A Brief Overview On Premature Ovarian Failure

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INTRODUCTION

Menopause is a physiological process that occurs approximately at the age of 51 where a female will no longer undergo menses due to the scarcity of ovarian follicles(1,2). However, in premature ovarian failure (POF) also known as premature ovarian insufficiency (POI) and hypergonadotropic ovarian failure, there is a significant decrease in ovarian function and substantial reduction in ovarian follicles after puberty and before the age of 40(3,4). Moraes-Ruehsen and Jones had first described this disease as non-physiological amenorrhoea in non-menopausal women and in 1950. Atria had recounted the characteristics that POI patients would present with, secondary to hypergonadotropic hypoestrogenism(5). Although, occasional resumption of ovarian function can be seen in such patients and spontaneous pregnancies can occur, being diagnosed with POF can have a mental and physical toll on one's health(2,5).

DIAGNOSIS AND CLINICAL PICTURE

POF is a complex heterogeneous disease that affects 0.1% of females who are 30 years of age or younger, while 1% are diagnosed by the age of 40(2). In addition, a greater prevalence of patients with POI was noted in countries having an intermediate or low human development index(6).

The symptoms of POI can vary across a broad spectrum from one patient to another as this disease can either evolve over the years or spontaneously. POF can be broadly classified into two groups in relation to how it may present. Up to 10% of POF patients present with the most severe form of the disease, where there is a complete absence of pubertal development together with primary amenorrhea, whilst the majority of patients undergo normal pubertal development and eventually show signs of secondary amenorrhoea and menopausal symptoms later on in life(6,7). Such symptoms may include hot flushes, increased sweating, decreased libido, tachycardia, mood swings, reduced sleep quality, dyspareunia, mucous dryness and hair loss due to oestrogen deficiency. Interestingly, these symptoms are not usually seen in patients with primary amenorrhea since their body was never exposed to oestrogen. Furthermore, patients may also be diagnosed with POF when visiting a fertility clinic due to having difficulties with conceiving(3,6,7). Therefore, since the clinical picture that patients may present with is not clear cut and always indicative of POF, tests need to be carried out to eliminate other diseases like polycystic ovarian syndrome (PCOS), hypothalamic amenorrhoea caused by stress or anorexia and pathologies like pituitary tumours that influence the hypothalamic-pituitary-gonadal (HPG) axis(3).

Blood analysis in POF patients shows lower oestradiol (<20pg/ml), anti-mÜllerian hormone (AMH) (<1.5ng/ml) and inhibin B levels as well as increased follicle stimulating hormone (FSH) (>25IU/L) levels, when taken on two separate occasions with a one-month interval(7–9). Furthermore, obtaining AMH levels indicates the extent of ovarian reserve(5).

DIAGNOSING POF HISTOLOGICALLY

When taking a closer look at the histological appearance of the ovaries, the ovaries' morphology in POF can be classified in two ways:

- In Type 1, also known as the afollicular form, the ovaries are observed to have no ovarian follicles. This can be either due to the depletion of follicles during embryonic development or shortly after birth. As a result, the ovaries would appear smaller having fibrous stroma. Causes include ovarian dysgenesis, chromosomal mutations and sex development disorders(5,6).

- In Type 2, which is the follicular form, follicles are still identified in the ovary meaning that ovarian function is still present to a certain extent. This type can be described in 3 ways: a) oophoritis; b) scarce follicles; or c) abundant primordial follicles in ovaries which is usually associated with resistant ovary syndrome (ROS). Type 2 can lead to the Type 1 form of POI(5,6).

Having a clearer understanding of the ovarian morphology and histology in POF would help in understanding the aetiology, pathogenesis, severity of the disease and what treatments would be best for the patient(6).

CAUSES OF POF

POF is a highly oligogenic and multifactorial disease that can have various aetiologies as seen in Figure 1. However, sadly, up to 90% of cases are of unknown origin(7,10).

