is a dependable method for evaluating the condition of follicles and the total ovarian reserve. The analysis of morphological changes in this specific condition can yield useful insights into the extent of follicular reserve dysfunction and growth, determine the specific kind of POI, and identify the root cause (Massin et al., 2004). Histological examinations have identified two separate phenotypes of POI: 1) people exhibiting small ovaries devoid of follicles, and 2) those with ovaries of typical dimensions but exhibiting inadequate follicular development. In the context of the follicular type, it is noteworthy that the ovaries retain a stroma and corpora albicantia, which are characterised by a collagen-rich connective tissue capsule encompassing an eosinophilic mass. It is important to highlight that despite the absence of atretic follicles and active primordial follicles, these structural elements persist. On the other hand, the follicular variant exhibits a substantial number of primordial follicles that are actively engaged in their developmental stage while lacking any follicles that have progressed to the growth stage. Occasionally, the presence of lymphoplasmacytic infiltration can be detected in the vicinity of the primordial follicles. In a study, Zhang et al. (2019) utilised light and transmission electron microscopy methodologies to examine the existence of dense connective tissue and multiple corpora albicantia within the ovaries of women who have been diagnosed with POI. Upon examination under light microscopy, the medulla, which is the inner region of the ovary, and the surrounding cortical region exhibit a fused appearance lacking clear delineation. The geographical distribution of fibrillar components and cells demonstrates heterogeneity. The application of transmission electron microscopy (TEM) demonstrates a significant presence of fibroblasts and collagen fibers within the ovarian stroma. In addition, it should be noted that the distribution of cells inside this compartment is not homogenous. Certain places have a higher accumulation of collagen, whereas others include a greater abundance of cellular materials (Zhang et al., 2019). Fibroblasts in the vicinity of the corpora albicanti have a notable abundance of cytoplasmic myofilaments. Ultrasound scans reveal that women diagnosed with POI present ovaries characterised by a coexistence of blood vessels and collagen, a reduced quantity of primordial follicles, and an irregular distribution of active fibroblasts (Haidar et al., 1994; Maclaran & Panay, 2011; Cox & Liu, 2014).

2.4. Pathophysiology of POI

The initial number of primordial follicles present at the time of birth ranges from 700,000 to 1 million. Over the course of the reproductive lifespan, this pool steadily diminishes due to the processes of atresia and folliculogenesis. By the age of 40, only a few thousand oocytes are typically left (Maclaran & Panay, 2015; Panay et al., 2020). POI can manifest through many causes, such as diminished peak follicle count, accelerated follicle depletion by apoptosis, or impaired folliculogenesis (Maclaran & Panay, 2015). Multiple exogenous factors, encompassing chemicals, recreational drugs, surgical interventions, and environmental influences, alongside endogenous factors like chromosomal abnormalities, genetic predisposition, congenital enzyme shortages, autoimmune disorders, and stress, possess the capability to launch these physiological processes (Huang et al., 2019). There is a prevailing belief that certain women may experience an accelerated aging phenomenon in relation to the occurrence of spontaneous POI. The inflammatory aging process is explained in a study piece, which posits that it holds significant implications for the pathophysiology of POI (Huang et al., 2019). The illness known as POI is characterised by its intricate and multifaceted nature, with its underlying causes still not comprehensively elucidated. POI can be categorised into two main types: primary and secondary. While many underlying factors contributing to POI have been found, the exact cause of this condition remains unknown in most cases, despite intensive research efforts.

3. Causes of Premature Ovarian Insufficiency (POI)

POI is commonly denoted as spontaneous or idiopathic POI due to the frequently incomplete establishment of its aetiology (Rudnicka et al., 2018). Fraison et al. (2019) believe that POI can be triggered by multiple underlying processes. These mechanisms include premature exhaustion of follicles, inhibition of follicular maturation, depletion of the oocyte pool, and resistant ovarian syndrome. The causes of POI that have been discovered as potentially implicated in these pathways can be classified into two main categories: hereditary causes and non-genetic causes. The aetiology of the condition includes genetic variables, such as genetic anomalies, as well as non-genetic ones, including infections, environmental factors, iatrogenic operations, autoimmune, and metabolic illnesses (Woad et al., 2006; Jiao et al., 2017; Rudnicka et al., 2018).

3.1. Genetic Factors in POI

Van Kasteren et al. (1999) reported that a notable finding was the presence of a familial history of early menopause, or POI, in around 30% of women

diagnosed with idiopathic POI. This finding suggests a potential hereditary cause for the condition. According to Jiao et al. (2012), the occurrence of primary amenorrhoea is associated with a karyotypic abnormality in 21% of cases, whereas secondary amenorrhoea is associated with a karyotypic abnormality in 11% of cases. In recent times, an increasing number of genetic mutations have been identified through the utilisation of whole genome sequencing techniques (Heddar et al., 2019). The genes that have been identified as involved primarily impact the X chromosome, although there are also instances of autosomal genetic variants playing a role, albeit less frequently. Gonadal growth and function can be influenced by various factors, including DNA replication and repair, meiosis, hormone regulation, immunological responses, and metabolic pathways (Tucker et al., 2016).

Problems with the X chromosome

- Turner syndrome: Turner syndrome is a chromosomal condition that is characterised by the absence or partial deletion of one X chromosome. It has an incidence rate of approximately 1 in 2500 births (Schlessinger et al., 2002). This condition can result from many genetic abnormalities, such as translocations, deletions, inversions, isochromosomes, and occasionally mosaicism. The occurrence of X inactivation arises when there is a deficiency of X-linked genes, resulting in the suppression of vital gene products linked to the X chromosome. However, certain X-related gene products manage to evade this inactivation process by the second X chromosome (Rossetti et al., 2017). In general, females are born with a standard number of primordial follicles, which undergo an accelerated phase of atresia (Singh & Carr, 1966). Certain individuals who identify as women and experience primary amenorrhoea, particularly those who possess Y material in their karyotype, may exhibit streak gonads. According to Castronovo et al. (2014), individuals who possess a mosaic X pattern in their genetic makeup have a higher probability of exhibiting diverse manifestations at different intervals following the onset of menarche. Individuals with this condition may exhibit various phenotypic characteristics, including but not limited to reduced height, lymphedema, a neck with excess skin folds, impaired vision, misalignment of the eyes, recurring middle ear infections, a palate with a high arch, nipples that are spaced farther apart than usual, a chest that appears shield-shaped, multiple pigmented skin lesions, an abnormal angle of the elbow joint, a shorter fourth metacarpal bone, and anomalies affecting the heart (such as coarctation) and the renal tract. The optimal approach for the management of women diagnosed with Turner syndrome is through the utilisation of multidisciplinary clinics. This is primarily due to the various pregnancy risks that these individuals may encounter, as well as the potential

for hearing and learning difficulties. Additionally, there is a likelihood of long-term health complications, including but not limited to diabetes, dyslipidemia, coronary artery disease, cerebrovascular disease, celiac disease, hypothyroidism, and hepatic dysfunction (Gravholt et al., 2017). According to Liu et al. (2014), gonadectomy is advised in cases where certain cells exhibit Y chromosomal material.

- Fragile X syndrome: The Fragile X mental retardation 1 gene (FMR1) harbours a mutation that is observed in around 1 in 250 women. This mutation results in modifications to the CGG trinucleotide repeat sequences situated in the 50 region of the X chromosome (Rousseau et al., 1955). The typical observation indicates a range of 5 to 45 repetitions. Males with a repetition rate of 200 experience the co-occurrence of intellectual impairment and autism. According to Sherman (2000), the presence of 55-200 repetitions, also known as permutations, is associated with a 20% likelihood of having POI. Additionally, the risk of ataxia seems to grow with age and affects 8-16% of individuals who carry these repeats. According to the American College of Obstetricians and Gynaecologists Committee on Genetics (2006), it is advisable to engage in genetic screening, which encompasses the evaluation of family members, as a means of averting intellectual disability in males. Additionally, this practice is particularly relevant for female family members who are contemplating oocyte preservation or engaging in pregnancy planning.

- Other X-linked and autosomal mutations: Less common aetiologies of POI encompass genetic aberrations on the X chromosome, specifically DIAPH2 and BMP-15, in addition to autosomal deficiencies in genes such as NOBOX, FSHR, LHR, GDF9, ESR1, POLG, CYP19A1, FOXL2, FSH, GALT, AIRE, NOGGIN, inhibin A, FOXO3, and steroidogenic factor 1. Certain uncommon mutations have been found to have a potential correlation with neurological, syndromic, and heightened cancer susceptibility, hence potentially contributing to the development of POI. Several syndromes, such as ataxia telangiectasia, Bloom, and Perrault, have been identified. Ataxia telangiectasia is characterised by telangiectasias, cerebellar degeneration, immunodeficiency, and oculomotor dysfunction. Bloom syndrome is characterised by individuals exhibiting reduced stature, prominent skin rashes, and accelerated ageing. Perrault syndrome is distinguished by the presence of sensorineural hearing impairment and ovarian dysgenesis (Rossetti et al., 2017). According to Rossetti et al. (2017), it is advisable to refer individuals with POI to a genetic counsellor for further evaluation of additional genetic tests when other phenotypic anomalies are present.

In certain instances, primary hypergonadotropic hypogonadism may arise due to genetic factors involving mutations in gonadotropin receptors. The existence of a non-functional variant of the LH gene and deficiencies in steroidogenic enzymes, specifically StAR mutation, CYP17, and aromatase, impede the production of estradiol, resulting in reduced oestrogen levels and increased FSH levels. This occurs despite the occurrence of some follicular expansion.

3.2. Non-Genetic Factors of POI

3.2.1. Autoimmune causes

The occurrence of spontaneous POI has been observed in individuals with autoimmune diseases, including, Type I diabetes mellitus, Hashimoto's thyroiditis, Sjo€gren's syndrome, adrenal insufficiency, multiple sclerosis, inflammatory bowel disease, myasthenia gravis, celiac disease, alopecia, and rheumatoid arthritis. This association has been reported in approximately 4-30% of cases, according to a study conducted by La Marca et al. in 2010. Nevertheless, the available data does not provide evidence to support the hypothesis that inflammatory oocyte destruction is responsible for the observed clustering of autoimmune disorders with POI.

The presence of POI can be observed in individuals who have hereditary autoimmune illnesses, such as those linked to type I (AIRE mutation) and type II polyglandular autoimmune syndromes. Autoimmune polyendocrinopathy syndrome type I (APS-I) commonly presents in children and is distinguished by the occurrence of adrenal insufficiency, Addison's disease, hypoparathyroidism, and chronic mucocutaneous candidiasis. Furthermore, it is important to highlight that approximately 15% of people afflicted by this disease also encounter premature ovarian insufficiency. The aetiology of this disorder can be attributed to genetic mutations that arise in the autoimmune regulatory gene AIRE, which is situated on chromosome 21. The occurrence of steroidogenic cell autoantibodies, which specifically target various endocrine and non-endocrine organs, has been observed to have a significant association with the onset of ovarian lymphocytic oophoritis in around 60% of individuals affected by this condition. Type II is commonly linked to autoimmune thyroid disease, adrenal insufficiency, type 1 diabetes mellitus, hypothyroidism/Graves' disease, and POI, with an incidence ranging from 3.6% to 10% (Schlessinger et al., 2002; Dittmar & Kahaly, 2003; La Marca et al., 2010).

A subset of women diagnosed with autoimmune POI exhibit the presence of adrenal or 21-hydroxylase autoantibodies, accounting for

roughly 4% of the total population of women affected by POI. The presence of these autoantibodies triggers an immunological response targeting ovarian tissue, which involves the activation of cytokines, B cells, and T cells. The immunological response under consideration is associated with the infiltration of lymphocytes and subsequent destruction of follicles, resulting in oophoritis (Hoek et al., 1997) and the early development of larger cystic ovaries. The occurrence of POI may precede the onset of adrenal insufficiency, making it advisable to refer individuals with adrenal antibodies to an endocrinologist (Bakalov et al., 2005; Silva et al., 2014).

3.2.2. Infectious causes

There exist two primary viruses that are under suspicion for their potential role in causing POI. One of the viruses associated with the condition known as mumps oophoritis is the epidemic parotitis virus. This viral infection has the potential to lead to complications such as ovarian failure, as documented by Morrison et al. in 1975. Nevertheless, the majority of women experience a restoration of normal gonadal function following their recovery. One such virus that has been identified is the human immunodeficiency virus (Tariq et al., 2016). This particular virus has been found to have detrimental effects on ovarian function, in addition to its impact on antiretroviral therapy. Previous studies have identified links between POI and many microbial or viral diseases, including varicella, tuberculosis, CMV, and malaria. However, the exact role of these infections in the development of POI is still not fully understood (Goswami et al., 2005; Kokcu, 2010).

