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Invited Review

Epidemiology, Genetic Etiology, and Intervention of Premature Ovarian Insufficiency

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Abstract

Premature ovarian insufficiency (POI) is a highly heterogeneous reproductive disorder in both its etiology and clinical presentation. The epidemiological characteristics of POI suggest that its occurrence likely involves a combination of genetic and environmental factors. Deciphering the pathogenic mechanisms of POI is crucial for improving reproductive outcomes as well as managing the long-term complications associated with ovarian dysfunction. Recent studies expand the list of POI causal genes and promote the viability of genetic diagnosis. However, whole exome sequencing studies in large-scale POI cohorts and genome-wide association studies on the age at natural menopause have uncovered a complex genetic architecture underlying POI that includes monogenic and oligogenic inheritance modes, emphasizing the difficulties in genetic diagnosis, especially for the isolated cases. Moreover, our understanding of the physiology of ovarian aging has greatly benefited from recent advances in multiomics analysis, expanding our perspective on the pathogenic mechanisms and potential targeted therapeutic strategies for POI. In this review, we summarize the epidemiological characteristics of POI, as well as progress in genetic and epigenetic etiologies, and discuss advances in pharmacology and material science that will likely contribute to new interventions for ovarian aging. Finally, this review offers new insights into prospects for early diagnosis and treatment of POI, while identifying persistent challenges and potential solutions to be addressed through future research.

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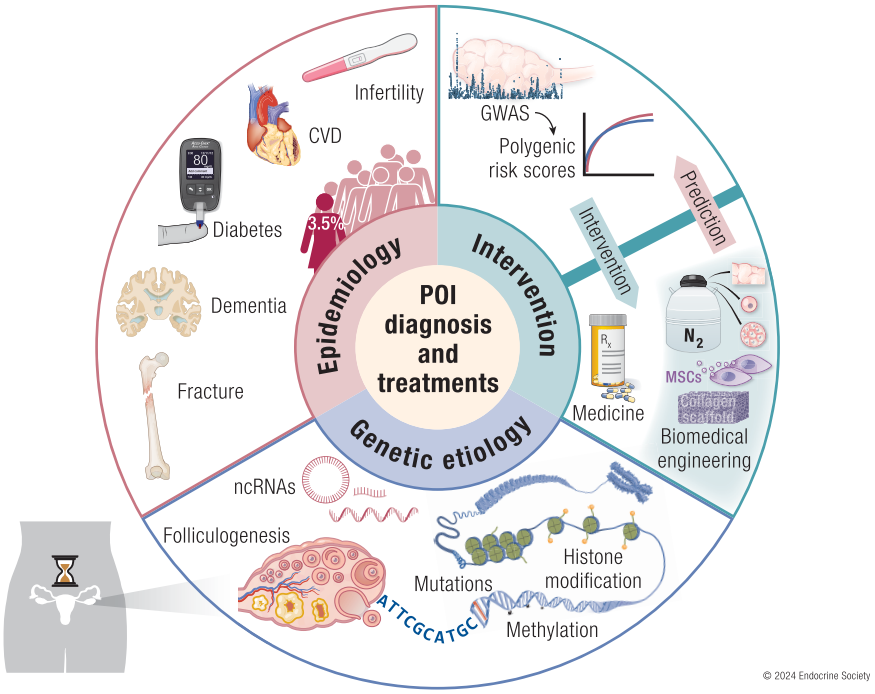
Graphical Abstract



Key Words: premature ovarian insufficiency, epidemiology, genetics, epigenetics, intervention

Abbreviations: AFC, antral follicle count; AMH, anti-Müllerian hormone; ANM, age at natural menopause; ART, assisted reproductive technology; CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; DOR, diminished ovarian reserve; DSB, double-strand break; FA, Fanconi anemia; FSH, follicle-stimulating hormone; GC, granulosa cell; GWAS, genome-wide association study; hAEC, human amniotic epithelial cell; hUC-MSC, human umbilical cord–derived mesenchymal stem cell; HDAC, histone deacetylase; HR, hazard ratio; HRT, hormone replacement therapy; IVA, in vitro activation; LoF, loss of function; LRPPRC, leucine-rich pentatricopeptide repeat containing protein; MR, Mendelian randomization; MSC, mesenchymal stem cell; OXPHOS, oxidative phosphorylation; OTC, ovarian tissue cryopreservation; OTT, ovarian tissue transplantation; PGC, primordial germ cell; PGS, polygenic score; POI, premature ovarian insufficiency; RRSO, risk-reducing salpingo-oophorectomy; SA, secondary amenorrhea; SC, synaptonemal complex; SNP, single nucleotide polymorphism; WES, whole exome sequencing.