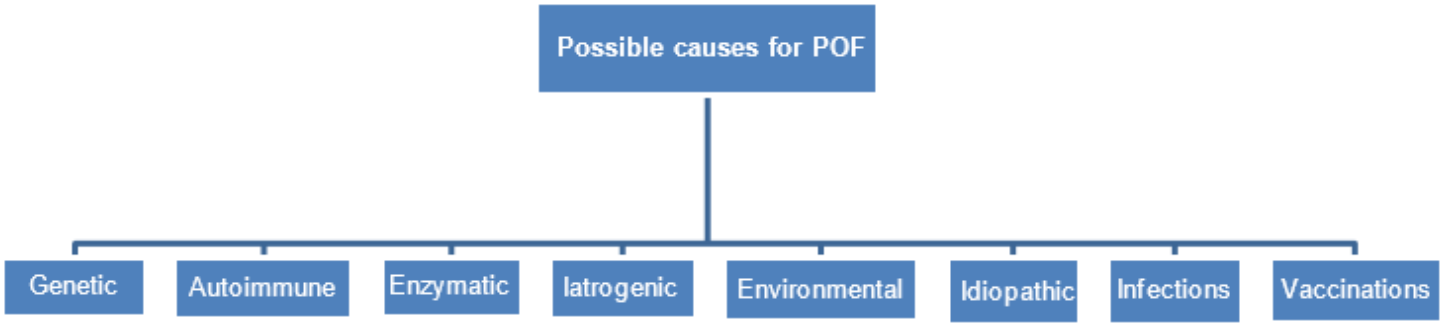

Figure 1: *Possible aetiologies for POF.3*

AUTOIMMUNE

POI may be caused by the presence of anti-ovarian antibodies which would lead to ovarian dysfunction. Interestingly, 20% of POF patients are usually diagnosed with other autoimmune diseases as seen in Table 1(7,10). Indeed, the most associated autoimmune disease with POF is Hashimoto's disease and autoimmune hypothyroidism followed by Addison's disease(2,5). Autoimmune regulator (AIRE) gene mutations can also lead to a phenomenon known as autoimmune polyglandular syndrome (APS), meaning that patients can develop other autoimmune disorders. Studies have shown that some patients having Addison's disease were diagnosed with POF 8-14 years prior. One must note that screening for anti-ovarian antibodies is not a reliable method to diagnose POF(5,7,11).

Autoimmune Diseases Associated with POI	
Rheumatoid arthritis	Systemic lupus erythematosus
Albinism	Coeliac disease
Addison's disease	Myasthenia gravis
Hashimoto's disease	Type 1 diabetes mellitus

Table 1: *Autoimmune diseases associated with POI (3,5)*

GENETIC

Up to 40% of POI cases account for genetic mutations due to its high genetic predilection, especially when concerning the X chromosome. In fact, more than 50 gene mutations can contribute to this disease. As seen in Table 2, various genetic mutations can influence the development and physiology of the ovaries, leading to POF(6,9,12).

Gene involved in mutation	**Effect**
Factor in germline alpha (FIGLA)	Loss of primordial follicles
Newborn ovary homeobox (NOBOX)	Loss of oocytes at birth
Forkhead box L2 (FOXL2), nuclear receptorsubfamily-five group A member 1 (NRSAA1), WT1	Impacts folliculogenesis
LHR	May cause primary or secondary amenorrhea
FSHR	May cause secondary amenorrhea

Table 2: *Genetic mutations associated with POF (3,6,7)*

Moreover, CGG repeats found in the fragile X mental retardation 1 (FMR1) gene in Fragile X syndrome are strongly linked with POF if the female inherits the permutation. However, if the normal or full mutation is passed down to the female, she is no longer at risk for POI. Additionally, downregulation of non-coding ribonucleic acids (nc-RNA) and Turner's syndrome have also been linked to POI(5,7). Genetic mutations leading to enzymatic deficiencies such as those concerning cholesterol desmolase, 17a-hydroxylase and aromatase can contribute to POF too(13,14).