3.2.3. Environmental factors

There is a wide array of toxic and environmental elements that have been empirically demonstrated to have an impact on fertility. These factors are commonly associated with systemic consequences that cannot be simply attributed to the depletion of the ovarian reserve. However, there are several factors that demonstrate a clear association with the reduction of the initial follicle reserve or the increase in the pace of follicle recruitment, both of which have substantial implications for the onset of POI. According to the findings of a meta-analysis conducted by Zhu et al. (2023), it is indicated that environmental contaminants and toxins could potentially contribute to the development of POI. The potential consequences for the ovaries might be profound, as they can manifest through various interconnected mechanisms. Several substances have been identified as potentially significant in various contexts. For instance, bisphenol A is commonly utilised in food packaging as a constituent of plastic. Additionally, polycyclic aromatic hydrocarbons,

polychlorinated biphenyls, pesticides, dioxins, genistein, and cigarette smoke have all been recognised as substances of potential importance (Vabre et al., 2017). Nevertheless, the available literature does not provide conclusive data regarding the impact of the environment on POI, with the exception of research specifically examining the effects of cigarette smoking (Willett et al., 1983; Ebrahimi et al., 2011; Vabre et al., 2017).

Animal studies have yielded empirical data regarding the impact of cigarette smoking on the reservoir of mammalian follicles (Jurisicova et al., 2007; Gannon et al., 2012). However, the results of human studies investigating the effect of smoking on primordial follicle populations have yielded inconsistent findings (Caserta et al., 2013; Peck et al., 2016). Nevertheless, a study conducted in Korea on a group of individuals with POI revealed a significant correlation between smoking and a heightened susceptibility to developing POI (Chang et al., 2007). Maternal smoking exposure has been linked to the activation of the aryl hydrocarbon receptor and consequent decrease in germ cell proliferation, as evidenced in the human foetal ovary. This phenomenon has significant consequences for germ cell loss, as it promotes apoptosis through downstream mechanisms (Mamsen et al., 2010; Anderson et al., 2014). However, further investigation including human participants is important to determine if the decline in the initial pool of primordial follicles, which is influenced by the activation of the aryl hydrocarbon receptor, is a direct consequence of exposure to constituents present in cigarette smoke.

Phthalates, which are frequently employed as plasticizers, possess hazardous properties and exhibit a tendency to leach into the surrounding environment (Hannon & Flaws, 2015). The study conducted by Muczynski et al. (2012) demonstrated the presence of modified lipid production in human foetal ovaries that were subjected to in vitro exposure to mono-(2-ethylhexyl) phthalate. Chen et al. (2012) demonstrated that the activation of the aryl hydrocarbon receptor by butyl benzyl phthalate, an additional phthalate compound, leads to a decrease in the vitality of granulosa cells. This adverse effect on granulosa cells has implications for the survival rates of follicles. The results of this study indicate that there is a correlation between exposure to phthalates and ovarian dysfunction, which in turn may lead to a decrease in fertility. Bisphenol A (BPA) is a prevalent hazardous substance that is readily accessible as a result of its utilisation in packaging materials and resin-based plastics. The impact of BPA on the ovaries is attributed to its structural resemblance to oestrogens, enabling it to interact with the oestrogen receptor alpha (Craig et al., 2011). BPA exposure has been extensively investigated in many animal studies, revealing a robust

association with follicle depletion. Notably, this impact has been consistently found irrespective of the timing of exposure, whether it occurred during the prenatal period, postnatal period, or in adulthood (Richardson et al., 2014). As a result, numerous countries have enacted restrictions on the usage of BPA based on evidence derived from animal studies, given the inconclusive nature of available human data about the reproductive impacts of BPA (Richardson et al., 2014; Mathew & Mahalingaiah, 2019). A study conducted on women experiencing infertility revealed that individuals with urinary BPA levels exceeding the average demonstrated a diminished ovarian reserve. Furthermore, a separate investigation conducted an analysis of the effects of in vitro fertilisation on women exhibiting excessive levels of BPA in their serum. The findings of this study revealed decreased pregnancy rates and increased susceptibility to miscarriage (Sugiura-Ogasawara et al., 2005; Kim et al., 2021).

3.2.4. Metabolic disorders

Metabolic diseases that might result in POI encompass 17-hydroxylase deficiency and galactosemia, as identified by Vabre et al. in 2017. The medical illness referred to as galactosemia is associated with a genetic mutation that takes place in the GALT gene, leading to reduced functionality of the galactose-1-phosphate uridylotransferase enzyme. This enzyme plays a crucial role in the metabolism of galactose. POI is observed as a chronic consequence that manifests in over 90% of individuals diagnosed with galactosemia. Potential mechanisms that could contribute to the observed effects include the potential toxicity of metabolites derived from galactose as well as impaired glycosylation processes involving proteins and lipids within ovarian tissue over the course of an individual's lifespan. The emergence of POI, even in individuals who have adhered to dietary restrictions throughout their lives and were diagnosed with the condition shortly after birth, implies that the onset of toxicity may originate during the perinatal period (Fridovich-Keil et al., 2011). The condition known as 17-OH deficiency is classified within the category of abnormalities of sexual differentiation, which are typically observed in individuals with a 46 XY or 46 XX karyotype. The enzymatic deficit being discussed is linked to CYP17A1, an enzyme that exhibits both steroid 17α-hydroxylase and 17-20-lyase functions. CYP17A1 has biological activity throughout the adrenal glands and gonads. The blockage of the synthesis of 19-carbon steroids, such as oestrogens, by the block, leads to the clinical manifestation of POI (Auchus, 2017).

3.2.5. Iatrogenic causes

Chemotherapeutics have been identified as a specific iatrogenic factor that is notably associated with alterations in the activation of primordial follicles and/or depletion of ovarian reserve. In conjunction with other variables such as surgical interventions, radiation therapy, and physical trauma to the ovary, these elements can also contribute to the onset and progression of POI. The iatrogenic disruption of gonadal tissue primarily occurs in individuals with cancer who have been subjected to radiation therapy or chemotherapeutic interventions. According to Larsen et al. (2003), the likelihood of experiencing POI as a result of oncologic treatment rises with age following puberty, as well as with the administration of high-dose chemotherapy regimens and the utilization of combined chemotherapy and radiation therapy. The impact of chemotherapy is contingent upon various factors, including the specific form of chemotherapy employed, the individual's prior ovarian reserve, the amount administered, and the age at which the treatment is received (Oktem & Oktay, 2007; Spears et al., 2019). According to Nguyen et al. (2019), cyclophosphamide, cisplatinum, and doxorubicin are among the chemotherapeutic agents that are frequently implicated in cancer treatment. According to Chen et al. (2019), there is evidence suggesting that gonadotropin-releasing hormone analogues could potentially offer a degree of ovarian protection when administered alongside chemotherapy. However, it is important to note that the findings in this area are frequently inconclusive and contradictory. The administration of combination chemotherapy and the utilisation of alkylating drugs have demonstrated the highest degree of gonadotoxicity in both the paediatric and adult populations. Following administration of the alkylating drug cyclophosphamide, there is a 40% probability that women will experience POI. However, the precise cellular mechanisms responsible for the onset of early menopause in this context have yet to be fully elucidated (Cox & Liu, 2014). Lande et al. (2017) reported that the use of active metabolites of cyclophosphamide for the cultivation of human ovarian tissue sections leads to a decrease in the number of primordial follicles while concurrently promoting the development of follicles. Nevertheless, the concomitant in vitro administration of chemotherapeutic agents, namely bleomycin, vinblastine, adriamycin, and dacarbazine, resulted in a notable augmentation in the abundance of quiescent follicles within human ovarian tissue specimens (Mclaughlin et al., 2017).

Lakhal et al. (2010) found a negative correlation between the use of antimetabolites, anthracyclic antibiotics, and vinca alkaloids and the risk of a certain outcome. Guida et al. (2016) have shown a noteworthy

propensity for POI among women who receive anthracyclines and alkylating medications as part of their treatment regimen. Additionally, individuals who have received allogeneic stem cell transplants face an even higher risk, exceeding 90%. Based on the findings of Sklar et al. (2006), it has been observed that exposure to radiation doses as low as 1 Gy, which are frequently employed in the treatment of some pediatric malignancies, has the potential to induce the occurrence of POI. This can manifest either in the immediate proximity of the radiation source or as a result of external beam radiation. Larsen et al. (2003) reported that the occurrence of ovarian failure is significantly elevated when radiation doses exceed 9 Gy. Surgical procedures have the potential to contribute to the occurrence of POI, either through direct removal of the ovaries or as a consequence of pelvic surgeries that may lead to diminished blood supply to the gonads. In a study conducted by Somigliana et al. (2012), it was observed that the laparoscopic excision of bilateral endometriomas is associated with a 2.4% incidence of premature ovarian failure. Additionally, surgical intervention for ovarian endometriomas has been linked to a reduction in serum AMH levels and a decline in ovarian reserve. Uterine artery embolisation and torsions might potentially contribute to the need for pelvic surgery, which encompasses various procedures such as the treatment of ovarian cysts, endometriomas, and pelvic malignancies. Additionally, elective surgeries may be performed for those who are carriers of the genetic BRCA mutation.

Ben-Aharon and Shalgi (2012) have similarly ascribed damage to the vasculature of the ovarian cortex to the loss of primordial follicles. In each of the aforementioned situations, patients face a substantial likelihood of developing POI. However, the precise mechanism by which gonadotoxic treatment leads to this condition, whether it is through rapid activation or an elevation in follicular atresia, is to be definitively established (Nguyen et al., 2019). Typically, chemotherapeutic agents are designed to selectively affect cells that are actively dividing. The impact of these therapies on granulosa cells might vary depending on factors such as dosage, duration, and a specific treatment regimen. It has been seen that these treatments can lead to a substantial reduction in primordial follicles, as documented by Abir et al. in 2008.

Fertility preservation methods, such as the cryopreservation of ovarian tissue followed by transplantation or the use of assisted reproductive technology, have been employed for women who are undergoing chemotherapy. However, ongoing advancements are necessary to ensure the widespread efficacy of this procedure (Fisch & Abir, 2018; Donnez & Dolmans, 2021). A study conducted by Winship et al. (2018) has revealed

that dacarbazine, a chemotherapeutic agent, has been found to contribute to the depletion of primordial follicles in mice. This finding highlights the need for additional research to explore the potential effects of dacarbazine on ovarian reserve in human subjects.

4. Symptoms and Complications of Premature Ovarian Insufficiency (POI)

Females diagnosed with POI may exhibit characteristic menopausal symptoms, occasionally preceding the occurrence of anomalies in their menstrual cycles. Menstrual problems or infertility often manifest for an extended period of time prior to achieving the established diagnostic criteria. According to the ESHRE POI Guideline Development Group (2015), individuals with secondary amenorrhoea may encounter an abrupt start of amenorrhoea; however, alterations in the menstrual cycle such as oligomenorrhea or polymenorrhea may occur prior to the onset of amenorrhoea. While the shift is fundamentally irreversible, it is worth noting that transient remission is observed in numerous instances. According to Bidet et al. (2011), a study involving 358 patients diagnosed with idiopathic POI revealed that spontaneous remission of ovarian function was observed in 24% of all instances. Furthermore, it was shown that 88% of these cases experienced remission within one year following their initial diagnosis. In a separate investigation with a cohort of 507 individuals diagnosed with idiopathic POI, it was shown that 117 patients, constituting approximately 23% of the sample, exhibited indications of the restoration of ovarian functionality (Bachelot et al., 2017). The decrease in ovarian reserve has a continuous pattern rather than a progressive one. However, there is a lack of key biochemical indicators to evaluate the reservoir of surviving follicles in patients with POI.

The prevalence of maternal gestational age and age-related infertility is progressively rising, leading to a corresponding surge in the need for assisted reproductive technology. The phenomenon of postponing childbearing is prevalent in industrialised nations, leading to a significant number of women seeking infertility treatment after surpassing the ideal age for conception. As a result, a significant number of individuals exhibit a reduced ovarian response when subjected to conventional protocols for inducing ovulation. The Bologna criteria for poor ovarian response were published by ESHRE in 2011. These criteria consist of an antral follicle count of less than 5-7 follicles and AMH levels below 0.5-1.0 ng/mL. Furthermore, the presence of a track record of inadequate response ($\leq$3 instances using standard stimulation protocols) and the advancement in age (over 40 years) are also regarded as

contributing variables in the identification of suboptimal ovarian response. Polycystic ovary syndrome (PCOS) may encompass diverse subpopulations and may serve as an initial manifestation of POI. Hence, in the event that a patient experiencing infertility falls within the aforementioned classification, it is advisable to consider the possibility of POI, particularly if the patient's age is below 40 years.

