Oxidative stress related Hallmarks of Premature Ovarian Insufficiency

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Premature ovarian insufficiency (POI) is a condition that arises from dysfunction or early depletion of the ovarian follicle pool accompanied by an earlier-than-normal loss of fertility in young women. Oxidative stress has been suggested as an important factor in the decline of fertility in women and POI. Genetic defects causing dysfunction in DNA repair machinery and mitochondria and leading to dysfunction of the host's antioxidant defences are likely to contribute to increased oxidative stress. Furthermore, an overactive immune system can lead to oxidative stress. On the other hand, iatrogenic POI, such as that induced by chemotherapy and radiotherapy, will result in increased oxidative stress due to tissue damage and apoptosis.

premature ovarian insufficiency | early menopause | ovarian ageing

1. Genetic Causes of POI

The role of a genetic contribution to the aetiology of POI is supported by the observation that in about 10–30% of idiopathic cases, a first-degree relative is also affected, as well as the observation that a woman with an affected mother is six times more likely to develop POI [1]. Genetic analyses of POI patients have identified many chromosomal abnormalities, single gene mutations and genetic polymorphisms from multiple different biological pathways associated with POI development [2]. However, the genetic defects investigated thus far have been shown to contribute only a small percentage towards the development of POI [3]. The diverse aetiology of POI is in line with these findings and suggests the pathogenesis of non-syndromic POI is unlikely to be caused by a single gene or genetic defect but rather supports the view of POI being a heterogeneous genetic disease involving the interaction of multiple genetic defects and environmental factors [4]. Therefore, current research is focused on increasing the understanding of the genetic basis of idiopathic POI. This information will provide greater insight into POI pathogenesis and allow for the identification of biomarkers which may have the ability to predict early onset, providing women at risk with the opportunity to plan their families earlier and perhaps delay the onset of POI by modifying known risk factors.

As a result of recent technological advances, knowledge of the molecular basis and pathophysiology of idiopathic POI is rapidly growing with a rapidly increasing number of gene variants associated with POI. A recent review [5] highlights 107 different genes associated with POI and suggests that approximately 78% of the genes are associated with ovarian development and meiosis. New genetic technologies based on next-generation sequencing have highlighted defects in the various hormones related to folliculogenesis, reproductive hormones and mitochondria function [6]. However, there is now a growing number of genes that are implicated in DNA

replication and repair, meiosis and chromosome stability that are associated with the age of menopause and POI [7]. Although the exact mechanism of how defects in DNA repair pathways and genomic instability contribute towards POI development is not yet known, it is likely that an accumulation of DNA damage and chromosomal instability in the ovary would lead to accelerated follicle atresia (which is the breakdown of the ovarian follicles, oocyte, granulosa cells and internal and external theca cells), therefore predisposing women to POI. Given that DNA damage and repair pathways are significant contributors towards POI pathogenesis, this also provides a tangible focus for potential targeted treatments [1], including lifestyle interventions such as diet and exercise. Given the already known different genetic backgrounds to the development of POI, this personalised medicine approach to match the molecular cause with potential therapeutic treatment is an important aspect to consider for the future. The role of oxidative stress and its interactions with genetic factors will be an important area of research in the future.

2. Autoimmunity and the Gut Microbiota in POI

The human ovary is commonly the target of autoimmune attacks leading to ovarian dysfunction. An estimated 20% of women with POI have an autoimmune disease comorbidity. The most common are autoimmune disorders of the thyroid, such as hypothyroidism, Hashimoto thyroiditis, and Grave's disease [8]. The second most common autoimmune disorders are related to the adrenal glands [9][10]. Furthermore, almost 50% of women with POI are positive for at least one anti-ovarian antibody. The mechanism of autoimmune ovarian damage may be a result of abnormalities in cellular immunity [11]. This includes elevated levels of peripheral blood T-lymphocytes and the decreased number and activity of natural killer cells. Additionally, women with POI are reported to have irregularities in their levels of cytotoxic T lymphocytes and a reduced capacity for dendritic cells to aggregate with T-lymphocytes. Furthermore, it was reported that regulatory T cells (Treg) play an important role in the pathogenesis of POI [12]. In one study, it was found that there is a reduction in the number of effector Treg cells in the peripheral blood of POI patients suggesting an overactive immune system in POI [12].