ESSENTIAL POINTS

- The global average prevalence of premature ovarian insufficiency (POI) is 3.5%, but varies among regional populations potentially due to genetic and environmental differences associated with race, geographic location, socioeconomic status, and education level
- Although fertility is severely impaired in patients with POI due to accelerated follicular loss, early recognition of POI risk and obtaining mature oocytes from the remaining follicles can improve reproductive outcomes
- Whole exome sequencing has accelerated the identification of POI causal genes, especially in processes from primordial germ cell development to follicle maturation, although genetic diagnosis remains difficult due to a lack of a definitive genotype–phenotype relationship
- Growing evidence from increasingly large cohort studies suggest that POI has characteristics of oligogenic or polygenic architectures
- Epigenetic modifications are involved in both physiological and pathological ovarian aging and may serve as potential biomarkers or therapeutic targets for POI
- Recent advances in the genetic and epigenetic etiologies of POI, combined with aging- and immunity-related biomarkers of the ovarian microenvironment, together enable construction of increasingly powerful predictive models of POI
- Standard hormone replacement therapy, in vitro follicle activation, stem cell transplantation, ovarian microenvironment remodeling, as well as improved techniques in fertility preservation offer both opportunities and challenges for treating POI

Premature ovarian insufficiency (POI), also referred to as primary ovarian insufficiency, is a reproductive disorder arising from exhaustion of the ovarian follicles before age 40 (1). The diagnostic criteria for POI, according to the guidelines of European Society of Human Reproduction and Embryology (ESHRE) (2) and National Institute for Health and Care Excellence (NICE) (3), include menstrual disturbance (such as primary amenorrhea, oligomenorrhea, or secondary amenorrhea (SA) for at least 4 months) and elevated follicle-stimulating hormone (FSH) levels exceeding 25 IU/L or 30 IU/L, respectively, measured on 2 different occasions at least 4 weeks apart (2, 3). Moreover, clinicians also recommend that POI should be considered when a woman presents with new-onset irregular menses or amenorrhea and possibly vasomotor symptoms, in order to prevent delayed diagnosis and treatment (1).

The POI prevalence ranges from 1% to 3.7% in different populations, and can be affected by race, geographic location,

socioeconomic status, and education level (4-7). POI not only poses challenges to fertility but can also increase the risk of age-related diseases. Comprehensive investigation into its etiology is therefore crucial for timely recognition, reproductive management, and treatment of POI, as well as to reduce risk of long-term complications. Despite its prevalence and broad impacts on affected individuals and families, the pathogenesis of POI remains poorly understood.

The etiologies of POI are complex, and include genetic, epigenetic, immune, and iatrogenic factors. In the last 2 decades, advances in high-throughput sequencing, coupled with refinement of the human reference genome have significantly advanced our understanding of the genetic etiology of POI. At present, more than 100 POI causal genes have been reported. However, despite guidelines and reviews about POI that emphasize the importance of genetic diagnosis (1, 2), our perspective of the genetic landscape of POI is still incomplete. Restricted by the technical limitations of whole exome sequencing (WES) for identifying variants in noncoding regions, along with the inability to fully and accurately recapitulate the impact of pathogenic variants on the establishment and depletion of human ovarian reserves in vitro or in animal models, the genetic architecture of POI remains unclear. Factors like incomplete penetrance of heterozygous variants, oligogenic modes, and gene–environment interactions further complicate the picture, and require further research.

Moreover, clinical diagnosis of POI is often too late for effective intervention, with hormone replacement therapy (HRT) and assisted reproductive technologies (ARTs) serving as the most common options among limited interventions (1). However, recent advances in machine learning and artificial intelligence have facilitated development of predictive models of age at menopause, based on genome-wide association study (GWAS) data (8), and evaluative models of ovarian reserve, based on clinical data (9). Given this confluence of factors, it is possible that increased identification of pathogenic genes or variants in POI, coupled with advanced algorithms, could enable the development of effective predictive or early diagnostic models of POI in the near future. Additionally, advanced multiomics analyses also help to expand our understanding of the physiological mechanisms underlying ovarian aging (10-14), offering new perspectives for POI interventions. Furthermore, progress in material sciences and regenerative medicine have led to other advances in treatment strategies, such as fertility preservation, in vitro activation (IVA) of early follicles, and remodeling of the ovarian microenvironment, presenting new avenues to potentially slow POI progression and improve pregnancy outcomes.

In this review, we update the epidemiological characteristics of POI and its influence on reproduction and long-term health consequences. Focusing on the processes involved in establishment or depletion of ovarian reserves, we also update the genetic etiologies of POI, delving into its complicated genetic architecture, and offering insights into current and future potential interventions.

The Lifelong Impacts of POI in Women

Prevalence of POI

POI reportedly affects almost 1% of women worldwide, with recent estimates ranging from 0.5% to 3.7% (4-7). The observed variation in POI prevalence is largely influenced by the differences in diagnostic criteria; for instance, some epidemiological studies have assessed POI prevalence based solely on menopausal age. A comprehensive meta-analysis of 13 cohort studies conducted from 2003 to 2021, and included 1 127 299 total participants, revealed a global average POI prevalence of 3.5% according to ESHRE diagnosis standard (6).

However, significant heterogeneity was reported across different ethnic and geographic populations. The incidence of premature menopause (before age 40) in East Asian countries, such as China (2.8%) (15), Korea (2.8%) (16), and India (5.5%) (17), is notably higher than that in Caucasian and Hispanic populations, where it is estimated to be around 1% and 1.4%, respectively (18). Additionally, 1 trend indicates that average age at menopause is lower in African, Latin American, Asian, and Middle Eastern countries, with Europe and Australia recording the highest ages, followed by the United States (19). These disparities may be attributed to genetic differences among races, as well as the economic and educational status of women in different countries, with lower socioeconomic status and education levels correlating with earlier onset of natural menopause.