Gonadotropin-resistant ovary syndrome (ROS) is characterized by the occurrence of primary or secondary amenorrhoea, accompanied by the appropriate development of secondary sexual characteristics. This condition is associated with hypergonadotropinization and is commonly observed in patients with POI who possess FOXL2 mutations (Koninckx & Brosens, 1977; Meduri et al., 2010; Woo et al., 2019). The findings of Tang et al. (2021) indicate that histologic examination and ultrasound scanning reveal the presence of primary, secondary, preantral, and antral follicles. This phenomenon is also considered a potential progression towards the development of POI. Nevertheless, it is important to acknowledge that there exist well-documented occurrences of FSH receptor mutations that consistently demonstrate the distinctive pattern of ROS (Woo et al., 2019). Research findings indicate that individuals with POI experience a reduced life expectancy of around two years compared to individuals who undergo menopause after the age of 55. The elevated death rates are believed to be attributed to chronic health issues associated with cardiometabolic, skeletal, and cognitive well-being (Maclaran & Panay, 2015).

4.1. Vasomotor Symptoms and Psychological Impact of POI

According to a study conducted by Ishizuka et al. (2019), it was found that a significant proportion of patients with POI experienced hot flashes. Specifically, almost 66% of the POI patients included in the study reported experiencing hot flashes. It is worth noting that the majority of these hot flashes were seen to occur within a specific timeframe, namely between two years prior to the commencement of amenorrhoea and the year in which amenorrhoea commenced. While the age of 25 and above does not appear to be a significant determinant of the prevalence of hot flashes in women, individuals below the age of 25 tend to have these episodes with a lower frequency. Women who undergo surgical menopause commonly face a range of severe symptoms. These observations indicate that the symptoms in question are associated with the ageing process and are a result of a lack of oestrogen rather than a complete absence of oestrogen.

Sleep disturbances are commonly linked to vasomotor symptoms, which can have negative effects on mood, social engagement, occupational productivity, and overall health-related quality of life (Utian, 2005). The findings of a cross-sectional study conducted on a sample of perimenopausal women revealed that 49% of participants reported experiencing hot flashes, while 45% reported experiencing sleeplessness. According to Ishizuka et al. (2008), a significant proportion of individuals exhibited symptoms of depression, headache, and weariness, with prevalence rates of 50%, 38%, and 63%, respectively. The diagnosis of POI has notable implications for the patient. Numerous females encounter depression and/or diminished sexual desire as a result of physiological alterations, including a perceived decline in reproductive capacity and vaginal dryness (Graziottin & Basson, 2004; de Almeida et al., 2011).

4.2. Impact on Neuro-Psychology of POI

The existing body of data suggests a positive association between exposure to persistent organic pollutants and an increased susceptibility to developing dementia, Alzheimer's disease, Parkinson's disease, neurological dysfunction, and impaired cognitive performance (Webber et al., 2016; Machura et al., 2018; Sochocka et al., 2023). The study conducted by Ryan et al. (2014) demonstrated a correlation between both iatrogenic and spontaneous POI and a heightened likelihood of cognitive impairment. The study findings indicate a notable increase of 30% in the likelihood of experiencing deterioration in psychomotor speed and overall cognitive function during a duration of seven years. The present study was conducted as a community-based cohort inquiry, encompassing a total of 4868 participants. In addition to its pivotal role in women's reproductive potential, oestrogen has numerous other significant effects on the human body. These effects encompass the elevation of HDL cholesterol, the reduction of LDL cholesterol, the induction of vasodilation, and the provision of protection against osteoporosis. The diminished levels of oestrogen in the early stages contribute to an increased susceptibility among women to several health conditions, including parkinsonism, depression, osteoporosis, cardiovascular disease, and cognitive impairment or dementia (Gilsanz et al., 2019; Yoo et al., 2020). Moreover, there is a correlation between premature menopause and several health conditions, such as hypertension, weight gain, and diabetes in middle age. These vascular risk factors have also been linked to cognitive decline and the development of dementia.

The oestrogen receptor network, which is a fundamental regulatory mechanism of the brain, plays a critical role in cognitive impairments. The

hippocampus, prefrontal cortex, amygdala, and posterior cingulate cortex are crucial regions involved in the processes of learning and memory. These regions have been found to possess significant oestrogen receptors, as highlighted in the study conducted by McEwen et al. in 2012. Oestrogen has a crucial role in facilitating the brain's ability to regulate brain energy metabolism within optimal temporal parameters, as observed in the ovarian-neural estrogen axis. Brinton et al. (2015) suggest that modifications in the presence of oestrogen or its receptor network, including β-receptors, possess the capacity to influence intracellular signalling, neuronal circuitry function, and energy availability inside brain neurons. Webber et al. (2016) state that the European Society for Human Reproduction and Embryology (ESHRE) proposes the consideration of hormone replacement treatment, specifically the incorporation of oestrogen, as a strategy to alleviate the potential decline in cognitive function. Research has indicated that oestrogen replacement therapy can effectively alleviate depressive symptoms and various mood disorders. The present body of research pertaining to the beneficial effects of testosterone supplementation on quality of life, self-esteem, and mood in patients with POI remains inconclusive, as suggested by Machura et al. (2018).

The incidence of cognitive impairment or dementia is significantly increased when oophorectomy is conducted prior to the onset of menopause (Vearncombe & Pachana, 2009; Rocca et al., 2011; Rocca et al., 2012; Bove et al., 2014; Rocca & Henderson, 2014). The data presented in this study indicate that an early shortage of oestrogen has a significant effect on cognitive performance. Nevertheless, the primary source of data was derived from patients who had undergone oophorectomy. In addition, the levels of cortisol and its effectiveness in performing its functions significantly influence several components of the hypothalamic-pituitary-adrenal (HPA) axis, as well as neurotransmitters such as serotonin and acetylcholine, neurotrophic factors, neuronal plasticity, and synaptic function. The aforementioned outcomes include stress-related problems, depressive symptoms, a sensation of burning and flushing, and cognitive deficits such as impairments in verbal memory and difficulties in presenting mnemonic goals (Lund et al., 2005; Weiser et al., 2008; Donner et al., 2009; Greendale et al., 2010). Hence, a significant association can be observed between cortisol levels, stress levels, and cognitive functioning, as evidenced by the research conducted by Karlamangla et al. (2005). According to the findings of a study conducted by Otte et al. (2005), there is a notable disparity in the impact of age on cortisol activity between women and men, with women exhibiting a much higher effect that is approximately three times stronger. Premature menopause

exerts direct and indirect effects on the central nervous system, manifesting in both transient and enduring manners. These effects have been elucidated to varying extents, with some aspects remaining to be fully explored.

4.3. Effects on Urogenital Symptoms of POI

A lack of oestrogen results in urogenital atrophy, which manifests in prevalent urogenital symptoms such as irritation, vaginal dryness, and itching (Portman & Gass, 2014). Extensive research has been conducted on the symptoms experienced by women throughout the menopausal transition, specifically focusing on individuals within the acceptable age range. However, there is a scarcity of studies examining the frequency and management of urogenital symptoms in patients with POI.

4.4. Effects on Cardiovascular Diseases of POI

Previous studies have indicated that individuals diagnosed with POI have a reduced lifespan, with cardiovascular disease being proposed as the primary contributing factor (Rocca et al., 2006; Shuster et al., 2010). Podfigurna-Stopa et al. (2016) have reported that there is evidence suggesting a correlation between the diagnosis of POI in women and the presence of certain risk factors related to the development of cardiovascular disease. These risk factors include an aberrant lipid profile, problems in insulin action, endothelial dysfunction, autonomic dysfunction, and metabolic syndrome. Individuals diagnosed with POI have been observed to exhibit a notable reduction in flow-mediated dilatation of the brachial artery, which is widely acknowledged as an indicator of endothelial function. Furthermore, research has demonstrated a reduction in the number of circulating endothelial progenitor cells, which is associated with a fall in blood oestrogen levels (Kalantaridou et al., 2004; Yorgun et al., 2013). According to a study conducted by Knauff et al. in 2008, individuals with POI exhibit elevated levels of carotid intima-media thickness and impaired left ventricular diastolic performance. Furthermore, Gulhan et al. (2012) conducted a study that showed that people diagnosed with POI exhibited a decrease in heart rate variability and a deterioration in baroreflex sensitivity in comparison to those without the aforementioned ailment.

Patients with POI have deviations in lipid profiles; nevertheless, the findings regarding individual lipoproteins present conflicting outcomes. According to Knauff et al. (2008), individuals diagnosed with POI exhibit elevated triglyceride levels and reduced levels of high-density lipoprotein cholesterol (HDL-C) in comparison to control subjects. Similarly, Ates et al. (2014) found that women with POI display heightened HDL cholesterol

and total cholesterol levels when compared to healthy control groups. The population under investigation had comparable levels of glucose, insulin, homeostasis assessment model-insulin resistance (HOMA-IR), low-density lipoprotein cholesterol (LDL-C), and triglycerides in comparison to the control group. However, there was a notable increase in the occurrence of metabolic syndrome within this population (Ates et al., 2014; Podfigurna-Stopa et al., 2016). On the contrary, previous studies have reported elevated levels of blood glucose, insulin, and HOMA-IR values in women with POI as compared to a control group (Kulaksizoglu et al., 2013; Podfigurna-Stopa et al., 2016).

While there is varying data about the lipid profile and insulin resistance indices in women with POI, it is apparent that there is a significant elevation in cardiovascular risk among this population (Podfigurna-Stopa et al., 2016). Specifically, the incidence of mortality due to ischemic heart disease exhibited an approximate 80% elevation in women experiencing POI in comparison to women who underwent menopause between the ages of 49 and 55 (Jacobsen et al., 1999; Podfigurna-Stopa et al., 2016).

4.5. Effect on Bone Mineral Density of POI

Numerous studies have provided compelling evidence to support the association between oestrogen insufficiency and osteoporosis in postmenopausal women (Schnatz, 2011). The initial discovery of a correlation between higher rates of fractures and a lack of estrogen in postmenopausal women was documented by Albright et al. in 1941 and later supported by Lana et al. in 2010. The presence of hypoestrogenism and hypoandrogenemia significantly influences the attainment of peak bone mass and bone mineral density status in young females (Meczekalski et al., 2010). Lana et al. (2010) conducted a study whereby they observed a positive link between serum FSH levels and the loss of bone mass in the spinal column and femoral neck among people diagnosed with spontaneous POI. Conversely, estradiol concentrations did not show a significant association with bone mass loss (Lana et al., 2010; Podfigurna-Stopa et al., 2016). Several investigations have documented a notable decline in bone mineral density among individuals with POI (Ratcliffe et al., 1992; Conway et al., 1996; Park et al., 1999; Popat et al., 2009; Bachelot et al., 2009). In their study, Uygur et al. (2005) observed a substantial decrease in both spinal bone and femoral neck bone mineral density among individuals with POI as compared to a control group. According to a study conducted by Popat et al. (2009), it was shown that individuals diagnosed with POI had a decreased level of bone mineral density in comparison to women who experience regular menstruation. This

study involved a total of 442 participants. According to a study conducted by Nelson et al. (2005), it was shown that 67% of individuals diagnosed with POI exhibited osteopenia. The study conducted by Leite-Silva et al. (2009) examined a cohort of 50 women diagnosed with POI. The results of their investigation revealed a significant reduction in bone mineral density in both the lumbar spine and femoral regions. The lumbar region of the spinal column had the greatest susceptibility to reduced bone mineral density. In general, the investigators noted that characteristics such as age, age at the onset of POI, and reproductive age demonstrated relationships with lumbar spine bone mineral density. The length of ovarian function in individuals with POI has been found to have a substantial association with whole-body bone mineral density (Podfigurna-Stopa et al., 2016; Bakhsh et al., 2015). The available data on fracture risk in patients with POI is minimal. Previous studies have conducted clinical trials to compare women in the normal-age menopausal group with those in the early menopausal group. These trials have revealed a relative risk of roughly 1.5 for fracture occurrence among women in the early menopause group (van Der Voort et al., 2003; Podfigurna-Stopa et al., 2016).

4.6. Association of POI with Type 2 Diabetes

The available data on alterations in insulin resistance indices among individuals diagnosed with POI present discrepancies, and the association between the age of menopause and the susceptibility to developing type 2 diabetes mellitus lacks a strong foundation in current academic research (Kulaksizoglu et al., 2013; Podfigurna-Stopa et al., 2016). According to a study conducted by Anagnostis et al. (2019), meta-analysis and a systematic review revealed that individuals with POI had a greater susceptibility to the development of type 2 diabetes mellitus in comparison to women experiencing menopause within the expected age range. The specific mechanisms underlying the association between POI and type 2 diabetes mellitus are incompletely comprehended at present. However, it is plausible that a reduced duration of exposure to naturally occurring oestrogens may contribute to the development of this condition. This is because endogenous oestrogens have a protective effect on the function of pancreatic beta cells and insulin resistance (Anagnostis et al., 2019). Estradiol is involved in the regulation of insulin synthesis and secretion, as well as the modification of beta-cell survival. This is achieved through its binding to the alpha receptor (ERa) on beta cells, which leads to the activation of extracellular signal-regulated kinases (ERK1/2). Hence, individuals diagnosed with POI face an elevated susceptibility to the onset of type 2 diabetes mellitus, particularly

when accompanied by additional risk factors such as a positive familial background of type 2 diabetes mellitus or obesity. According to Anagnostis et al. (2019), it is advisable to prescribe a lifestyle intervention at an earlier stage for these women in comparison to the general population.