ENVIRONMENTAL CAUSES & INFECTION

Malaria, tuberculosis, cytomegalovirus, mumps, varicella and other infectious diseases can also lead to POF(5). In addition, elevated levels of pro-inflammatory agents like cytokines and interleukin 6 have an undesirable influence on oocyte quality and abundance. Although these events have been described in ovarian inflammation, a direct link to the causation of POF has not been observed yet(15).

Smoking can also mediate the development of POI since the smoke has polycyclic aromatic hydrocarbons (PAHs) which upon binding to the aryl hydrocarbon receptor (AHR) on the oocyte, it will promote the activation of the Bax gene which is a pro-apoptotic gene. As a result, this stimulates the death of oocytes causing oocyte depletion and thus POI(13,16).

IATROGENIC

Radiotherapy, chemotherapy and surgical treatment (eg. oophorectomy) can cause permanent and irrevocable damage to the ovaries leading to POI(5). There have been case reports that the human papillomavirus vaccine (HPV4) can cause amenorrhea, oligomenorrhea, autoantibodies, depressed oestradiol levels and elevated FSH levels as well as premature menopause, thus creating a possible link between the vaccine and POF. Although, this may be due to the post-vaccination autoimmune phenomenon, not enough research and evidence has been presented to solidify the connection between the two(17,18).

POF AND ITS COMPLICATIONS

Since in POF, ovarian dysfunction is present, oestrogen is not being produced. Therefore this would lead to oestrogen deficiency and thus a decrease in bone marrow density. In addition, low free and total T levels seen in POI also contribute to a reduction in bone density. This increases the risk of such patients developing osteopenia, osteoporosis or easily fracturing a bone(5,7,19).

An increase in morbidity and mortality is also seen in patients with untreated and uncontrolled POF due to their risk of developing cardiovascular diseases such as atherosclerosis, hypercholesterolemia, strokes and ischaemic heart diseas(7).

Being diagnosed with POF can be devastating for many women, especially on an emotional level since their reproductive life span has been drastically decreased. These patients have been known to struggle with anxiety, stress, depression, relationship problems with fears of annulment, reduced self-esteem and a poor quality of life. Thus, apart from providing the patient with the necessary treatment, psychological support should be considered(7,20). However,although POI negatively impacts fertility, 10% of women with POI are able to conceive and carry to term since 25% of patients can ovulate spontaneously due to the ovaries' erratic function(7).

Undergoing a bilateral oophorectomy before the typical age of menopause would result in no ovarian function following the surgery, resulting in spontaneous surgical POI. This iatrogenic cause for POF has been linked to a reduced neurocognitive function, especially if the surgery is performed at a young age. This increases the patient's risk of developing Alzheimer's disease later on. However, evidence has shown that by administering hormone replacement therapy (HRT) as soon as possible following the surgery, decreases the decline in cognition and thus the risk for other neurological diseases(7,21).

Oestradiol is vital in maintaining outer hair cell function in the ear, and since oestradiol levels are reduced in POF, hearing is negatively impacted in these women. However, further studies on the impact of inner ear function in POF patients are required(22).

CORONAVIRUS DISEASE OF 2019 (COVID-19) AND POF

The respiratory, central nervous and cardiovascular systems are the main areas where COVID-19 infects and invades cells by binding to angiotensin-converting enzyme 2 (ACE 2) receptors(23).

Prolonged inflammation by COVID-19, termed as Long COVID, can also impact the reproductive system negatively due to the presence of ACE 2 in the ovaries which are vital for folliculogenesis, ovulation and luteal angiogenesis. Thus any alteration in ACE 2 activity and angiotensin II availability can easily lead to POF and infertility(23).