In line with these findings, the global incidence of POI is higher in developing nations (5.3%) than in developed countries (3.1%) (6). Another meta-analysis has affirmed this pattern, showing that countries with high Human Development Index scores have a lower prevalence of premature menopause (3.6%), in contrast to nations with medium (4.9%) or low (23.8%) Human Development Index scores (5). Mendelian randomization (MR) analysis has also suggested that lower educational attainment could act as a potential risk factor for early menopause (before age 45) (20). This interplay between ethnicity, geography, and living conditions in POI incidence underscores the complexity of this disease due to the influence of both genetic and environmental factors.

Reproductive Obstacles

Fertility is severely impaired in the patients with POI due to accelerated follicular loss. Although infertility may be the initial symptom of POI, the reproductive outcomes exhibit variability due to wide variation in the menstrual cycle profile, age of amenorrhea, and fertility history among individual patients (21, 22). Several retrospective studies and case reports have found that recovery of menstruation occurs in ~25% of patients after HRT treatment, with spontaneous pregnancy rates ranging from 3.6% to 4.2% (23-26). Higher pregnancy rates (5.8-6.3%) have been reported following ovulation induction therapy in the patients who retain spontaneous menstrual cycles, with increased live birth rates in those receiving treatment before age 35 (27, 28). Therefore, POI does not signify complete depletion of ovarian reserve. Exploring strategies to efficiently utilize the remaining follicles in patients to obtain mature oocytes and embryos is crucial for improving their reproductive outcomes.

Long-term Health Consequences

Ovarian aging is one of the earliest signs of organismal aging (29). Age-related changes in ovarian perfusion, interstitial fibrosis and immune cell infiltration may impact follicle development, leading to follicular atresia and ovarian dysfunction. Conversely, estrogen deficiency and elevated gonadotropin levels due to follicular exhaustion can induce metabolic disturbances, potentially promoting aging in other organs. As a

pathological condition, POI accelerates ovarian aging while also elevating the risk of other age-related diseases (30). Comprehensive health management for patients with POI thus depends on a firm grasp of correlations between POI and age-related diseases.

POI and common age-related diseases

Menopause is acknowledged as a risk factor for cardiovascular diseases (CVDs). A large cohort study from UK Biobank (encompassing 144 260 postmenopausal women) reported premature menopause (both spontaneous and iatrogenic) was significantly associated with increased risks of CVD, including coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism, with a hazard ratio (HR) ranging from 1.21 to 4.13 compared with age at menopause of 50 or older (31). Similarly, pooled data including more than 30 000 women across 5 countries uncovered that women with premature menopause had a higher risk of first nonfatal CVD event (HR 1.88) or CVD (HR 1.55). Further analysis revealed an elevated risk for both coronary heart disease (HR 1.52) and stroke (HR 1.72) (32). A meta-analysis involving 190 588 women also revealed that premature menopause increased the risk of developing/dying from ischemic heart disease or CVD by 69% or 61%, respectively (33). A large-scale MR study reports a higher risk of stroke associated with premature menopause (HR 1.54), indicating a correlation, though not establishing a causal genetic relationship (34).

The impact of POI on serum lipids remains uncertain. Females with POI exhibited a higher susceptibility to type 2 diabetes mellitus than those experiencing menopause after the age of 45 (OR 1.53) (35). A recent meta-analysis reported a potential impaired glucose tolerance and insulin resistance in patients with POI (36). Moreover, the cohort study from UK biobank reported a statistically strong association between type 2 diabetes mellitus and both spontaneous and surgical premature menopause (31). MR study further revealed the causal relationship between early menopause and the higher homeostasis model of insulin resistance (37). These conditions may stem from the effects of elevated FSH on insulin secretion and glucose metabolism (38).

Additionally, observational studies have consistently demonstrated an association between POI and osteoporotic fractures (39-41), with approximately 58% to 67% of POI cases exhibiting decreased bone mineral density (42, 43). The risk of fracture incidence was reported to increase by 5% for each year earlier in the onset of menopause (44). A meta-analysis involving 462 393 postmenopausal women revealed that early menopause increased the risk of fractures in all sites (OR 1.36) (45), and this causal relationship has been confirmed by MR analysis (8, 46, 47). Osteoporosis following POI is thought to be caused by hypoestrogenism (48), which can be mitigated by treatment with HRT, as emphasized in the POI management guidelines (3).

POI and neurodegenerative diseases and neuropsychiatry disorders

Estrogen has been found to have neuroprotective effect in some neurological disease models (49-51). The association between decreased estrogen levels resulting from iatrogenic POI and the increased risk of neurodegenerative conditions, cognitive impairment, or dementia also has been established through epidemiological studies (52, 53). Compared with women who experience natural menopause at the typical age, those with premature menopause face a higher risk of all-cause dementia (54-57) or specific types of dementia, such as Alzheimer disease and vascular dementia. Additionally, POI has been linked to mental health disorders (58, 59). A recent meta-analysis indicated that individuals with POI are at a 4.89-fold increased risk of anxiety and a 3.33-fold increased risk of depression compared with controls (60). Because both POI and psychiatric disorders have genetic susceptibility, further investigation is warranted to determine if they share some genetic pathogenic mechanisms.

Due to menstrual irregularity, patients with POI often manifest menopausal symptoms, including mood disorders and sleep disruption (61). Additionally, an unexpected diagnosis of POI can profoundly affect patients' mental health and self-esteem (59). Moreover, some of the patients experience reduced satisfaction with their sex life due to vulvovaginal atrophy, low libido, and dyspareunia (62, 63), which in turn contributes to an overall decline in life satisfaction. Although current perceptions tend to prioritize physical symptoms over psychological ones in women with POI, more attention should be directed towards the mental health of those patients in the future.