4.8. Effect on Reproductive Health of POI

Infertility is a significant and profound consequence frequently associated with POI, which can have a transformative impact on individuals' lives. In the majority of cases, a complete "failure" of the ovaries is not commonly observed. Instead, there is intermittent and unpredictable ovarian functioning that contributes to the loss of reproductive well-being. Around a quarter of women who are diagnosed with POI experience spontaneous ovulation, presenting a potential opportunity for natural conception in approximately 5% to 10% of affected individuals. According to Lambrinoudaki et al. (2021), the probability of conception is greatest within the initial year following diagnosis. Nevertheless, it is important to note that the occurrence of spontaneous pregnancies in women with POI remains improbable and infrequent, as indicated by studies conducted by Ben-Nagi and Panay (2014) and Panay and Anderson (2020). Despite extensive research on enhancing pregnancy rates among women attempting to conceive with their own eggs, whether through natural means or assisted reproductive technologies, there is still insufficient information to determine the most optimal treatment approach. This assertion is substantiated by a recent comprehensive analysis that investigates the incidence of pregnancy in women with POI, both under natural circumstances and with various therapeutic interventions. Fraison et al. (2019) conducted an evaluation that revealed a range of pregnancy rates reported in different research, spanning from 2.2% to 14.2%. Additionally, the average age of patients who successfully achieved pregnancy was determined to be 30 years. These findings show that young individuals with POI may retain good oocyte quality. Currently, there is ongoing research on several innovative therapeutic approaches, such as stem cell therapy, platelet-rich plasma, and primordial follicle stimulation. However, more study is needed to substantiate their effectiveness and ensure their safety (Panay & Anderson, 2020). At present, oocyte donation stands as the most effective therapeutic strategy for addressing infertility linked to POI, demonstrating success rates that range between 40% and 50% every menstrual cycle (Maclaran & Panay, 2015). Additional alternatives encompass embryo donation, the utilisation of a surrogate, and the process of adoption. It is crucial to offer comprehensive counseling to women who have been diagnosed with POI, which should include a complete discussion

of the available treatment options, success rates associated with each option, and the effectiveness of alternative approaches. This approach ensures that patients are equipped with the necessary knowledge to make well-informed decisions regarding their healthcare. In certain instances, individuals may opt to make a proactive life choice, such as abstaining from parenthood altogether (Maclaran & Panay, 2015).

5. Treatment of Premature Ovarian Insufficiency (POI)

In the aforementioned physical and psychological illnesses, it is imperative that treatment strategies prioritise the preservation of the patient's overall well-being. In the past, infertility therapy was commonly seen as having limited or negligible efficacy. In recent times, there have been reported endeavours to enhance reproductive outcomes in women diagnosed with POI. This section aims to provide a concise overview of current advancements in enhancing the welfare of patients with POI, as well as research conducted on fertility-related aspects in POI patients.

5.1. Hormone Replacement Therapy

The occurrence of vasomotor symptoms serves as a notable incentive for individuals diagnosed with POI to commence hormone replacement therapy. The study conducted by Absolom et al. (2008) provides evidence regarding the impact of hormone replacement therapy (HRT) in mitigating vasomotor symptoms in women with iatrogenic POI. According to a study conducted by Piccioni et al. in 2004, it was found that 66% of patients with POI who had chemotherapy and received HRT experienced a notable decrease in symptoms such as hot flushes, sleeplessness, and psychological and emotional alterations. The utilisation of HRT by women with POI was found to be associated with a lower prevalence of urogenital symptoms, including urinary frequency, vaginal dryness, irritation, and incontinence. This conclusion was drawn from several studies conducted by Nachtigall (1994), Bygdeman and Swahn (1996), Piccioni et al. (2004), and Madalinska et al. (2006), which examined the occurrence of these symptoms between HRT users and nonusers among women with POI.

Multiple studies have provided data supporting the notion that HRT has a mitigating effect on the detrimental effects of POI on bone health. This assertion is supported by the findings of Prior et al. (1997), Crofton et al. (2010), Kodama et al. (2012), Popat et al. (2014), and Cartwright et al. (2016). Several extensive, randomized trials have provided evidence that HRT has a positive impact on bone mineral density and decreases the likelihood of hip and vertebral fractures in women who have undergone

menopause (The Writing Group for the PEPI, 1996; Wells et al., 2002; Cauley et al., 2003). Research studies have demonstrated that oestrogen replacement therapy yields favourable outcomes in terms of bone mineral density among premenopausal women who have had oophorectomy. The study conducted by Lindsay et al. (1980) examined the effects of mestranol on bone loss and vertebral body height in a group of 58 post-oophorectomized women. The results indicated that mestranol was effective in reducing bone loss and resulted in a lesser reduction in vertebral body height. According to Prior et al. (1997), the use of oestrogen therapy was found to decrease the increase in bone resorption indicators subsequent to oophorectomy. In the context of cardiovascular health, the administration of HRT for a duration of 6 months resulted in a significant enhancement of flow-mediated dilation in the brachial artery, exhibiting a 2.4-fold increase. This improvement was comparable to the levels observed in individuals without any cardiovascular abnormalities (Goldmeier et al., 2013). Goldemeier et al. (2013) also reported the observation of intact endothelium-dependent vasodilation in females diagnosed with early ovarian insufficiency and receiving hormone replacement therapy. Several studies have demonstrated that the administration of combined HRT, specifically oestrogen and progesterone, has been associated with improvements in endothelial dysfunction among women with POI. Moreover, research has demonstrated that this particular therapeutic approach has the potential to reduce the likelihood of developing ischemic heart disease and mitigate the increased mortality rates linked to cardiovascular illness subsequent to bilateral oophorectomy (Bain et al., 1981; Kalantaridou et al., 2004; Lokkegaard et al., 2006; Rivera et al., 2009; Faubion et al., 2015). Therefore, HRT is advised as a suitable approach for addressing vasomotor and urogenital symptoms in women who have been diagnosed with POI. Additionally, it is advised to prioritise the preservation of bone health in order to mitigate the risk of developing osteoporosis. HRT has been observed to potentially play a significant role in the primary prevention of cardiovascular disease.

There has been a suggestion that HRT might possess neuroprotective properties. When administered during the perimenopausal phase, HRT may exhibit adverse effects and might elevate the likelihood of cognitive impairment in elderly women. The potential negative consequences seen by older women could potentially be associated with preexisting vascular or neurologic conditions or an elevated susceptibility to venous thromboembolism. Oral contraceptives that contain a pharmacologic dose rather than a physiologic dose, have been found to have negative effects on hemostatic factors and lipid profiles. Additionally, their use is associated

with an elevated risk of venous thromboembolism (Shumaker et al., 2004; Mendelsohn & Karas, 2007; Rocca et al., 2011; Rocca et al., 2014; Faubion et al., 2015). The findings of this study indicate that the initiation of HRT should be undertaken promptly following diagnosis.

There is a scarcity of empirical evidence pertaining to the effects of various progestins in HRT on women who have been diagnosed with POI. The available evidence suggests that micronized natural progesterone is the preferred option for physiologically postmenopausal older women. This choice is supported by its association with improved cardiovascular health and a potentially reduced risk of breast cancer. Additionally, micronized natural progesterone has demonstrated comparable effectiveness in protecting the endometrium, as indicated by studies conducted by The Writing Group for the PEPI in 1996, Mueck in 2012, and Davey in 2013. The implementation of continuous oestrogen replacement is considered advantageous in order to mitigate the occurrence of symptoms associated with oestrogen insufficiency. According to O'Donnell et al. (2012), women who are pursuing conception through oocyte donation necessitate cyclical regimens instead of continuous combination regimens in order to boost the active functioning of the endometrium. There is a possibility that this could result in a slightly increased susceptibility to hyperplasia or carcinoma of the endometrium, as indicated by studies conducted by Furness et al. (2012) and Morch et al. (2012). The duration of the cycle can be customised to suit individual needs, but it is generally recommended to limit it to a maximum of 12 weeks in order to safeguard the integrity of the endometrium. According to Furness et al. (2012), the utilisation of continuous, combined HRT has been found to decrease the likelihood of developing endometrial cancer among postmenopausal women and perhaps in women with POI. Progestins have the potential to be delivered via oral or transdermal routes. No comparative studies examining the various routes of delivery of progesterone for patients with POI have been found. Nevertheless, a theoretical framework has been suggested that suggests the comparable effectiveness of endometrial protection in both younger and older menopausal women, mirroring the observations reported in postmenopausal women without any pathological problems. According to Ewies and Alfhaily (2012), when women choose a bleeding-free regimen, the use of a progestogen-secreting intrauterine device is an effective method for preventing endometrial hyperplasia. In summary, it is imperative to ensure that women diagnosed with POI are well educated about the necessity of HRT prior to reaching the typical age of menopause, unless there are specific contraindications. There is no evidence to suggest that it is associated with an elevated risk of developing breast

cancer. With the exception of women who have undergone a hysterectomy, it is recommended to provide progestogene in conjunction with oestrogen in order to save the endometrium. It is imperative to provide counselling to patients who exhibit lifestyle risk factors for venous thromboembolism, emphasising the significance of actively reducing these risks.

5.2. Infertility Treatment

The prevalence of POI among women who are actively wanting to conceive has witnessed a notable rise, primarily attributed to the growing prevalence of delayed marriage and/or childbearing in developed nations. POI is emerging as a significant clinical issue necessitating the implementation of infertility treatment. A cohort study comprising 358 individuals diagnosed with idiopathic POI revealed that a collective proportion of 24% of the cases exhibited spontaneous restoration of ovarian function. The remission status was ascertained based on the restoration of regular menstrual cycles and/or the normalisation of FSH levels. According to Bidet et al. (2011), the incidence of spontaneous pregnancy following diagnosis in these individuals was found to be 4.4%. In a cross-sectional study conducted by Bachelot et al. (2017), a total of 507 patients diagnosed with idiopathic POI were examined. The study findings revealed that within the cohort, 117 individuals (23%) experienced spontaneous resumption of ovarian function, while 18 individuals (3.6%) achieved spontaneous pregnancy. Moreover, according to Nelson et al. (1992), the pregnancy rate among patients with POI who underwent oestrogen replacement therapy was found to be 4.8% in observational studies. The overall pregnancy rate resulting from ovulation induction interventions in infertile patients with POI was found to be 6.3%. Several controlled studies have been conducted to compare the use of a gonadotropin-releasing hormone agonist (GnRH-a) with a placebo in suppressing gonadotropins, but no significant difference in pregnancy rates was observed (Nelson et al., 1992; van Kasteren et al., 1995; van Kasteren & Schoemaker, 1999). Hence, the utilisation of oocyte donation has been acknowledged as the most rational therapeutic approach for addressing infertility among patients with POI (van Kasteren & Schoemaker, 1999; ESHRE POI Guideline Development Group, 2015).

The inability to have biological children continues to be a significant issue for women diagnosed with POI. Furthermore, it is important to note that certain cultures have strict prohibitions on oocyte donation. These women actively pursue and earnestly request any medical interventions that can enhance their prospects of becoming pregnant. Tartagni et al. and Badawy et al. conducted randomised studies to investigate the effects of

ovulation induction in patients with POI (Badawy et al., 2007; Tartagni et al., 2007). In a study conducted by Tartagni et al. (2007), a randomised trial was carried out with a cohort of 50 women diagnosed with POI. The participants were administered either ethinylestradiol or a placebo for a duration of 2 weeks prior to and during gonadotropin treatment. The primary objective of the study was to evaluate the impact of both interventions on ovulation, which served as the major end measure. Out of the cohort of 25 female individuals who were administered ethinylestradiol, a total of eight individuals experienced ovulation, and among them, four individuals successfully achieved conception. No instances of ovulation were seen among the 25 women in the placebo group. An observation was made during the administration of ethinylestradiol that women with FSH levels below 15 mIU/mL exhibited ovulation. The research undertaken by Badawy et al. (2007) encompassed a cohort of 58 individuals who had been clinically diagnosed with idiopathic POI. The individuals in question were receiving medical intervention involving the administration of gonadotropin-releasing hormone agonists (GnRH-a) and gonadotropin therapy. The individuals involved in the study were randomised in a random manner to receive either dexamethasone or a placebo. This randomization was based on the assumption that certain patients might have an immunological cause for their POI. The occurrence of ovulation was seen in six out of twenty-nine women who received dexamethasone treatment, whereas only three out of twenty-nine women in the placebo group exhibited ovulation. The observed disparity has significance; however, it is important to use caution in drawing conclusions given the limited sample size of the study. The findings from the ESHRE POI Guideline Development Group substantiate the prevalence of follicular growth and probable ovulation among women diagnosed with POI, particularly when accompanied by a shorter duration of amenorrhea. The recorded evidence regarding the potential beneficial effects of immunosuppression in patients with POI and probable autoimmune aetiology is limited to case reports (Ferrau et al., 2011; ESHRE POI Guideline Development Group, 2015).

