Review
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The role of mitochondria in premature ovarian failure: A review

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Abstract Premature ovarian failure (POF) is used to describe women under 40 years old with amenorrhea, hypergonadotropic hypogonadism, and infertility as a result of cessation of ovarian function. It has been reported that almost 20% of women who consult for infertility have signs of premature ovarian ageing. The mitochondrial disorder is one of the critical agents in premature menopause and the occurrence of POF. Due to the maternal inheritance of POF along with the dependence of folliculogenesis upon the mitochondrial biogenesis and bioenergetics, it has been suggested that a generalized mitochondrial defect is likely involved in POF. A fuller understanding of the mitochondrial role in POF could contribute to the better management of women with POF in the future. The aim of this review was to illustrate the role of mitochondria in POF. The oocyte mitochondrial DNA (mtDNA) content in women with diminished ovarian reserve is significantly lower than women with normal ovarian reserve. It has been evidenced that mitochondrial genetic disorders and mitochondrial oxidative stress are associated with POF. According to the maternal inheritance of mtDNA, genetic testing should be performed to detect mtDNA mutations involved in POF before starting treatment strategies. If these mutations are present, it could suggest that healthy mitochondrial transfer during assisted reproductive technology should be used to prevent the transmission of POF caused by mtDNA mutation to the female offspring. Future strategies aimed at treatment of POF-related infertility should take into account the significance of the oocyte mitochondrial role in the occurrence of this disorder.
Keywords premature ovarian failure, low ovarian reserve, mitochondria, infertility

Introduction

Premature ovarian failure (POF), also known as premature ovarian insufficiency, is used to describe women under 40 years old with amenorrhea, hypergonadotropic hypogonadism, and infertility as a result of cessation of ovarian function.[1,2] It has been estimated that POF affects 1 in 100 women under 40 years, 1 in 1000 women under 30 years, and 1 in 10,000 of women under 20 years.[1,3] There is a higher risk of early menopause in women with poor response to ovarian stimulation undergoing assisted reproductive technology (ART). The results of a 10-year follow-up of women younger than 40 years of age with poor ovarian response in IVF cycles indicated that 11% of them developed early menopause and 3% of them developed POF.[4]

In the large majority of cases, ovarian failure is initiated after puberty.[5] Secondary amenorrhea associated with premature depletion of ovarian follicles or arrest of folliculogenesis occurs in women with post-pubertal POF. The clinical characteristics of patients with POF include flushes, heat intolerance, irritability, night sweats, sleep disturbance, palpitations, fatigue, anxiety, depression, hair coarseness, infertility, vaginal dryness, and decreased libido.[3] Furthermore, POF and a long-term delay in estrogen replacement therapy may result in early-onset osteoporosis. Deficiency of sex hormones is considered a crucial risk factor for metabolic, cardiovascular, or neurological diseases.[3] Hormonally, POF is characterized by low levels of estrogens and inhibins and high levels of LH and FSH.[3]

Estrogen/progestin preparations are effective to treat hormonal deficiency in patients with POF. It has been reported that almost 20% of women who consult for infertility have signs of premature ovarian ageing.[6] Although, restoration of fertility cannot presently be done if the diagnosis of POF is made after the full depletion of the follicular pool, early diagnosis by genetic testing may provide the opportunity for fertility preservation. At present, ovum donation is the only option available for treatment of infertility in women with absence of ovarian reserve.[3]

Although in majority of cases, the underlying cause of POF is not identified, the known causes include: genetic aberrations; autoimmune ovarian damage; iatrogenic complications following surgery, radiation therapy, and chemotherapy; and environmental factors such as viral infections and toxins.[7] Furthermore, several studies have reported an association between mitochondrial diseases and POF in both animals and humans.[8–11] Oocyte mitochondrial depletion has been observed in patients with poor recovery rates of mature oocytes after ovarian hyperstimulation and in women with ovarian insufficiency.[12,13] Due to the maternal inheritance of POF along with the dependence of folliculogenesis upon the mitochondrial biogenesis and bioenergetics, it has been suggested that a generalized mitochondrial defect is likely involved in POF.[14] The aim of this review was to illustrate the role of mitochondria in POF. A fuller understanding of the mitochondrial role in POF could contribute to the better management of women with POF in the future.