POI and mortality

Although POI affects a small proportion of women, studies have reported a higher mortality rate among these patients. According to the data from National Health and Nutrition Examination Survey cohort, all-cause mortality for women with premature menopause was increased compared with those who had natural menopause (HR 1.53) (64). Another 3-decade follow-up cohort of Chilean women found POI was one of the main factors associated with mortality (HR 1.60), ranking closely behind diabetes and arterial hypertension (65). Moreover, premature menopause has been linked to an increased risk of cancer-specific mortality (HR 1.38) (15). Interestingly, an observational study reported a decreased incidence of breast cancer in the women with premature menopause (OR 0.59) (15), whereas a recent study found increased risk of breast cancer (OR 2.20) and ovarian cancer (OR 3.67) in the patients with POI (defined as FSH > 20IU/L or anti-Müllerian hormone (AMH) <0.08 ng/mL) (66). These conflicting findings may be attributed to differences in hormone exposure durations and varying hormonal sensitivities of breast cancer subtypes. Genetic studies have revealed loss of function (LoF) variants in DNA damage repair genes were significantly enriched in the patients with POI (67-69). Given that aberrant DNA damage response is implicated in tumorigenesis, the patients carrying recessive variants in DNA damage response genes, such as *MCM8* (70), *MCM9* (71), and *BRCA2* (72), may present with early-onset cancers, although the penetrance can be highly variable. There are also early cancer syndromes associated with POI (73-75). Therefore, investigating the role of DNA damage repair genes in POI pathogenesis and conducting joint analyses with tumor risk could facilitate the discovery of shared genetic susceptibility loci, holding promise for the prediction and treatment of tumors. Additionally, the influence of age at menopause in the patients with POI, as well as the dosage and duration of HRT treatment, on the burden of hormonally sensitive tumors should be further investigated.

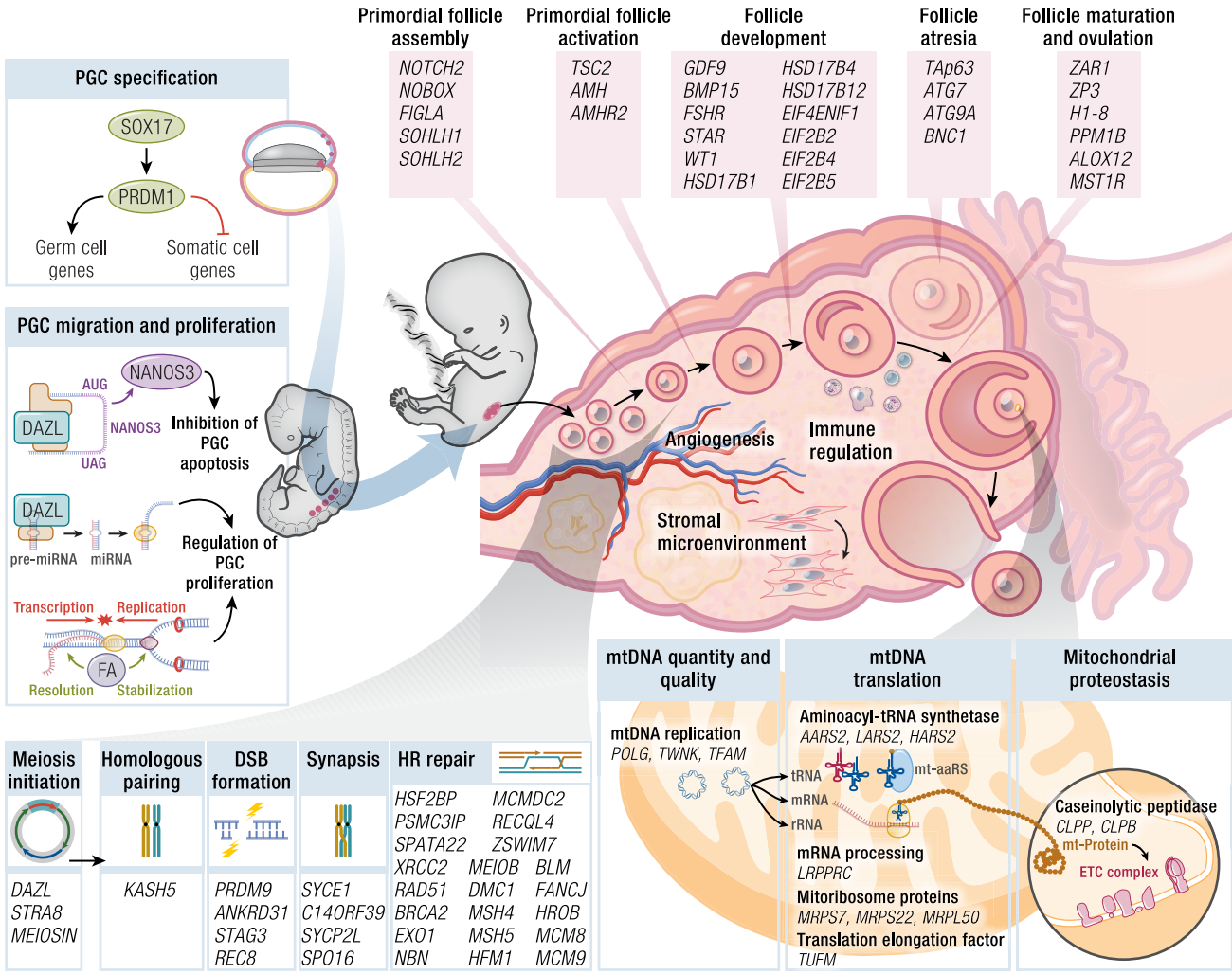


Figure 1. Genetic etiologies of POI. POI causal genes are involved in the processes from primordial germ cell development to follicle maturation.