There has been a notable rise in the number of patients experiencing POI following cancer therapy, which has subsequently led to an upsurge in the long-term survival rates among these individuals. The prevention of iatrogenic POI resulting from chemotherapy, radiation therapy, or surgical procedures is of utmost importance. The consideration of ovarian transposition and protection during radiotherapy and fertility-sparing surgery is recommended for young women receiving cancer treatment. The use of GnRH analogues during chemotherapy has been observed to

significantly reduce the likelihood of POI in adolescent and young adult cancer patients. However, it has not demonstrated protective benefits for fertility, as reported by Del Mastro et al. (2014) and Sun et al. (2014). The cryopreservation of embryos and mature oocytes has been widely accepted as a clinically established technique, demonstrating favourable outcomes in terms of pregnancy rates and live births, with success rates reported to be as high as 25% (Rodriguez-Wallber et al., 2012; Kasum et al., 2014). More recent techniques, such as the collection of immature oocytes for later maturation in a laboratory setting and the preservation of reproductive tissue through freezing, show great potential. However, it is important to note that these procedures are still in the experimental stage (Suzuki et al., 2012).

The study conducted by Check et al. (1990) reported the greatest rate of pregnancies among prior uncontrolled interventional investigations. The objective of this study was to utilise GnRH-a and oestrogen replacement therapy to inhibit the production of gonadotropins, followed by the administration of human menopausal gonadotropin (hMG) to induce stimulation. Nevertheless, a limited number of prior investigations have endeavoured to achieve extended ovulation induction using hMG or recombinant follicle-stimulating hormone (recFSH), while concurrently suppressing gonadotropin levels using GnRH-a and implementing oestrogen replacement across many menstrual cycles. Based on the findings of Gougeon (1986), it has been suggested that a longer duration of stimulation with hMG/recFSH, in combination with oestrogen replacement and GnRH-a therapy, may yield more effectiveness in stimulating follicle growth among individuals diagnosed with established POI. The extended duration of follicle development, progressing from the secondary-preantral to the preovulatory stage, is a result of this phenomenon. In the current context, the utilisation of ovulation induction via extended ovarian stimulation using high-dose hMG or recFSH, coupled with the suppression of gonadotropins through oestrogen replacement therapy using gonadotropin-releasing hormone agonists (GnRH-a), specifically by diminishing serum LH levels, holds promise for improving ovulation and augmenting the probability of attaining pregnancy in individuals diagnosed with POI. In a study conducted by Jiao (2017), it has been posited that women diagnosed with POI and exhibiting an aberrant karyotype may have diminished prospects of achieving conception from their own oocytes, in contrast to cases of POI resulting from non-genetic factors. Nevertheless, there is a limited amount of existing data regarding the reproductive effects of POI on individuals with atypical karyotypes.

Platelet-rich plasma (PRP), which refers to the plasma component of an individual's own blood with a significantly elevated platelet concentration (Sundman et al., 2011), has been employed in the field of regenerative medicine for the past ten years (Alsousou et al., 2013; Reurink et al., 2014; Liao et al., 2015; Leo et al., 2015). According to Nikolidakis and Jansen (2008), plasma is known to include a diverse range of growth factors that have been proposed to facilitate the processes of angiogenesis, regeneration, and cell proliferation. The aforementioned growth factors have been identified as significant contributors to the regulation of folliculogenesis inside the ovary (Kawamura et al., 2005; Nagashima et al., 2011; Chang et al., 2019). Several studies have demonstrated positive outcomes in infertile women with a low likelihood of achieving pregnancy, such as those with POI and poor ovarian response (Sills et al., 2018; Pantos et al., 2019; Sfakianoudis et al., 2019; Farimani et al., 2019; Cakiroglu et al., 2020).

In a study conducted by Reddy et al. (2008), a novel approach to stimulating dormant follicles was introduced. The experimental approach employed in this study was the in vitro cultivation of ovarian fragments, which were exposed to PI3K stimulators and PTEN inhibitors. Li et al. (2010) have proposed that ovarian fragmentation may induce ovarian follicle growth through its disruption of the ovarian Hippo signalling system. Kawamura et al. (2013) employed a combination of these two methodologies within an in vitro activation strategy for the purpose of addressing infertility in individuals with POI. Suzuki et al. (2015) have reported two instances of successful full-term births following in vitro activation in individuals diagnosed with established POI.

The occurrence of spontaneous stimulation of latent primordial follicles into the secondary stage has been documented in patients who exhibit an early inadequate ovarian response, or POI. To stimulate the development of secondary follicles, a method called lysis and prompt re-implantation of ovarian cortex tissue without tissue culture, also referred to as drug-free in vitro activation, can be utilised. According to the findings of Kawamura et al. (2020), a majority of the patients diagnosed with poor ovarian response exhibited a notable rise in the quantity of antral follicles during many growth cycles. These observations were made subsequent to drug-free in vitro activation and the administration of hMG and FSH treatments. Hence, the authors posited that these methodologies could potentially be applicable in the initial stages of the phenomenon of interest (Kawamura et al., 2020). It is imperative to conduct additional randomised, controlled trials in order to provide further support and evaluation for these novel methodologies.

This discovery has the potential to create novel opportunities for addressing infertility in individuals with POI.

6. Conclusion

Primary Ovarian Insufficiency (POI) is distinguished by the premature cessation of ovarian function, resulting in a persistent state of low oestrogen levels in women who are younger than 40 years old. This condition can occur either spontaneously or as a result of medical intervention. The issue of infertility resulting from POI is a significant concern in developed nations, mostly due to the reduction in ovarian reserve associated with advancing age and a trend towards delayed childbearing. POI continues to be a substantial medical issue that exerts a significant impact on the patient's quality of life and raises considerable concerns for many reasons. Women who have POI through either spontaneous or surgical means and subsequently reach menopause at an earlier age face a considerably higher chance of developing several chronic disorders, including cardiovascular, bone, cognitive, and other ailments, in comparison to women who undergo menopause at the average age of 51. In light of the significant health implications associated with this condition, it is imperative that POI be recognised as a matter of public health importance. This recognition would ensure that enough assistance and information are provided to women affected by POI while also facilitating the early identification of those who may be at risk of developing this condition. It is recommended that patients have annual follow-up evaluations, particularly focusing on their smoking history, maintenance of a healthy weight, and identification of any blood pressure anomalies. These factors are crucial for assessing cardiovascular health. The provision of suitable counselling, psychological support, and hormone replacement therapy (HRT) is crucial to the treatment of POI and should be made available to all women diagnosed with this condition. The identification of dependable biomarkers for the prognostication and diagnosis of POI, comprehension of the pathophysiology and genetic causation of POI, evaluation of the long-term effects of various HRT combinations on overall, psychological, and sexual well-being, and determination of the most effective dosage for hormone replacement are among the principal areas of research that warrant significant attention. This necessitates additional investigation through prospective randomised controlled trials. Subsequent investigations ought to prioritise domains characterised by limited comprehension or unresolved inquiries.

References

Abir R, Ben-Haroush A, Felz C, Okon E, Raanani H, Orvieto R, Nitke S, Fisch B. Selection of patients before and after anticancer treatment for ovarian cryopreservation. Hum Reprod. 2008;23:869-77.

Absolom K, Eiser C, Turner L, Ledger W, Ross R, Davies H, Coleman R, Hancock B, Snowden J, Greenfield D; Late Effects Group Sheffield. Ovarian failure following cancer treatment: current management and quality of life. Hum Reprod. 2008;23:2506-12.

Albright F, Smith P, Richardson AM. Postmenopausal osteoporosis: its clinical features. JAMA. 1941;116:2465–74.

Allshouse AA, Semple AL, Santoro NF. Evidence for prolonged and unique amenorrhea-related symptoms in women with premature ovarian failure/primary ovarian insufficiency. Menopause. 2015;22:166-74.

Alsousou J, Ali A, Willett K, Harrison P. The role of platelet-rich plasma in tissue regeneration. Platelets. 2013;24:173-82.

Alvaro Mercadal B, Imbert R, Demeestere I, Gervy C, De Leener A, Englert Y, Costagliola S, Delbaere A. AMH mutations with reduced in vitro bioactivity are related to premature ovarian insufficiency. Hum Reprod. 2015;30:1196-202.

American College of Obstetricians and Gynecologists Committee on Genetics. ACOG committee opinion. No. 338: Screening for fragile X syndrome. Obstet Gynecol. 2006;107:1483-5.

Anagnostis P, Christou K, Artzouchaltzi AM, Gkekas NK, Kosmidou N, Siolos P, Paschou SA, Potoupnis M, Kenanidis E, Tsiridis E, Lambrinoudaki I, Stevenson JC, Goulis DG. Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: a systematic review and meta-analysis. Eur J Endocrinol. 2019;180:41-50.

Anasti JN. Premature ovarian failure: an update. Fertil Steril. 1998;70:1-15.

Anderson RA, McIlwain L, Coutts S, Kinnell HL, Fowler PA, Childs AJ. Activation of the aryl hydrocarbon receptor by a component of cigarette smoke reduces germ cell proliferation in the human fetal ovary. Mol Hum Reprod. 2014;20:42-8.

Ates S, Yesil G, Sevket O, Molla T, Yildiz S. Comparison of metabolic profile and abdominal fat distribution between karyotypically normal women with premature ovarian insufficiency and age-matched controls. Maturitas. 2014;79:306-10.

Auchus RJ. Steroid 17-hydroxylase and 17,20-lyase deficiencies, genetic and pharmacologic. J Steroid Biochem Mol Biol. 2017;165:71-8.

Bachelot A, Nicolas C, Bidet M, Dulon J, Leban M, Golmard JL, Polak M, Touraine P. Long-term outcome of ovarian function in women with

intermittent premature ovarian insufficiency. Clin Endocrinol (Oxf). 2017;86:223-8.

Bachelot A, Rouxel A, Massin N, Dulon J, Courtillot C, Matuchansky C, Badachi Y, Fortin A, Paniel B, Lecuru F, Lefrère-Belda MA, Constancis E, Thibault E, Meduri G, Guiochon-Mantel A, Misrahi M, Kuttenn F, Touraine P; POF-GIS Study Group. Phenotyping and genetic studies of 357 consecutive patients presenting with premature ovarian failure. Eur J Endocrinol. 2009;161:179-87.

Badawy A, Goda H, Ragab A. Induction of ovulation in idiopathic premature ovarian failure: a randomized double-blind trial. Reprod Biomed Online. 2007;15:215-9.

Bain C, Willett W, Hennekens CH, Rosner B, Belanger C, Speizer FE. Use of postmenopausal hormones and risk of myocardial infarction. Circulation. 1981;64:42-6.

Bakalov VK, Anasti JN, Calis KA, Vanderhoof VH, Premkumar A, Chen S, Furmaniak J, Smith BR, Merino MJ, Nelson LM. Autoimmune oophoritis as a mechanism of follicular dysfunction in women with 46,XX spontaneous premature ovarian failure. Fertil Steril. 2005;84:958-65.

Bakhsh H, Dei M, Bucciantini S, Balzi D, Bruni V. Premature ovarian insufficiency in young girls: repercussions on uterine volume and bone mineral density. Gynecol Endocrinol. 2015;31:65-9.

Ben-Aharon I, Shalgi R. What lies behind chemotherapy-induced ovarian toxicity? Reproduction. 2012;144:153-63.

Ben-Nagi J, Panay N. Premature ovarian insufficiency: how to improve reproductive outcome? Climacteric. 2014;17:242-6.

Bidet M, Bachelot A, Bissauge E, Golmard JL, Gricourt S, Dulon J, Coussieu C, Badachi Y, Touraine P. Resumption of ovarian function and pregnancies in 358 patients with premature ovarian failure. J Clin Endocrinol Metab. 2011;96:3864-72.

Bove R, Secor E, Chibnik LB, Barnes LL, Schneider JA, Bennett DA, De Jager PL. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. Neurology. 2014;82:222-9.

Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Perimenopause as a neurological transition state. Nat Rev Endocrinol. 2015;11:393-405.

Bygdeman M, Swahn ML. Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women. Maturitas. 1996;23:259-63.