Mitochondria and Ovarian Function

Mitochondria are the site of cellular respiration/oxidative phosphorylation that produce the energy needed for all aspects of cellular function.[15] The oxidative phosphorylation system of mitochondria consists of five multi-enzymatic complexes: complexes I–IV of the electron transport chain and complex V (Adenosine triphosphate (ATP) synthase).[6]

It has been reported that disruption of mitochondrial oxidative phosphorylation in mouse oocytes leads to abnormalities in the meiotic spindle and the potential reduction of embryonic preimplantation.[16] Mitochondria functions directly affect several aspects of the reproductive process including oocyte quality, fertilization process, and embryo development.[17] The mitochondrial biogenesis and bioenergetics have an important role in maturation of the oocyte and embryonic development.[18,19] Moreover, the results of studies showed that the oocyte mitochondrial content could affect fertilizability of the oocyte.[17] Mature oocytes need large number of mitochondria and it has been shown that the mitochondrial DNA (mtDNA) content of an oocyte is strictly related to the probability of zygote development.[17,20]

Much of the endogenous reactive oxygen species (ROS), as a toxic by-product of oxidative phosphorylation, is generated in the mitochondria. Mitochondrial dysfunctions lead to inhibition of oxidative phosphorylation and increased ROS generation that can induce apoptosis.[6] Mitochondria are distributed and localized in regions of the ooplasm that require higher ATP levels for an energy-consuming event, resulting in cytoplasmic and nuclear maturation of oocytes including germinal vesicle breakdown, and assembly and disassembly of microtubules for the formation of meiotic spindles.[19,21,22]

It seems that mitochondrial biogenesis plays a key role in determining the initial size of the ovarian follicular pool during embryonic life.[23] Age-associated deterioration of mitochondria negatively influences ovarian reserve, segregation of chromosomes, and embryo competence.[24] It is well-known that female germline aging is accompanied by mitochondrial dysfunction correlated with reduced levels of oxidative phosphorylation and ATP.[25] Ovarian ageing is correlated with reduced mtDNA content in oocytes.[6] Older women or women with diminished ovarian reserve (DOR) have significantly lower oocyte mtDNA content compared to younger women or women with normal ovarian reserve.[12,26–28] According to the findings of study by Hamatani et al., the expression patterns of genes related to mitochondrial functions and oxidative stress show an age-associated alteration on mouse oocytes.[29] In women with ovarian ageing, the impaired quality of the oocytes associated with insufficient mtDNA content can result in premature biogenesis of mitochondria and embryonic development failure.[6] Research on mice have shown that mitochondria are involved in follicle pool exhaustion with ageing by affecting the initial size of the follicular pool and the rate of follicular atresia.[6] In various mammalian species, including human, the apoptotic process is involved in germ cell elimination at all oogenesis stages and in depletion of ovarian reserve.[30] This process in the mammalian oocytes involves both the intrinsic mitochondrial pathway as well as the extrinsic death receptor pathway.[30,31] It has been reported that mitochondria and B-cell lymphoma 2 (Bcl-2) family members are involved in ovarian apoptosis.[32] Taken together, these findings strongly support the role of mitochondria in POF.

Mitochondrial Genetic Disorders and Incidence of POF

Several human diseases have been identified that are associated with mtDNA mutations.[33] The higher mutation rate of mtDNA (approximately 25 times) compared to that of nuclear DNA is due to the proximity of mtDNA with the respiratory chain, the absence of histones, and efficient DNA repair mechanisms.[34] It is known that oocytes have the largest mitochondrial genome content of an organism.[17] However, the oocyte mtDNA content in women with DOR is significantly lower than in women with normal ovarian reserve.[6] It has been demonstrated that some cases of POF may be due to follicular atresia and eliminating primary oocytes with harmful mtDNA mutations.[35]