The gut microbiota has an important role in the modulation and maturation of the immune system. The majority of the bacteria that colonise the gut fall within the *Bacteriodetes* and *Firmicutes* phyla, and the balance between these two phylum are important in maintaining gut homeostasis. Additionally, peptides produced from some bacterial species that colonise the gut are known to mimic molecular patterns of human tissue, resulting in a cross-reactive immune system and autoimmunity [13]. Moreover, gut dysbiosis or imbalance of the bacterial composition of the gut can activate the adaptive immunity and upregulate the innate immunity and production of autoantibodies leading to increased inflammation.

A recent study has shown that the gut microbiota was different between women with POI and healthy women [14]. Specifically, women with POI had a greater abundance of phylum *Bacteroidetes*, genera *Butyricimonas*, *Dorea*, *Lachnobacterium* and *Sutterella*. On the other hand, Phylum *Firmicutes*, genera *Bulleidia* and *Faecalibacterium* were more abundant in healthy women. The study also found that the differences in the gut microbiome of women with POI were associated with their sex hormones. In the study, oestrogen levels were significantly negatively correlated with *Bacteroidetes* and positively correlated with *Firmicutes* and *Faecalibacterium*. On the other hand,

Follicle Stimulating Hormone (FSH) was significantly positively correlated with *Bacteroidetes* and negatively correlated with *Firmicutes*. Luteinising Hormone (LH) was significantly positively correlated with *Bacteroidetes*/*Firmicutes* ratio. A higher ratio of *Bacteriodetes* to *firmicutes* in women with POI indicates an imbalance in the bacterial composition and increased dysbiosis and inflammation. More recently, a study found a significantly increased abundance of genus *Eggerthella* in the faecal samples of women with POI compared to healthy women [15]. *Eggerthella* is a genus that is known to be a normal part of the microbiota but has also been linked with systemic inflammation and gastrointestinal infections [16]. Furthermore, the study found that the abundance of *Eggerthella* was not significantly different between healthy women and women with POI that were on hormone replacement therapy for more than one year [15].

Evidence suggests that there is a complex but important relationship between gut microbiota composition and sex hormones such as oestrogen [17]. Specifically, non-ovarian oestrogens in male and post-menopausal women were associated with bacterially produced β-glucuronidase enzymes [18]. β-glucuronidase is reported to block the binding of oestrogen to glucuronic acid. As a result, the levels of unconjugated/active oestrogen increase [17]. However, the influence of the gut microbiota on ovarian oestrogen and POI is not clear.

3. Iatrogenic POI: Chemotherapy and Radiotherapy

Iatrogenic POI is becoming more of an important issue as survival after treatment of malignancy through surgery, radiotherapy, and chemotherapy continues to improve [19]. Chemotherapy induces apoptosis of mature ovarian follicles, causing damage to ovaries by impairing follicular maturation or primordial follicle depletion [19]. Histological studies have shown fibrosis, vascular damage and reduced follicle numbers after chemotherapy. Chemotherapy-induced ovarian damage is dependent on the age of the patient, type of agent and the women's ovarian reserve [20]. Older women have a higher incidence of ovarian failure after chemotherapy and an increasing likelihood of permanent infertility compared to younger women [20]. In the case of radiotherapy, irradiation of the hypothalamus, pituitary gland and pelvis is known to cause POI [21]. The application of a radiation dose of 14.3 Gray to an ovary of a woman younger than 30 years can lead to irreversible POI, while lower doses can cause reversible ovarian dysfunction [21].

Abnormalities in immunity and the gut microbiota seen in POI as well as environmental factors that induce POI, will result in increased tissue damage, inflammation and the presence of oxidative stress.

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