Cakiroglu Y, Saltik A, Yuceturk A, Karaosmanoglu O, Kopuk SY, Scott RT, Tiras B, Seli E. Effects of intraovarian injection of autologous platelet rich plasma on ovarian reserve and IVF outcome parameters in women with primary ovarian insufficiency. Aging (Albany NY). 2020;12:10211-22.

Cartwright B, Robinson J, Seed PT, Fogelman I, Rymer J. Hormone Replacement Therapy Versus the Combined Oral Contraceptive Pill in Premature Ovarian Failure: A Randomized Controlled Trial of the Effects on Bone Mineral Density. J Clin Endocrinol Metab. 2016;101:3497-505.

Caserta D, Bordi G, Di Segni N, D'Ambrosio A, Mallozzi M, Moscarini M. The influence of cigarette smoking on a population of infertile men and women. Arch Gynecol Obstet. 2013;287:813-8.

Castronovo C, Rossetti R, Rusconi D, Recalcati MP, Cacciatore C, Beccaria E, Calcaterra V, Invernizzi P, Larizza D, Finelli P, Persani L. Gene dosage as a relevant mechanism contributing to the determination of ovarian function in Turner syndrome. Hum Reprod. 2014;29:368-79.

Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, LeBoff M, Lewis CE, McGowan J, Neuner J, Pettinger M, Stefanick ML, Wactawski-Wende J, Watts NB; Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA. 2003;290:1729-38.

Chang HM, Wu HC, Sun ZG, Lian F, Leung PCK. Neurotrophins and glial cell line-derived neurotrophic factor in the ovary: physiological and pathophysiological implications. Hum Reprod Update. 2019;25:224-42.

Chang SH, Kim CS, Lee KS, Kim H, Yim SV, Lim YJ, Park SK. Premenopausal factors influencing premature ovarian failure and early menopause. Maturitas. 2007;58:19-30.

Check JH, Nowroozi K, Chase JS, Nazari A, Shapse D, Vaze M. Ovulation induction and pregnancies in 100 consecutive women with hypergonadotropic amenorrhea. Fertil Steril. 1990;53:811-6.

Chen H, Xiao L, Li J, Cui L, Huang W. Adjuvant gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in premenopausal women. Cochrane Database Syst Rev. 2019;3:CD008018.

Chen HS, Chiang PH, Wang YC, Kao MC, Shieh TH, Tsai CF, Tsai EM. Benzyl butyl phthalate induces necrosis by AhR mediation of CYP1B1 expression in human granulosa cells. Reprod Toxicol. 2012;33:67-75.

Conway GS, Kaltsas G, Patel A, Davies MC, Jacobs HS. Characterization of idiopathic premature ovarian failure. Fertil Steril. 1996;65:337-41.

Cox L, Liu JH. Primary ovarian insufficiency: an update. Int J Womens Health. 2014;6:235-43.

Craig ZR, Wang W, Flaws JA. Endocrine-disrupting chemicals in ovarian function: effects on steroidogenesis, metabolism and nuclear receptor signaling. Reproduction. 2011;142:633-46.

Crofton PM, Evans N, Bath LE, Warner P, Whitehead TJ, Critchley HO, Kelnar CJ, Wallace WH. Physiological versus standard sex steroid replacement in young women with premature ovarian failure: effects on bone mass acquisition and turnover. Clin Endocrinol (Oxf). 2010;73:707-14.

Davey DA. HRT: some unresolved clinical issues in breast cancer, endometrial cancer and premature ovarian insufficiency. Womens Health (Lond). 2013;9:59-67.

de Almeida DM, Benetti-Pinto CL, Makuch MY. Sexual function of women with premature ovarian failure. Menopause. 2011;18:262-6.

Del Mastro L, Ceppi M, Poggio F, Bighin C, Peccatori F, Demeestere I, Levaggi A, Giraudi S, Lambertini M, D'Alonzo A, Canavese G, Pronzato P, Bruzzi P. Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: systematic review and meta-analysis of randomized trials. Cancer Treat Rev. 2014;40:675-83.

Dittmar M, Kahaly GJ. Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. J Clin Endocrinol Metab. 2003;88:2983-92.

Donner N, Handa RJ. Estrogen receptor beta regulates the expression of tryptophan-hydroxylase 2 mRNA within serotonergic neurons of the rat dorsal raphe nuclei. Neuroscience. 2009;163:705-18.

Donnez J, Dolmans MM. Fertility preservation in men and women: Where are we in 2021? Are we rising to the challenge? Fertil Steril. 2021;115:1089-90.

Ebrahimi M, Akbari Asbagh F. Pathogenesis and causes of premature ovarian failure: an update. Int J Fertil Steril. 2011;5:54-65.

The Writing Group for the PEPI. JAMA. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. 1996;276:1389-96.

ESHRE POI Guideline Development Group. Management of women with premature ovarian insufficiency. Guideline Eur Soc Hum Reprod Embryol (2015), p.30.

ESHRE POI Guideline Development Group. Management of women with premature ovarian insufficiency. Guideline Eur Soc Hum Reprod Embryol (2015), p.55.

ESHRE POI Guideline Development Group. Management of women with premature ovarian insufficiency. Guideline Eur Soc Hum Reprod Embryol (2015), p.56–7.

European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI; Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, Cifkova R, de Muinck Keizer-Schrama S, Hogervorst E, Janse F, Liao L, Vlaisavljevic V, Zillikens C, Vermeulen N. ESHRE

Guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016;31:926-37.

Ewies AA, Alfhaily F. Use of levonorgestrel-releasing intrauterine system in the prevention and treatment of endometrial hyperplasia. Obstet Gynecol Surv. 2012;67:726-33.

Farimani M, Heshmati S, Poorolajal J, Bahmanzadeh M. A report on three live births in women with poor ovarian response following intra-ovarian injection of platelet-rich plasma (PRP). Mol Biol Rep. 2019;46:1611-6.

Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. Climacteric. 2015;18:483-91.

Ferraù F, Gangemi S, Vita G, Trimarchi F, Cannavò S. Pregnancy after azathioprine therapy for ulcerative colitis in a woman with autoimmune premature ovarian failure and Addison's disease: HLA haplotype characterization. Fertil Steril. 2011;95:2430.e15-7.

Fisch B, Abir R. Female fertility preservation: past, present and future. Reproduction. 2018;156:F11-F27.

Fraison E, Crawford G, Casper G, Harris V, Ledger W. Pregnancy following diagnosis of premature ovarian insufficiency: a systematic review. Reprod Biomed Online. 2019;39:467-76.

Fridovich-Keil JL, Gubbels CS, Spencer JB, Sanders RD, Land JA, Rubio-Gozalbo E. Ovarian function in girls and women with GALT-deficiency galactosemia. J Inherit Metab Dis. 2011;34:357-66.

Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database Syst Rev. 2012;2012:CD000402.

Gannon AM, Stämpfli MR, Foster WG. Cigarette smoke exposure leads to follicle loss via an alternative ovarian cell death pathway in a mouse model. Toxicol Sci. 2012;125:274-84.

Gilsanz P, Lee C, Corrada MM, Kawas CH, Quesenberry CP Jr, Whitmer RA. Reproductive period and risk of dementia in a diverse cohort of health care members. Neurology. 2019;92:e2005-e2014.

Goldmeier S, De Angelis K, Rabello Casali K, Vilodre C, Consolim-Colombo F, Belló Klein A, Plentz R, Spritzer P, Irigoyen MC. Cardiovascular autonomic dysfunction in primary ovarian insufficiency: clinical and experimental evidence. Am J Transl Res. 2013;6:91-101.

Goswami D, Conway GS. Premature ovarian failure. Hum Reprod Update. 2005;11:391-410.

Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, Lin AE, Mauras N, Quigley CA, Rubin K, Sandberg DE, Sas TCJ, Silberbach M, Söderström-Anttila V, Stochholm K, van Alfen-van derVel-

den JA, Woelfle J, Backeljauw PF; International Turner Syndrome Consensus Group. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017;177:G1-G70.

Graziottin A, Basson R. Sexual dysfunction in women with premature menopause. Menopause. 2004;11:766-77.

Greendale GA, Wight RG, Huang MH, Avis N, Gold EB, Joffe H, Seeman T, Vuge M, Karlamangla AS. Menopause-associated symptoms and cognitive performance: results from the study of women's health across the nation. Am J Epidemiol. 2010;171:1214-24.

Gulhan I, Bozkaya G, Uyar I, Oztekin D, Pamuk BO, Dogan E. Serum lipid levels in women with premature ovarian failure. Menopause. 2012;19:1231-4.

Haidar MA, Baracat EC, Simões MJ, Focchi GR, Evêncio Neto J, de Lima GR. Premature ovarian failure: morphological and ultrastructural aspects. Sao Paulo Med J. 1994;112:534-8.

Hannon PR, Flaws JA. The effects of phthalates on the ovary. Front Endocrinol (Lausanne). 2015;6:8.

Heddar A, Dessen P, Flatters D, Misrahi M. Novel STAG3 mutations in a Caucasian family with primary ovarian insufficiency. Mol Genet Genomics. 2019;294:1527-34.

Hoek A, Schoemaker J, Drexhage HA. Premature ovarian failure and ovarian autoimmunity. Endocr Rev. 1997;18:107-34.

Huang Y, Hu C, Ye H, Luo R, Fu X, Li X, Huang J, Chen W, Zheng Y. Inflamm-Aging: A New Mechanism Affecting Premature Ovarian Insufficiency. J Immunol Res. 2019;2019:8069898.

Ishizuka B, Kudo Y, Tango T. Cross-sectional community survey of menopause symptoms among Japanese women. Maturitas. 2008;61:260-7.

Ishizuka B, Matsui D, Chenga Z, Kimura M, Namba C, Furuya M, et al. Endocrine Syndrome 3rd edition (III). Ryoikibetsu Shokogun Shirizu No.3. 2019;3:143–52.

Ishizuka B. Current Understanding of the Etiology, Symptomatology, and Treatment Options in Premature Ovarian Insufficiency (POI). Front Endocrinol (Lausanne). 2021;12:626924.

Jacobsen BK, Knutsen SF, Fraser GE. Age at natural menopause and total mortality and mortality from ischemic heart disease: the Adventist Health Study. J Clin Epidemiol. 1999;52:303-7.

Jankowska K. Premature ovarian failure. Prz Menopauzalny. 2017;16:51-6.

Jiao X, Qin C, Li J, Qin Y, Gao X, Zhang B, Zhen X, Feng Y, Simpson JL, Chen ZJ. Cytogenetic analysis of 531 Chinese women with premature ovarian failure. Hum Reprod. 2012;27:2201-7.

Jiao X, Zhang H, Ke H, Zhang J, Cheng L, Liu Y, Qin Y, Chen ZJ. Premature Ovarian Insufficiency: Phenotypic Characterization Within Different Etiologies. J Clin Endocrinol Metab. 2017;102:2281-90.

Jurisicova A, Taniuchi A, Li H, Shang Y, Antenos M, Detmar J, Xu J, Matikainen T, Benito Hernández A, Nunez G, Casper RF. Maternal exposure to polycyclic aromatic hydrocarbons diminishes murine ovarian reserve via induction of Harakiri. J Clin Invest. 2007;117:3971-8.

Kalantaridou SN, Naka KK, Papanikolaou E, Kazakos N, Kravariti M, Calis KA, Paraskevaidis EA, Sideris DA, Tsatsoulis A, Chrousos GP, Michalis LK. Impaired endothelial function in young women with premature ovarian failure: normalization with hormone therapy. J Clin Endocrinol Metab. 2004;89:3907-13.

Karlamangla AS, Singer BH, Chodosh J, McEwen BS, Seeman TE. Urinary cortisol excretion as a predictor of incident cognitive impairment. Neurobiol Aging. 2005;26 Suppl 1:80-4.

Kasum M, Beketić-Orešković L, Peddi PF, Orešković S, Johnson RH. Fertility after breast cancer treatment. Eur J Obstet Gynecol Reprod Biol. 2014;173:13-8.

Kawamura K, Cheng Y, Suzuki N, Deguchi M, Sato Y, Takae S, Ho CH, Kawamura N, Tamura M, Hashimoto S, Sugishita Y, Morimoto Y, Hosoi Y, Yoshioka N, Ishizuka B, Hsueh AJ. Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment. Proc Natl Acad Sci U S A. 2013;110:17474-9.

Kawamura K, Ishizuka B, Hsueh AJW. Drug-free in-vitro activation of follicles for infertility treatment in poor ovarian response patients with decreased ovarian reserve. Reprod Biomed Online. 2020;40:245-53.

Kawamura K, Kawamura N, Mulders SM, Sollewijn Gelpke MD, Hsueh AJ. Ovarian brain-derived neurotrophic factor (BDNF) promotes the development of oocytes into preimplantation embryos. Proc Natl Acad Sci U S A. 2005;102:9206-11.