To date, there is one case report of a woman who has shown signs of infertility and oligomenorrhea after infection with COVID-19 the year previously(23). After ruling out any other possible causes for her symptoms, it was concluded that COVID-19 had led to POF by modulating ACE 2 expression in the ovaries(23).

TREATMENT AND MANAGEMENT OF POF

HRT, which is a combination of oestrogen and progesterone hormones, is recommended until the natural age of menopause (~50 years) in POF. This helps alleviate the effects and potential risks for certain diseases like atherosclerosis and osteoporosis due to oestrogen deficiency. Patients with a history of ovarian and breast cancer are advised against such treatment. In addition to oestrogen supplementation, adequate calcium intake, maintaining a healthy lifestyle and daily physical activity is advised(2,7,21).

Hormone Replacement Therapy

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Immunomodulation Therapy

This treatment is only viable if the underlying cause of POF is an autoimmune response resulting in ovarian dysfunction. In this case, corticosteroids and monoclonal antibodies are used for immunosuppression(5,12).

Dehydroepiandrosterone (DHEA) Supplementation

In the ovaries, DHEA promotes follicular steroidogenesis and oestradiol synthesis. When patients suffering from POF are given DHEA, it prevents miscarriages, increases their chances of conceiving and improves in-vitro fertilization (IVF) outcomes(5). However, patients having normal adrenal function should not be given DHEA supplementation(5,12).

Melatonin Supplementation

FSH, luteinising hormone (LH), androgen and oestrogen receptors are found in the pineal gland which is responsible for melatonin synthesis(5). Melatonin has been described as a time-keeping hormone due to its ability to control pituitary hormone secretions. Although it is believed that melatonin, which is also found in follicular fluid, supports folliculogenesis, reinstates fertility and prevents depression following menopause, further studies are required to determine this hormone's exact role in ovarian function(5,12).

In-Vitro Activation (IVA)

If a female with POF wants to start a family, apart from oocyte donation and in-vitro fertilisation, IVA is another option that allows the female to have her own genetically and biological children since intracellular signalling pathways responsible for folliculogenesis are manipulated by pharmacological techniques to recharge and activate residual dormant primordial follicles(24). Although, oocyte maturity is enhanced in IVA, this treatment becomes less effective the older the patient's age due to reduced oocyte quality(25).

Stem Cell Therapy

Although stem cells taken from different parts of the body cannot improve oocyte quality, they do

enhance folliculogenesis, local ovarian vascularization, and follicle and stromal cell proliferation. Stem cells also have the ability to decrease cell apoptosis and follicular atresia. Healthy and successful pregnancies have been reported in POF patients upon undergoing bone marrow-derived stem cell therapy(26).

Furthermore, similar results have been reported using platelet-rich autologous plasma (PRP) therapy which promotes ovarian rejuvenation. PRP has been proven to increase FSH, LH, oestradiol and AMH levels. As a result, this improves the fertility of POI patients(27).

Additionally, small extracellular vesicles obtained from stem cells also have the potential to restore ovarian function to a certain extent. These vesicles can activate phosphatidylinositol-3-kinase and protein kinase B (PI3K-AKT), sirtuin (SIRT) and SIRT7 signalling pathways that play a vital role in folliculogenesis, granulosa cell proliferation and apoptosis regulation.

CONCLUSION

The tendency of people to have children at an older age is increasing. As a result, a woman's reproductive life span would be shorter by the time she would want to have children. Therefore, one can only imagine how devastating it would be to be diagnosed with POF. Thus, if one begins to experience symptoms pointing to POI, it is important to contact the healthcare provider and get tested for POF and to discuss the possible treatments and complications that may arise. Furthermore, follow-up visits and monitoring patients with POF in a holistic approach is recommended.

Finally, although several treatments are available, further studies are needed to increase our understanding of the disease's aetiology, how Long COVID complications resulting in POF can be prevented and how treatments concerning melatonin supplementation, ovarian stem cell therapy and rejuvenation can be improved, to decrease the emotional and physical stress of women with POF.

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