The human mitochondrial genome contains genes coding for 13 polypeptides, 2 rRNAs, and 22 tRNAs.[36] Deficiency in the mitochondrial tRNA (mt-tRNA) genes is known to be an important factor in clinical disease.[37] Ding and his colleagues assessed the association between mt-tRNA mutations and premature ovarian insufficiency. Their results indicated that levels of FSH, LH, and ROS production were increased in POF compared to control groups. In addition to estradiol, total testosterone levels and ATP content showed a significant reduction in the POF group. Moreover, a high incidence of mt-tRNA mutations was observed in these patients. The A4435G ($tRNA^{Met}$), C3303T ($tRNA^{Leu}$), G5821A ($tRNA^{Cys}$), T4363C ($tRNA^{Gln}$), and A15951G ($tRNA^{Th}$) mutations were recognized as pathogenic mutations related to premature ovarian insufficiency. However, their outcomes revealed that the mt-tRNA mutation itself was inadequate to cause the clinical disorders, and other risk factors may also contribute to POF development.[38]

In each human cell, mtDNA are replicated by DNA polymerase gamma (pol γ), which is a holoenzyme consisting of a 140-kDa catalytic subunit (POLG) and a dimeric form of 52-kDa accessory subunit (POLG2). The POLG subunit has three main functions including DNA polymerase, 3′-5′ exonuclease, and 5′ dRP lyase activities.[39, 40] After identifying the first disease associated with POLG gene mutation, progressive external ophthalmoplegia (PEO), association with other diseases and syndromes such as Alpers syndrome, ataxia-neuropathy syndromes, Charcot-Marie-Tooth disease, and idiopathic Parkinsonism were discovered.[11, 41, 42]

The Y955C mutation in POLG is commonly associated with autosomal dominant PEO. Due to this mutation, many women with PEO, present indicatives of POF.[9, 11] Luoma et al., in a clinical and molecular genetic study, investigated female patients with early menopause and used PEO as a POLG mutation marker. They showed that the co-segregation of premature menopause with POLG mutations was significant and suggested POLG-associated PEO could become an important method in understanding the mechanisms of oxidative stress and mitochondrial dysfunction in premature menopause.[9]

In 2006, a study investigated three-generation pedigree with familial premature menopause associated with PEO which had apparent maternal transmission of disease.[11] The proband, her mother, and her maternal grandmother all presented with PEO and subsequently developed POF at ages of 28, 35, and 32 years, respectively. The researcher found that PEO disease can be distinguished via a dominant Y955C mutation in the POLG gene and concluded that the variation of the POLG mutation can affect the age of women's menopause.[11] However, Tong et al. screened the genomic DNA of patients with POF for the 5 POLG mutations and concluded that these POLG mutations cannot be prevalent genetic etiologies for POF.[43] In a small size study on the etiology of POF in young girls, a pediatric endocrinologist found that these patients had different etiologies compared to those cases seen in adults which included congenital disorder of glycosylation syndrome and mitochondrial

diseases. However, in their study only one POF patient was diagnosed with a mitochondrial disorder. The authors suggested a larger size survey should be done for further clinical recommendations among these cases.[44]

Chen et al. identified two different homozygous missense mutations with variants c.404G>A (p.R135Q) and c.605G>A (p.R202H) in four young females from two independent families. These mutations were considered a novel genetic cause of POF in adolescents. This study showed that MRPS22 deficiency, especially in the somatic cells of the ovary, had no effect on fertility but that its mutation in germ cells results in the absence of germ cells and infertility in a Drosophila model. These findings collectively identify that MRPS22 is required for reproduction and ovarian development and may contribute to ovarian dysfunction.[45]

Cytochrome c oxidase (COX) is one of the main enzymes in the electron transport chain of mitochondria. A mutation in the gene encoding mitochondrial COX 1 (MT-CO1) reduces COX activity and ATP production, which is correlated with dysfunction of mitochondria, increase in apoptosis,[46] and follicular depletion in early adulthood, and is followed by POF.[47] With this hypothesis, Zhen et al. screened the mitochondrial genome of patients with POF and healthy females. They observed a significant incidence of MT-CO1 missense mutations in POF patients. Also, there were significant increases in FSH, LH, and E2 levels, and a significant decrease in ovarian volume and ATP levels compared to the control group. They proposed that MT-CO1 gene mutations may be one of the causals in POF.[48] Further molecular studies are required to uncover other genetic mitochondrial disorders involved in POF. Mitochondrial genetic mutations known to be involved in POF are shown in Table 1.