Genetic Etiology of POI

POI displays significant heterogeneity in phenotype and etiology. It can be classified into sporadic and syndromic types based on symptoms besides ovarian phenotypes, further categorized as primary or secondary POI depending on the presence or absence of menarche (76).

Extensive evidence has indicated familial aggregation characteristics of POI, with 10% to 30% of cases having family members affected by POI (77). A recent study reported an 18-fold increased risk of POI (defined as FSH > 20 IU/L or AMH <0.08 ng/mL) in the first-degree relatives of patients with POI compared with the controls (78, 79), supporting the contribution of genetic factors to POI pathogenesis. Chromosomal abnormalities and gene mutations are the common genetic causes of POI (80). Patients with primary amenorrhea (PA) or SA exhibit distinct genetic features. In women with PA, around 20% to 30% exhibit chromosomal abnormalities and 25.8% carry gene mutations, while lower frequency was observed in patients with SA (4.5-11.6% and 17.8%, respectively) (67, 76, 81, 82). Moreover, patients with PA appear to carry multiple genetic variants more frequently than those with SA (83). Thus, genetic factors contribute to the diverse clinical phenotypes of POI. However, a comprehensive understanding of the genotype–phenotype relationship is still lacking.

Here, we provide an overview regarding the POI causal genes involved in oogenesis and folliculogenesis (Fig. 1), and have summarized their molecular mechanisms related to insufficient establishment or accelerated depletion of ovarian reserve. Also discussed are the inheritance modes of pathological mutations, giving insight into the complex genetic architecture of POI.

Disrupted Primordial Germ Cell Development and POI

Primordial germ cell (PGC), the germline precursor that gives rise to oocyte and sperm, undergoes specification, migration, and proliferation, essential for forming the ovarian reserve (84). Any errors during PGC development could disrupt the establishment of ovarian reserve and impair fertility, which play a crucial role in the pathogenesis of POI. Research on PGCs has historically been hindered by challenges in sample acquisition and scarcity of available cells for testing, stemming from their emergence in early embryonic development. However, recent strides in micro-omics technologies have facilitated a deeper exploration of the dynamic alterations

within PGCs' transcriptome, DNA methylome, histone modifications, and chromatin accessibility (85-88). These advancements have enhanced our understanding of gene expression profiles throughout human PGC (hPGCs) development, offering valuable insights into the genetic mechanisms underpinning the pathogenesis of POI.

Genes involved in PGC specification

Specification of hPGCs is triggered by BMP and WNT signaling via regulating gene expression, such as *PRDM1*, *TFAP2C*, and *SOX17* (89). Among these genes, *PRDM1* plays a significant role in initiating the germ cell program and repressing somatic genes (90, 91). Mechanistically, PRDM1 acts downstream of SOX17 to initiate the transcriptional network of human germ cells (92). It could selectively recruit HDAC3 to somatic genes, leading to the subsequent repression of somatic gene expression (93). In the embryos of *Prdm1* knockout mice, only a few PGC-like cells formed and PGC development seemed to be blocked at an early stage, for these cells could not migrate or proliferate (94). In patients with idiopathic sporadic POI, LoF variants of *PRDM1* were enriched, as revealed by case–control analysis of WES data. These variants resulted in truncated proteins or were verified to decrease the stability of PRDM1 (67). Additionally, another novel heterozygous missense variant in *PRDM1* was identified in Brazilian patients with POI (95). However, the pathogenetic mechanism and inherited mode, such as dominant negative or haploinsufficiency effect, of the heterozygous *PRDM1* variant in POI has not been clarified yet.

RNA transcription–translation regulators associated with PGC development

RNA-binding proteins represent intriguing candidate factors for POI, given that DAZL and NANOS3 play vital roles in germ cell development and maintenance. DAZL is not only essential for the onset of meiosis and oocyte maturation but also directly binds to pre-miRNAs, enhancing their processing into mature miRNAs and thereby influencing the proliferation of hPGCs (96-98). Moreover, a recent study found that DAZL regulates the expression of NANOS3 (99), which is required to prevent PGCs from undergoing apoptosis during migration (100, 101). Reduced expression of DAZL and NANOS3 results in a decrease in the number of germ cells derived from human embryonic stem cells and the expression of genes critical for pluripotency and meiosis (102). In patients with POI, 2 cases with homozygous variants in *DAZL* and 2 sisters with homozygous variants in *NANOS3* were identified, suggesting that biallelic defects in these genes could shorten the reproductive lifespan by increasing PGC apoptosis (99, 103, 104). Additionally, 3 individuals carrying missense heterozygous *DAZL* variants reported early menopause and having children (103), and 1 POI case carried a heterozygous variant of *NANOS3*, suggesting that variants on these genes might influence the phenotype of ovarian reserve decline by a dosage-dependent effect (105).