Kim HK, Ko DH, Lee W, Kim KR, Chun S, Song J, Min WK. Body fluid concentrations of bisphenol A and their association with in vitro fertilization outcomes. Hum Fertil (Camb). 2021;24:199-207.

Knauff EA, Westerveld HE, Goverde AJ, Eijkemans MJ, Valkenburg O, van Santbrink EJ, Fauser BC, van der Schouw YT. Lipid profile of women with premature ovarian failure. Menopause. 2008;15:919-23.

Kodama M, Komura H, Kodama T, Nishio Y, Kimura T. Estrogen therapy initiated at an early age increases bone mineral density in Turner syndrome patients. Endocr J. 2012;59:153-9.

Kokcu A. Premature ovarian failure from current perspective. Gynecol Endocrinol. 2010;26:555-62.

Koninckx PR, Brosens IA. The "gonadotropin-resistant ovary" syndrome as a cause of secondary amenorrhea and infertility. Fertil Steril. 1977;28:926-31.

Kovanci E, Schutt AK. Premature ovarian failure: clinical presentation and treatment. Obstet Gynecol Clin North Am. 2015;42:153-61.

Kulaksizoglu M, Ipekci SH, Kebapcilar L, Kebapcilar AG, Korkmaz H, Akyurek F, Baldane S, Gonen MS. Risk factors for diabetes mellitus in women with primary ovarian insufficiency. Biol Trace Elem Res. 2013;154:313-20.

La Marca A, Brozzetti A, Sighinolfi G, Marzotti S, Volpe A, Falorni A. Primary ovarian insufficiency: autoimmune causes. Curr Opin Obstet Gynecol. 2010;22:277-82.

Lakhal B, Braham R, Berguigua R, Bouali N, Zaouali M, Chaieb M, Veitia RA, Saad A, Elghezal H. Cytogenetic analyses of premature ovarian failure using karyotyping and interphase fluorescence in situ hybridization (FISH) in a group of 1000 patients. Clin Genet. 2010;78:181-5.

Lambrinoudaki I, Paschou SA, Lumsden MA, Faubion S, Makrakis E, Kalantaridou S, Panay N. Premature ovarian insufficiency: A toolkit for the primary care physician. Maturitas. 2021;147:53-63.

Lana MB, Straminsky V, Onetto C, Amuchastegui JM, Blanco G, Galluzzo L, Provenzano S, Nolting M. What is really responsible for bone loss in spontaneous premature ovarian failure? A new enigma. Gynecol Endocrinol. 2010;26:755-9.

Lande Y, Fisch B, Tsur A, Farhi J, Prag-Rosenberg R, Ben-Haroush A, Kessler-Icekson G, Zahalka MA, Ludeman SM, Abir R. Short-term exposure of human ovarian follicles to cyclophosphamide metabolites seems to promote follicular activation in vitro. Reprod Biomed Online. 2017;34:104-14.

Larsen EC, Müller J, Schmiegelow K, Rechnitzer C, Andersen AN. Reduced ovarian function in long-term survivors of radiation- and chemotherapy-treated childhood cancer. J Clin Endocrinol Metab. 2003;88:5307-14.

Leite-Silva P, Bedone A, Pinto-Neto AM, Costa JV, Costa-Paiva L. Factors associated with bone density in young women with karyotypically normal spontaneous premature ovarian failure. Arch Gynecol Obstet. 2009;280:177-81.

Leo MS, Kumar AS, Kirit R, Konathan R, Sivamani RK. Systematic review of the use of platelet-rich plasma in aesthetic dermatology. J Cosmet Dermatol. 2015;14:315-23.

Li J, Kawamura K, Cheng Y, Liu S, Klein C, Liu S, Duan EK, Hsueh AJ. Activation of dormant ovarian follicles to generate mature eggs. Proc Natl Acad Sci U S A. 2010;107:10280-4.

Liao HT, James IB, Marra KG, Rubin JP. The Effects of Platelet-Rich Plasma on Cell Proliferation and Adipogenic Potential of Adipose-Derived Stem Cells. Tissue Eng Part A. 2015;21:2714-22.

Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomised women. Lancet. 1980;2:1151-4.

Liu AX, Shi HY, Cai ZJ, Liu A, Zhang D, Huang HF, Jin HM. Increased risk of gonadal malignancy and prophylactic gonadectomy: a study of 102 phenotypic female patients with Y chromosome or Y-derived sequences. Hum Reprod. 2014;29:1413-9.

Løkkegaard E, Jovanovic Z, Heitmann BL, Keiding N, Ottesen B, Pedersen AT. The association between early menopause and risk of ischaemic heart disease: influence of Hormone Therapy. Maturitas. 2006;53:226-33.

Lund TD, Rovis T, Chung WC, Handa RJ. Novel actions of estrogen receptor-beta on anxiety-related behaviors. Endocrinology. 2005;146:797-807.

Machura P, Grymowicz M, Rudnicka E, Pięta W, Calik-Ksepka A, Skórska J, Smolarczyk R. Premature ovarian insufficiency - hormone replacement therapy and management of long-term consequences. Prz Menopauzalny. 2018;17:135-8.

Maclaran K, Panay N. Current concepts in premature ovarian insufficiency. Womens Health (Lond). 2015;11:169-82.

Maclaran K, Panay N. Premature ovarian failure. J Fam Plann Reprod Health Care. 2011;37:35-42.

Madalinska JB, van Beurden M, Bleiker EM, Valdimarsdottir HB, Hollenstein J, Massuger LF, Gaarenstroom KN, Mourits MJ, Verheijen RH, van Dorst EB, van der Putten H, van der Velden K, Boonstra H, Aaronson NK. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. J Clin Oncol. 2006;24:3576-82.

Mamsen LS, Lutterodt MC, Andersen EW, Skouby SO, Sørensen KP, Andersen CY, Byskov AG. Cigarette smoking during early pregnancy reduces the number of embryonic germ and somatic cells. Hum Reprod. 2010;25:2755-61.

Massin N, Gougeon A, Meduri G, Thibaud E, Laborde K, Matuchansky C, Constancis E, Vacher-Lavenu MC, Paniel B, Zorn JR, Misrahi M, Kuttenn F, Touraine P. Significance of ovarian histology in the management of patients presenting a premature ovarian failure. Hum Reprod. 2004;19:2555-60.

Mathew H, Mahalingaiah S. Do prenatal exposures pose a real threat to ovarian function? Bisphenol A as a case study. Reproduction. 2019;157:R143-R157.

McEwen BS, Akama KT, Spencer-Segal JL, Milner TA, Waters EM. Estrogen effects on the brain: actions beyond the hypothalamus via novel mechanisms. Behav Neurosci. 2012;126:4-16.

McLaughlin M, Kelsey TW, Wallace WH, Anderson RA, Telfer EE. Non-growing follicle density is increased following adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy in the adult human ovary. Hum Reprod. 2017;32:165-74.

Meczekalski B, Podfigurna-Stopa A, Genazzani AR. Hypoestrogenism in young women and its influence on bone mass density. Gynecol Endocrinol. 2010;26:652-7.

Méduri G, Bachelot A, Duflos C, Bständig B, Poirot C, Genestie C, Veitia R, De Baere E, Touraine P. FOXL2 mutations lead to different ovarian phenotypes in BPES patients: Case Report. Hum Reprod. 2010;25:235-43.

Méduri G, Massin N, Guibourdenche J, Bachelot A, Fiori O, Kuttenn F, Misrahi M, Touraine P. Serum anti-Müllerian hormone expression in women with premature ovarian failure. Hum Reprod. 2007;22:117-23.

Mendelsohn ME, Karas RH. HRT and the young at heart. N Engl J Med. 2007;356:2639-41.

Mørch LS, Løkkegaard E, Andreasen AH, Kjaer SK, Lidegaard O. Hormone therapy and different ovarian cancers: a national cohort study. Am J Epidemiol. 2012;175:1234-42.

Morrison JC, Givens JR, Wiser WL, Fish SA. Mumps oophoritis: a cause of premature menopause. Fertil Steril. 1975;26:655-9.

Muczynski V, Lecureuil C, Messiaen S, Guerquin MJ, N'tumba-Byn T, Moison D, Hodroj W, Benjelloun H, Baijer J, Livera G, Frydman R, Benachi A, Habert R, Rouiller-Fabre V. Cellular and molecular effect of MEHP Involving LXRα in human fetal testis and ovary. PLoS One. 2012;7:e48266.

Mueck AO. Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone. Climacteric. 2012;15 Suppl 1:11-7.

Nachtigall LE. Comparative study: Replens versus local estrogen in menopausal women. Fertil Steril. 1994;61:178-80.

Nagashima T, Kim J, Li Q, Lydon JP, DeMayo FJ, Lyons KM, Matzuk MM. Connective tissue growth factor is required for normal follicle development and ovulation. Mol Endocrinol. 2011;25:1740-59.

Nelson LM, Covington SN, Rebar RW. An update: spontaneous premature ovarian failure is not an early menopause. Fertil Steril. 2005;83:1327-32.

Nelson LM, Kimzey LM, White BJ, Merriam GR. Gonadotropin suppression for the treatment of karyotypically normal spontaneous premature ovarian failure: a controlled trial. Fertil Steril. 1992;57:50-5.

Nguyen QN, Zerafa N, Liew SH, Findlay JK, Hickey M, Hutt KJ. Cisplatin- and cyclophosphamide-induced primordial follicle depletion is caused by direct damage to oocytes. Mol Hum Reprod. 2019;25:433-44.

Nikolidakis D, Jansen JA. The biology of platelet-rich plasma and its application in oral surgery: literature review. Tissue Eng Part B Rev. 2008;14:249-58.

O'Donnell RL, Warner P, Lee RJ, Walker J, Bath LE, Kelnar CJ, Wallace WH, Critchley HO. Physiological sex steroid replacement in premature ovarian failure: randomized crossover trial of effect on uterine volume, endometrial thickness and blood flow, compared with a standard regimen. Hum Reprod. 2012;27:1130-8.

Oktem O, Oktay K. Quantitative assessment of the impact of chemotherapy on ovarian follicle reserve and stromal function. Cancer. 2007;110:2222-9.

Otte C, Hart S, Neylan TC, Marmar CR, Yaffe K, Mohr DC. A meta-analysis of cortisol response to challenge in human aging: importance of gender. Psychoneuroendocrinology. 2005;30:80-91.

Panay N, Anderson RA, Nappi RE, Vincent AJ, Vujovic S, Webber L, Wolfman W. Premature ovarian insufficiency: an International Menopause Society White Paper. Climacteric. 2020;23:426-46.

Pantos K, Simopoulou M, Pantou A, Rapani A, Tsioulou P, Nitsos N, Syrkos S, Pappas A, Koutsilieris M, Sfakianoudis K. A Case Series on Natural Conceptions Resulting in Ongoing Pregnancies in Menopausal and Prematurely Menopausal Women Following Platelet-Rich Plasma Treatment. Cell Transplant. 2019;28:1333-40.

Park KH, Lee SJ, Kim JY, Kim JY, Bai SW, Kim JW. A concomitant decrease in cortical and trabecular bone mass in isolated hypogonadotropic hypogonadism and gonadal dysgenesis. Yonsei Med J. 1999;40:444-9.

Peck JD, Quaas AM, Craig LB, Soules MR, Klein NA, Hansen KR. Lifestyle factors associated with histologically derived human ovarian non-growing follicle count in reproductive age women. Hum Reprod. 2016;31:150-7.

Piccioni P, Scirpa P, D'Emilio I, Sora F, Scarciglia M, Laurenti L, De Matteis S, Sica S, Leone G, Chiusolo P. Hormonal replacement therapy after stem cell transplantation. Maturitas. 2004;49:327-33.

Podfigurna-Stopa A, Czyzyk A, Grymowicz M, Smolarczyk R, Katulski K, Czajkowski K, Meczekalski B. Premature ovarian insufficiency: the context of long-term effects. J Endocrinol Invest. 2016;39:983-90.

Popat VB, Calis KA, Kalantaridou SN, Vanderhoof VH, Koziol D, Troendle JF, Reynolds JC, Nelson LM. Bone mineral density in young women with primary ovarian insufficiency: results of a three-year randomized controlled trial of physiological transdermal estradiol and testosterone replacement. J Clin Endocrinol Metab. 2014;99:3418-26.

Popat VB, Calis KA, Vanderhoof VH, Cizza G, Reynolds JC, Sebring N, Troendle JF, Nelson LM. Bone mineral density in estrogen-deficient young women. J Clin Endocrinol Metab. 2009;94:2277-83.

Portman DJ, Gass ML; Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. J Sex Med. 2014;11:2865-72.