Mitochondrial ROS Production and Incidence of POF

Mitochondria are responsible for the generation of most of a cell's energy and their dysfunction lead to increased levels of ROS and low ATP levels.[49] Accumulation of ROS leads to oxidative stress, which can activate apoptosis in the majority of germ cells in the ovary.[50–52] Furthermore, pathologic accumulation levels of ROS in ovaries may result in tissue inflammation including oophoritis, necrosis, and apoptosis.[53] On the other hand, increased levels of ROS induce lipid peroxidation and cause increased nuclear DNA damage,[54] and mitochondrial DNA nucleotide changes.[55] Some of the female reproductive disorders such as endometriosis, polycystic ovary syndrome, POF, and infertility are due to oxidative stress.[56,57]

It has been well-known that POF is correlated with some mitochondrial disorders, and a correlation between idiopathic POF and increased oxidative stress has been described.[58,59] Propionic acidemia is an autosomal recessively inherited inborn error of propionate metabolism that is caused by a deficiency of the mitochondrial enzyme propionyl-CoA

Table 1. **Summary of mitochondrial genetic mutations involved in the POF.**

Authors	Species	Gene	Results
Luoma et al. (2004)	Human	POLG	POLG mutation is involved in the etiology of parkinsonism, PEO, and premature menopause. Most women with PEO experienced early menopause before age 35.
Pagnamenta et al. (2006)	Human	POLG	The Y955C mutation in POLG can result in mtDNA depletion. POLG mutations can cause POF and parkinsonism.
Tong et al. (2010)	Human	POLG	These POLG mutations including Y955C and R943H (c2767G>A, c2828G>A, c2857C>T, c2864A>G, and c2869G>T) are not a prevalent genetic etiology for spontaneous 46, XX POF.
Brauner et al. (2015)	Human	NR5A1, BMP15, GDF9, and NOBOX	In two cases, an NR5A1 gene mutation was detected in the pediatric population with POF.
Zhen et al. (2015)	Human	MT-CO1	A high incidence of MT-CO1 missense variants (MT-CO1 c.790A>G, MT-CO1c.802T>C, MT-CO1 c.1165A>G, and MT-CO1 c.667G>T) was identified in POF patients that could lead to reduction of COX activity, decrease in ATP level, and mitochondrial dysfunction. MT-CO1 gene mutation may be causal in POF.
Chen et al. (2018)	Human	MRPS22	Missense mutations in MRPS22 [variants c.404G>A (p.R135Q) and c.605G>A (p.R202H)] lead to autosomal recessive inheritance of POF. No changes were detected in mRNA expression or protein levels of MRPS22, in POF patient-derived fibroblasts. Also, defects in mitochondrial oxidative phosphorylation or rRNA levels were not detected, which suggests a non-bioenergetic or tissue-specific mitochondrial defect.
	Mouse		Heterozygous *Mrps22* knockout mice revealed no signs of abnormalities and were fertile. Embryonic lethality was observed in heterozygous *Mrps22* knockout mice.
	Drosophila		The mRpS22 deficiency in ovarian somatic cells had no effect on fertility, whereas mRpS22 deficiency in germ cells resulted in absence of gametes and infertility, demonstrating a cell-autonomous requirement for mRpS22 in development of germ cell.
Ding et al. (2019)	Human	mt-tRNA	Mitochondrial dysfunction, lower level of ATP production, and high levels of ROS were detected in POF patients carrying mt-tRNA mutations including the A4435G (tRNAMet), C3303T (tRNALeu), G5821A (tRNACys), T4363C (tRNAGln), and A15951G (tRNATh). These mt-tRNA mutations may have active roles in the pathogensis and progression of POF.