Fanconi anemia genes related to PGC proliferation

Fanconi anemia (FA) typically manifests as a recessive genetic disorder attributed to mutations in genes within the FANC group. It is characterized by bone marrow failure, heightened susceptibility to cancer, and severe germline defects (106, 107). The FA pathway consists of 22 FA proteins and 5 FA-associated proteins. In the large-scale POI-WES study, LoF variants in the FA gene were significantly enriched in patients with POI, suggesting a potential role of FA gene variants in POI pathogenesis (67). The complex influence of FA genes on ovarian reserve includes their involvement in PGC proliferation and oocyte meiosis. In this section we focus on the function of FA genes in PGC proliferation; later we will discuss their roles in oocyte meiosis.

To data, *FANCA*, *FANCL*, *FANCM*, and *FANCI* have found to be POI causal genes. FANCA, FANCL, and FANCM are components of the FA core complex, FANCI is a binding partner and essential for ubiquitination of FANCD2. They are crucial for repairing DNA interstrand crosslinks and protecting replication forks (108), thereby resolving transcription–replication conflicts and maintaining genomic stability during PGC proliferation (109, 110). Monoallelic variants of *FANCA* (111) and *FANCL* (112), as well as biallelic variants of *FANCM* (113) and *FANCI* (114), have been reported to be causative for POI. As all the variant carriers exhibit PA or early SA (around 20 years old), the genotype–phenotype relationship among those genes and POI have not been illustrated clearly yet. Because heterozygous deletion of *Fanca* in mice showed decreased follicle number and impaired fertility, as well as in vitro experiments revealed the activity of those genes were dosage-sensitive to interstrand crosslinks (111, 115), the effect of above gene variants on PGC proliferation and ovarian function may be dosage dependent.

Meiosis Defects and POI

Along with specification and proliferation, hPGCs migrate into the genital ridge (116). For the hPGCs determined to be oocytes, meiosis is initiated by a group of proteins at around 11 to 12 weeks of gestation (116). Meiotic prophase I is a specialized stage to ensure the completion of numerous meiosis-specific chromosome events predominately through programmed double-strand breaks (DSBs) formation and homologous recombination (117), determining the genomic stability and diversity of oocyte (118). Any abnormalities of the processes will result in meiotic arrest and subsequent apoptosis of the oocytes (119). Meiotic genes constitute a substantial portion of known POI causal genes. They can be classified into the following categories.

Meiotic initiation

Mammalian meiotic initiation is synergistically regulated by DAZL, BMP, and retinoic acid signaling pathways (117). DAZL, which functions as both translational repressor and activator, is required for PGC formation, meiotic initiation, and maturation (97). Biallelic variant in *DAZL* has been found to induce POI by insufficient PGC formation as described before. However, whether there is a dosage-dependent effect of *DAZL* variants on meiotic initiation or maturation has not been well explored. The BMP pathway involve in meiotic initiation by activating the expression of STRA8 and MEIOSIN, which are essential retinoic acid–dependent transcriptional factors for meiotic initiation (120). Other factors, such as DMRT1 and MSX, have been suggested to negatively regulate meiotic entry (121). In mouse models, defects in these meiotic initiation genes lead to excessive apoptosis of oocytes before birth, resulting in female infertility (117, 122-126).

Recently, homozygous variants of the retinoic acid–dependent proteins STRA8 and MEIOSIN have been found in the patients

with POI (67, 126). Under physiological conditions, STRA8 and MEIOSIN form a complex to facilitate nuclear entry of proteins and regulate the transcription of meiosis-related genes. The variants of *STRA8* and *MEIOSIN* carried by POI cases resulted in meiotic arrest and oocyte apoptosis due to impaired protein nuclear entry and suppression of meiosis-related gene expression in a recessive mode (67, 126). The carrier of *STRA8* variant exhibited PA, while the *MEIOSIN* variant carrier presented with SA at the age of 26. These results suggested that biallelic variants in meiotic initiation genes often lead to early-onset POI. Therefore, timely identification of those patients at early stage by genetic testing might improve their pregnancy outcome through fertility preservation and ART.

Meiotic DSB formation

After meiosis initiation in the oocytes, the next hallmark event is programmed DSB formation and homologous recombination, which preferentially occurs in specialized sites called meiotic recombination hotspots. PRDM9 is a meiosis-specific histone H3 methyltransferase and a major determinate of the sites of meiotic recombination hotspots (86, 127). Subsequently, the topoisomerase SPO11 cleaves at hotspots to generate DSBs with the assistance of TOPOVIBL, MEI1, MEI4, ANKRD31, and REC114 (128). Afterward, DSBs are repaired by homologous recombination, ensuring the equal exchanges between maternal and paternal chromosomes, which are essential for fertility and genome evolution (129).