Prior JC, Vigna YM, Wark JD, Eyre DR, Lentle BC, Li DK, Ebeling PR, Atley L. Premenopausal ovariectomy-related bone loss: a randomized, double-blind, one-year trial of conjugated estrogen or medroxyprogesterone acetate. J Bone Miner Res. 1997;12:1851-63.

Ratcliffe MA, Lanham SA, Reid DM, Dawson AA. Bone mineral density (BMD) in patients with lymphoma: the effects of chemotherapy, intermittent corticosteroids and premature menopause. Hematol Oncol. 1992;10:181-7.

Rebar RW. Premature ovarian failure. Obstet Gynecol. 2009;113:1355-63.

Reddy P, Liu L, Adhikari D, Jagarlamudi K, Rajareddy S, Shen Y, Du C, Tang W, Hämäläinen T, Peng SL, Lan ZJ, Cooney AJ, Huhtaniemi I, Liu K. Oocyte-specific deletion of Pten causes premature activation of the primordial follicle pool. Science. 2008;319:611-3.

Reurink G, Goudswaard GJ, Moen MH, Weir A, Verhaar JA, Bierma-Zeinstra SM, Maas M, Tol JL; Dutch Hamstring Injection Therapy (HIT) Study Investigators. Platelet-rich plasma injections in acute muscle injury. N Engl J Med. 2014;370:2546-7.

Richardson MC, Guo M, Fauser BC, Macklon NS. Environmental and developmental origins of ovarian reserve. Hum Reprod Update. 2014;20:353-69.

Rivera CM, Grossardt BR, Rhodes DJ, Brown RD Jr, Roger VL, Melton LJ 3rd, Rocca WA. Increased cardiovascular mortality after early bilateral oophorectomy. Menopause. 2009;16:15-23.

Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol. 2006;7:821-8.

Rocca WA, Grossardt BR, Shuster LT, Stewart EA. Hysterectomy, oophorectomy, estrogen, and the risk of dementia. Neurodegener Dis. 2012;10:175-8.

Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, estrogen, and dementia: a 2014 update. Mol Cell Endocrinol. 2014;389:7-12.

Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, menopause, estrogen treatment, and cognitive aging: clinical evidence for a window of opportunity. Brain Res. 2011;1379:188-98.

Rocca WA, Henderson VW. Is there a link between gynecologic surgeries and Alzheimer disease? Neurology. 2014;82:196-7.

Rodriguez-Wallberg KA, Oktay K. Options on fertility preservation in female cancer patients. Cancer Treat Rev. 2012;38:354-61.

Rossetti R, Ferrari I, Bonomi M, Persani L. Genetics of primary ovarian insufficiency. Clin Genet. 2017;91:183-98.

Rousseau F, Rouillard P, Morel ML, Khandjian EW, Morgan K. Prevalence of carriers of premutation-size alleles of the FMRI gene--and implications for the population genetics of the fragile X syndrome. Am J Hum Genet. 1995;57:1006-18.

Rudnicka E, Kruszewska J, Klicka K, Kowalczyk J, Grymowicz M, Skórska J, Pięta W, Smolarczyk R. Premature ovarian insufficiency-aetiopathology, epidemiology, and diagnostic evaluation. Prz Menopauzalny. 2018;17:105-8.

Ryan J, Scali J, Carrière I, Amieva H, Rouaud O, Berr C, Ritchie K, Ancelin ML. Impact of a premature menopause on cognitive function in later life. BJOG. 2014;121:1729-39.

Schlessinger D, Herrera L, Crisponi L, Mumm S, Percesepe A, Pellegrini M, Pilia G, Forabosco A. Genes and translocations involved in POF. Am J Med Genet. 2002;111:328-33.

Schnatz PF. The 2010 North American Menopause Society position statement: Updates on screening, prevention and management of postmenopausal osteoporosis. Conn Med. 2011;75:485-7.

Sfakianoudis K, Simopoulou M, Nitsos N, Rapani A, Pantou A, Vaxevanoglou T, Kokkali G, Koutsilieris M, Pantos K. A Case Series on Platelet-Rich Plasma Revolutionary Management of Poor Responder Patients. Gynecol Obstet Invest. 2019;84:99-106.

Sherman SL. Premature ovarian failure in the fragile X syndrome. Am J Med Genet. 2000;97:189-94.

Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, Fillit H, Stefanick ML, Hendrix SL, Lewis CE, Masaki K, Coker LH; Women's Health Initiative Memory Study. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004;291:2947-58.

Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: long-term health consequences. Maturitas. 2010;65:161-6.

Sills ES, Rickers NS, Li X, Palermo GD. First data on in vitro fertilization and blastocyst formation after intraovarian injection of calcium gluco-

nate-activated autologous platelet rich plasma. Gynecol Endocrinol. 2018;34:756-60.

Silva CA, Yamakami LY, Aikawa NE, Araujo DB, Carvalho JF, Bonfá E. Autoimmune primary ovarian insufficiency. Autoimmun Rev. 2014;13:427-30.

Singh RP, Carr DH. The anatomy and histology of XO human embryos and fetuses. Anat Rec. 1966;155:369-83.

Sklar CA, Mertens AC, Mitby P, Whitton J, Stovall M, Kasper C, Mulder J, Green D, Nicholson HS, Yasui Y, Robison LL. Premature menopause in survivors of childhood cancer: a report from the childhood cancer survivor study. J Natl Cancer Inst. 2006;98:890-6.

Sochocka M, Karska J, Pszczołowska M, Ochnik M, Fułek M, Fułek K, Kurpas D, Chojdak-Łukasiewicz J, Rosner-Tenerowicz A, Leszek J. Cognitive Decline in Early and Premature Menopause. Int J Mol Sci. 2023;24:6566.

Somigliana E, Berlanda N, Benaglia L, Viganò P, Vercellini P, Fedele L. Surgical excision of endometriomas and ovarian reserve: a systematic review on serum antimüllerian hormone level modifications. Fertil Steril. 2012;98:1531-8.

Spears N, Lopes F, Stefansdottir A, Rossi V, De Felici M, Anderson RA, Klinger FG. Ovarian damage from chemotherapy and current approaches to its protection. Hum Reprod Update. 2019;25:673-93.

Sugiura-Ogasawara M, Ozaki Y, Sonta S, Makino T, Suzumori K. Exposure to bisphenol A is associated with recurrent miscarriage. Hum Reprod. 2005;20:2325-9.

Sun X, Dongol S, Jiang J, Kong B. Protection of ovarian function by GnRH agonists during chemotherapy: a meta-analysis. Int J Oncol. 2014;44:1335-40.

Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. Am J Sports Med. 2011;39:2135-40.

Suzuki N, Hashimoto S, Igarashi S, Takae S, Yamanaka M, Yamochi T, Takenoshita M, Hosoi Y, Morimoto Y, Ishizuka B. Assessment of long-term function of heterotopic transplants of vitrified ovarian tissue in cynomolgus monkeys. Hum Reprod. 2012;27:2420-9.

Suzuki N, Yoshioka N, Takae S, Sugishita Y, Tamura M, Hashimoto S, Morimoto Y, Kawamura K. Successful fertility preservation following ovarian tissue vitrification in patients with primary ovarian insufficiency. Hum Reprod. 2015;30:608-15.

Tang H, Liu Y, Fan Y, Li C. Therapeutic Effects of Low-Intensity Pulsed Ultrasound on Premature Ovarian Insufficiency. Ultrasound Med Biol. 2021;47:2377-87.

Tariq S, Anderson J, Burns F, Delpech V, Gilson R, Sabin C. The menopause transition in women living with HIV: current evidence and future avenues of research. J Virus Erad. 2016;2:114-6.

Tartagni M, Cicinelli E, De Pergola G, De Salvia MA, Lavopa C, Loverro G. Effects of pretreatment with estrogens on ovarian stimulation with gonadotropins in women with premature ovarian failure: a randomized, placebo-controlled trial. Fertil Steril. 2007;87:858-61.

Taylor HS, Pal L, Sell E. Speroff's clinical gynecologic endocrinology and infertility. Lippincott Williams & Wilkins. 2019.

The Writing Group for the PEPI. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA. 1996;276:1389-96.

Torrealday S, Kodaman P, Pal L. Premature Ovarian Insufficiency - an update on recent advances in understanding and management. F1000Res. 2017;6:2069.

Tucker EJ, Grover SR, Bachelot A, Touraine P, Sinclair AH. Premature Ovarian Insufficiency: New Perspectives on Genetic Cause and Phenotypic Spectrum. Endocr Rev. 2016;37:609-35.

Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: a comprehensive review. Health Qual Life Outcomes. 2005;3:47.

Uygur D, Sengül O, Bayar D, Erdinç S, Batioğlu S, Mollamahmutoglu L. Bone loss in young women with premature ovarian failure. Arch Gynecol Obstet. 2005;273:17-9.

Vabre P, Gatimel N, Moreau J, Gayrard V, Picard-Hagen N, Parinaud J, Leandri RD. Environmental pollutants, a possible etiology for premature ovarian insufficiency: a narrative review of animal and human data. Environ Health. 2017;16:37.

van Der Voort DJ, van Der Weijer PH, Barentsen R. Early menopause: increased fracture risk at older age. Osteoporos Int. 2003;14:525-30.

van Kasteren YM, Hoek A, Schoemaker J. Ovulation induction in premature ovarian failure: a placebo-controlled randomized trial combining pituitary suppression with gonadotropin stimulation. Fertil Steril. 1995;64:273-8.

van Kasteren YM, Hundscheid RD, Smits AP, Cremers FP, van Zonneveld P, Braat DD. Familial idiopathic premature ovarian failure: an overrated and underestimated genetic disease? Hum Reprod. 1999;14:2455-9.

van Kasteren YM, Schoemaker J. Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. Hum Reprod Update. 1999;5:483-92.

Vearncombe KJ, Pachana NA. Is cognitive functioning detrimentally affected after early, induced menopause? Menopause. 2009;16:188-98.

Weiser MJ, Wu TJ, Handa RJ. Estrogen receptor-beta agonist diarylpropionitrile: biological activities of R- and S-enantiomers on behavior and hormonal response to stress. Endocrinology. 2009;150:1817-25.

Wells G, Tugwell P, Shea B, Guyatt G, Peterson J, Zytaruk N, Robinson V, Henry D, O'Connell D, Cranney A; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. Endocr Rev. 2002;23:529-39.

Welt CK. Primary ovarian insufficiency: a more accurate term for premature ovarian failure. Clin Endocrinol (Oxf). 2008;68:499-509.

Wesevich V, Kellen AN, Pal L. Recent advances in understanding primary ovarian insufficiency. F1000Res. 2020;9:F1000 Faculty Rev-1101.

Willett W, Stampfer MJ, Bain C, Lipnick R, Speizer FE, Rosner B, Cramer D, Hennekens CH. Cigarette smoking, relative weight, and menopause. Am J Epidemiol. 1983;117:651-8.

Winship AL, Bakai M, Sarma U, Liew SH, Hutt KJ. Dacarbazine depletes the ovarian reserve in mice and depletion is enhanced with age. Sci Rep. 2018;8:6516.

Woad KJ, Watkins WJ, Prendergast D, Shelling AN. The genetic basis of premature ovarian failure. Aust N Z J Obstet Gynaecol. 2006;46:242-4.

Woo I, Zhang Y, Hui H, Mor E. Resistant Ovary Syndrome Masquerading as Premature Ovarian Insufficiency. J Clin Gynecol Obstet (JCGO). 2019; 8:111-3.

Yoo JE, Shin DW, Han K, Kim D, Won HS, Lee J, Kim SY, Nam GE, Park HS. Female reproductive factors and the risk of dementia: a nationwide cohort study. Eur J Neurol. 2020;27:1448-58.

Yoon SH, Choi YM, Hong MA, Kim JJ, Lee GH, Hwang KR, Moon SY. Association study of anti-Mullerian hormone and anti-Mullerian hormone type II receptor polymorphisms with idiopathic primary ovarian insufficiency. Hum Reprod. 2013;28:3301-5.

Yorgun H, Tokgözoğlu L, Canpolat U, Gürses KM, Bozdağ G, Yapıcı Z, Sahiner L, Kaya EB, Kabakçı G, Oto A, Tuncer M, Aytemir K. The cardiovascular effects of premature ovarian failure. Int J Cardiol. 2013;168:506-10.

Zhang X, Han T, Yan L, Jiao X, Qin Y, Chen ZJ. Resumption of Ovarian Function After Ovarian Biopsy/Scratch in Patients With Premature Ovarian Insufficiency. Reprod Sci. 2019;26:207-13.

Zhu X, Liu M, Dong R, Gao L, Hu J, Zhang X, Wu X, Fan B, Chen C, Xu W. Mechanism Exploration of Environmental Pollutants on Premature Ovarian Insufficiency: a Systematic Review and Meta-analysis. Reprod Sci. 2023. doi: 10.1007/s43032-023-01326-5. Epub ahead of print.