POF, premature ovarian failure; POLG, Mitochondrial DNA polymerase γ; PEO, progressive external ophthalmoplegia; mtDNA, mitochondrial DNA; MT-CO1, mitochondrial cytochrome c oxidase 1 gene; COX; cytochrome c oxidase; MRPS22, mitochondrial ribosomal protein S22; mt-tRNA, mitochondrial tRNA.

carboxylase. This enzyme plays an important role in catabolizing branched-chain amino acids, odd-chain fatty acids, cholesterol, and other metabolites.[60] Lam et al. reported a 45-year-old patient who had been diagnosed with propionic acidemia and experienced severe renal failure and POF.[61] Mitochondrial dysfunction and increased oxidative stress have been considered as possible mechanisms for these complications.[61]

As a study on mice oocytes has demonstrated, there is an age-associated alteration in the expression patterns of genes involved in mitochondrial functions and oxidative stress.[29] There have been several studies on the role of mitochondrial ROS in POF. Some mitochondrial mutations increase the ROS level and decrease ATP production in germ cells, and consequently lead to disruption of normal oogenesis and accelerated germ cell apoptosis, ultimately leading to POF.[62] As oocytes have greater number of mtDNA copies than any cell in the body, pathological levels of ROS cause mtDNA damage, and mitochondria with nucleotide DNA changes produce more free radicals.[55] The results of several studies have shown that mutations in the ATPase 6 gene, which maintains mitochondrial genome stability and integrity, are associated with excessive ROS production and several disorders.[63,64] Venkatesh et al. found that the mutation of the mitochondrial ATPase6 gene can lead to a higher ROS level in ovarian cells. The high ROS level can damage the mtDNA and membrane as a result, and may cause premature cessation of ovarian function by interruption of cell growth, expansion of atresia, and eventually germ cell apoptosis.[59] Moreover, it has been shown that in patients with ovarian ageing and POF, the ROS level in granulosa cells is extremely high.[65]

According to these findings, mitochondrial ROS production and oxidative stress may influence normal oogenesis and ovarian reserve through activation of the apoptotic process, increased follicular atresia, induction of ovarian inflammation, and development of mtDNA disorders that can lead to POF.

Approaches to Fertility Preservation in Patients with POF by Influencing the Function of Mitochondria

Due to the cumulative adverse effects of POF over time, making a timely diagnosis and initiating appropriate strategies are important for managing the symptoms, supporting patients' emotional needs, and reducing risk.[3] Hormone replacement therapy is the most popular treatment for POF-related symptoms, but there are some serious side-effects for this treatment, including increased risks for breast and endometrial cancers.[66] Other treatments for POF involve influencing the function of mitochondria. Coenzyme Q10 is one of these treatments studied by Ben-Meir and their colleagues in aged mice. The results of this study showed that Coenzyme Q10 supplementation could enhance the activity of mitochondria and amending the mitochondrial gene expression. Consequently, the Coenzyme Q10 supplementation can prevent depletion of ovarian reserve and POF.[25]

Antioxidants are another treatment that can postpone POF. Melatonin is known as a highly effective antioxidant and potent ROS scavenger[67] that protects cells against oxidative stress and diminishes the harmful effects of ROS.[68] Recently, it has been reported that melatonin may be beneficial for reducing and preventing POF in patients who receive chemotherapy treatment.[69] Melatonin improves POF by reducing oxidative stress damage that was mediated by the SIRT1 signaling pathway.[70] Furthermore, it has been demonstrated that melatonin prevents primordial follicle depletion in cisplatin-treated mice through suppression of the phosphorylation of PTEN/AKT/FOXO3a pathway members.[71] Although, the specific mechanisms underlying the actions of melatonin protection against ovarian follicle death are not yet clearly understood, it is well-known that its antioxidant effect can maintain the follicular morphology and growth, and can affect oxidative stress response by influencing ROS and glutathione production, mitochondrial activity, and apoptosis in follicular cells.[67,72]