The knockout mouse models of the aforementioned genes involved in DSB formation all demonstrated defective meiotic homologous recombination and ovarian dysfunction (130). Recently, Wang et al identified heterozygous variants of *PRDM9* and *ANKRD31* in patients with sporadic POI, with the age of amenorrhea ranging from 23 to 37 years (131). Functional studies found that $Prdm^{+/-}$ primordial follicles exhibited increased sensitivity to exogenous stress, indicating that the heterogenous clinical presentation of *PRDM9* variant carriers might be influenced by environmental exposures. In addition, defective DSB formation could affect the position of recombination hotspots, thereby impacting the recombination and segregation of homologous chromosomes, potentially leading to aneuploid oocytes (132). It has been reported that biallelic variants of *TOROVIBL*, *MEI1*, and *REC114* lead to androgenetic hydatidiform moles (133). Furthermore, female carriers of biallelic variants of *MEI4* and *REC114* have been reported to have embryonic arrest and infertility (134, 135). These findings indicate that biallelic variants of meiotic DSB formation genes have pleiotropic effects on reproductive phenotypes. Patients with POI carrying those variants may have an increased risk of embryonic arrest or implantation failure even when they still have follicles for spontaneous pregnancy or ART treatment.

Homologous recombination repair for meiotic DSB

The meiotic DSBs are repaired through homologous recombination pathway, a series of orchestrated events that encompass DSB end procession, DNA single-strand invasion, intermediate formation and homologous recombination (130). To date, approximately 60 meiotic genes have been found to be involved in homologous recombination process, with over 27 genes implicated in the pathogenesis of POI.

Homologous recombination repair operates in both germ cells and somatic cells, albeit with distinct features (136). A subset of homologous recombination genes is specifically expressed during meiosis, and individuals harboring variants in these meiosis-specific homologous recombination genes often manifest isolated POI. These includes genes involved in strand invasion such as *PSMC3IP* (137), *SPATA22* (138), *MEIOB* (139, 140), *DMC1* (141, 142), and *ZSWIM7* (143, 144), as well as those that promote the formation and stability of recombination intermediate, including *MSH4*, *MSH5* (145), *MCMDC2* (67), and *HFM1* (146-148). Moreover, most of these genes induced POI by recessive mode. And the carriers of biallelic LoF variants presented with PA or onset of SA before 30 years old.

Furthermore, another subset of homologous recombination genes is implicated in DSB repair during both meiosis and mitosis, including DSB terminal processing genes, such as *EXO1*, *NBN*, single-strand invasion genes *HSF2BP*, *RAD51*, and recombinant intermediate formation and stabilization genes *RECQL4*, *BLM*, *HROB*, *MCM8*, and *MCM9* (130). Patients with POI with biallelic variants in these genes more likely present with PA or SA onset before the age of 25. This may be related to the cumulative effects of gene variants on PGCs proliferation, oocyte meiosis and granulosa cell (GC) survival. While, the carriers of monoallelic variant presented with a milder ovarian phenotype, such as POI with SA onset after 30 years old or early menopause, indicating those genes may have a dosage-dependent effect on ovarian function. Notably, the variants in the aforementioned genes are also associated with syndromic POI, with the main symptom being tumor development. Therefore, although some patients with POI carrying those gene mutations do not have tumors or other diseases at the time of diagnosing isolated POI, long-term follow-up is still necessary.

In the above section of PGC proliferation, we mentioned that some FA genes are also involved in oocyte meiosis. FANCD1 (BRCA2), FANCJ, and FANCU (XRCC2) have been known to participate in homologous recombination for DSBs initiated by the processing of interstrand crosslinks. They also participate in homologous recombination for the programed meiotic DSBs, as shown in knockout mice by the accumulation of DSBs and meiotic arrest in the oocytes (149-152). Carriers of homozygous variants in *XRCC2* exhibited SA 1 year after menarche (153). Meanwhile, carriers of biallelic variants in *BRCA2* from the United States, Italy, China, and Turkey all exhibited PA (72, 154, 155), indicating a potential correlation between biallelic variants of *XRCC2* and *BRCA2* and severe ovarian dysgenesis. In contrast, monoallelic variant carriers present with a milder ovarian phenotype. For instance, a recent study found that the carriers of heterozygous *FANCJ* variant experienced amenorrhea at 29 and 39 years of age, respectively (152). Moreover, the data from GWASs on the age at natural menopause (ANM) revealed an association between *BRCA2* variants and early menopause (8). These findings indicate the genotype–phenotype relationship between *FANCJ* and *BRCA2* variants and ovarian function might depend on the residual dosage of functional protein.

Additionally, different biallelic *BRCA2* variants have varying effects on systemic symptoms. For instance, *BRCA2* variant carriers from the United States developed acute myelocytic leukemia at 5 years of age (154), while those from Italy presented with multiple adult cancers (72). However, Chinese

and Turkish patients did not have a history of tumors at the time of consultation (72, 155). Variations in residual BRCA2 function due to different mutations likely explain the differing speeds of ovarian function decline and occurrence of tumorigenesis. Due to the technical limitations of WES, oligogenic effects, and gene–environment interactions cannot be ruled out either (156). Furthermore, the increased risk of tumors in carriers with FA gene variants suggests that young women with POI should have genetic analysis and increased cancer surveillance when FA gene mutation were identified (157).

Meiotic chromosome movement and synapsis

At the beginning of meiosis homologous recombination, the LINC complex, composed of KASH5 and SUN1, connects telomeres to the inner nuclear membrane with the facilitation of the TERB1-TERB2-MAJIN complex, promoting telomere-led rapid prophase movements, followed by chromosome pairing and synapsis. Studies have shown that knockout mice of the above genes exhibit infertility due to abnormalities in homologous chromosome pairing and meiotic arrest (158, 159). Biallelic variants in *KASH5* have been found in several families with POI (158, 160). Moreover, a recent study reported a *KASH5* homozygous variant carrier exhibited diminished ovarian reserve (DOR) and recurrent miscarriages (161), further expanding the pleiotropic function of *KASH5* on reproductive phenotypes. Other proteins, such as TERB1, TERB2, and MAJIN, have been found to participate in the pathogenesis of nonobstructive azoospermia. Although no mutation in these genes has been detected in patients with POI, they are potential candidate genes for the disease.