Studies have shown that the use of herbal medicine is especially important in POF.[73–75] Cistanches Herba is a parasitic plant that is used in traditional Chinese medicine (TCM)[76] for treatment of different diseases including female infertility by increasing sex hormone levels, though the exact regulating mechanisms are unknown.[77] Cistanches Herba can prevent cisplatin-induced apoptosis which causes POF in mice. Cistanches Herba upregulated mitofusin-2 (a mitochondria dynamin-like GTPase) expression and altered mitochondrial membrane structure via interaction with Bcl-2/Bax proteins.[78] Dendrobium officinal polysaccharides (DOP), which are one of the main active components of Dendrobium officinal, another TCM, has recently been found to show good efficacy in producing anti-oxidative and anti-inflammatory effects[75,79] and may have the potential to the treatment of POF. Wu et al. found that DOP improves the function of mitochondria, thus increasing the body's antioxidant capacity and protecting the body from POF effects on mice. Their results also have shown that DOP could decrease the symptoms of POF, by increasing the body's antioxidant capacity, balancing inflammation, and improving mitochondrial function. The potential mechanism signaling pathway may work through regulating the nuclear factor-κB and p53/Bcl-2.[80] Zuogui Pills (ZGP) are a component in TCM used in the treatment of POF, increasing proliferation and decreasing apoptosis in the ovarian cells.[81] The therapeutic effects of ZGP on the treatment of POF due to chemotherapy were investigated by Peng et al. They illustrated that the number of follicles, ovarian ultrastructures, and the estrous cycle notably ameliorated in rats with POF. Furthermore, ZGP increased the FSH levels and decreased estradiol levels in serum. Moreover, it declines Bax, cytochrome c (Cyt-c) on both gene and protein levels and elevates Bcl-2 gene expression and protein levels. They proposed that ZPG can mediate POF through the balance of Bax/Bcl-2 in ovaries and suppression of mitochondria-dependent apoptosis.[75]

Women with early identified ovarian ageing can have good reproductive potential, and spontaneous pregnancy remains a choice for women with adequate ovarian reserve who are ready to have a child.[4] There are a number of treatment options available for women who are infertile due to POF which include ovarian cortical tissue cryopreservation, oocyte, or embryo cryopreservation; oocyte, or embryo donation; and adoption. These treatment options can recommended before or during ovarian failure.[82] Since mitochondria act as a vehicle for mtDNA transmission to subsequent generations, evaluation of mitochondrial disorders prior to any protocol of oocyte reconstruction would allow selection of healthy fertilizable oocytes.[83] Although, Kasteren et al. analyzed the incidence of familial cases of POF and concluded that

in these families the risk of other females developing POF will depend on the modes of inheritance and transmission, and further demonstrated that mitochondrial inheritance is not one common mode among their studied families.[84] However, different research teams found other conditions that can be investigated for finding occurrence of POF related to mitochondrial genetic diseases, and showed a correlation between mitochondrial diseases and POF.[9,48] It has been reported that mitochondrial transfer into an oocyte can lead to prevention of apoptosis in this cell and promotion of embryonic development.[85,86] Mitochondrial supplementation of oocytes is a strategy for overcoming mtDNA deficiency and improving developmental competence. Furthermore, supplementation of oocytes exhibiting mtDNA deficiency with autologous mitochondria can improve the outcome of *in vitro* fertilization.[83]

Conclusions

The mitochondrial disorder is one of the critical agents in premature menopause and the occurrence of POF. Mitochondrial ROS production and mitochondrial genetic disorders have been reported as causes of POF. Due to the cumulative adverse effects of POF over time, making a timely diagnosis and initiating appropriate strategies are important for managing symptoms, supporting patients' emotional needs , and reducing risk. The early diagnosis of POF can provide the opportunity to make good reproductive decisions such as having kids earlier and freezing oocytes or embryos. Given the maternal inheritance of mtDNA, genetic testing should be performed to detect mtDNA mutations involved in POF before starting treatment strategies. If these mutations are present, healthy mitochondrial transfer during ART should be used to prevent the transmission of POF caused by the mtDNA mutation to the female offspring. A fuller understanding of the mitochondrial role in POF could contribute to the better management of women with POF in the future. Future strategies aimed at treatment of POF-related infertility should take into account the significance of the oocyte mitochondrial role in the occurrence of this disorder.

Conflict of interest

All authors declare that there is no known conflict of interest regarding this publication.

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