The formation of a synaptonemal complex (SC) between homologous chromosomes provides a platform for precise recombination and crossover formation of gametes. The SC is consisted of the lateral elements (SYCP1), axial elements (SYCP2, SYCP3), central elements (C14ORF39, SYCE1-3, TEX12), and the protein SPO16, which contributes to the structural stability of the SC (162, 163). Currently, biallelic variants in the central elements *SYCE1* and *C14ORF39*, the lateral element *SYCP2L* and SC stabilizer *SPO16* have been identified in patients with POI (164-166). All these patients with POI presented with relatively late-onset SA, except carriers of *SYCE1* mutations who exhibited PA or SA before 25 years old. Moreover, there has been report of an association between heterozygous mutations in *SYCP3* and recurrent spontaneous abortion (164). These findings suggest that mutations in SC genes contribute to the development of POI through the recessive mode. While, the participation of these genes in recurrent spontaneous abortion by a monogenic or oligogenic pattern require further verification.

During oocyte meiosis, sister chromatids are tethered together by the ring-shaped cohesion complex from DNA replication to the beginning of chromosome segregation (167). The cohesion complex consists of STAG3, RAD21L, SMC1B, SMC3, and REC8. Among them, STAG3 interacts with REC8 to stabilize the cohesion complex (168), and biallelic variants of them have been reported in the patients with POI. Sixteen cases with *STAG3* variants consistently presented with PA (137), while 1 carrier of REC8 variants experiences SA before the age of 20 (169), indicating that STAG3 and REC8 are the core components of the cohesion complex involved in maintaining oocytes' genomic stability and ovarian reserve.

Folliculogenesis Abnormalities and POI

Follicle development is a complex process including stages like construction of the primordial follicle pool, follicle activation, gonadotropin-independent/dependent follicle development, follicle maturation, and ovulation. This process is governed by a finely regulated network involving oocyte-specific regulatory factors, somatic–germ cell communication, hormone synthesis, and cell death regulation. Any malfunction in these components can lead to depletion of primordial follicle pool and eventually ovarian failure. Genetic abnormalities in folliculogenesis have long been noticed as an important part for POI pathogenesis; exploration of that will also have insight into intervention of the disease. In this section, we will summarize these genes following the folliculogenesis stages.

Primordial follicle assembly

At the 15th week of gestation, oocytes are arrested at the diplotene stage of meiosis prophase I. Then, pregranulosa cells encapsulate the oocytes via signaling originating from oocytes or other pregranulosa cells to construct the primordial follicles, which stay dormancy until activation at puberty in response to gonadotropins. A transcription factor network and NOTCH signaling pathway regulates primordial follicle formation through oocyte growth and bilateral communications between oocytes and pregranulosa cells, disruption of which leads to insufficient establishment of ovarian reserve, as evidenced by knockout mouse models and genetic identifications in human POI.

NOBOX, *FIGLA*, *SOHLH1*, and *SOHLH2* encode oocyte-specific transcription factors that regulate the expression of oocyte-specific genes, ensuring the generation of primordial follicles (170-173). Although there is no doubt about the contribution of these genes in POI pathogenesis, the increasing evidence has progressively expanded our understanding of their inheritance mode in POI and the genotype–phenotype relationships. Heterozygous variants in these genes were primarily reported when the predominant method of genetic screening was Sanger sequencing (174-176). Functional assays have demonstrated that these variants lead to impaired protein function through dominant negative or haploinsufficiency effects. However, as the use of WES became more widespread, several pedigree studies identified that homozygous deleterious variants in these genes were causative for POI (177-180). Notably, biallelic carriers exhibited PA, whereas most patients with POI carrying monoallelic variants exhibited SA, suggesting a dosage-dependent effect of these gene variants on ovarian function. Meanwhile, in the POI pedigrees, the mothers who carried heterozygous variants did not affected by POI, indicating that the dominant negative or haploinsufficiency effect of heterozygous variants found in sporadic POI was not prevalent in familial cases (177). Therefore, for the heterozygous variants, more evidence from functional experiments is needed. Additionally, we cannot rule out the possibility of a second variant in the regulatory region, a variant in an exon not well covered by WES, or the effects of polygenic and environmental factors contributing to the occurrence of POI.

The NOTCH pathway–mediated communication between oocytes and pregranulosa cells also plays a crucial role in primordial follicle formation. Conditional knockout of *Notch2* in pregranulosa cell led to a failure of oocyte cysts breakdown, resulting in follicles with enlarged oocytes but

lacking somatic cell growth (181). A study in a Caucasian cohort of POI found the involvement of *NOTCH2* variants in the pathogenesis of POI (182). Additionally, in a Chinese family (183), where the mother and daughter experienced SA at the age of 35 and 20, respectively, familial segregation analysis and functional experiments indicated a *NOTCH2* heterozygous variant was associated with POI occurrence. The dominant inheritance mode of *NOTCH2* in the POI pedigree, which contrasts with the recessive pattern observed in oocyte-specific genes, could potentially be attributed to its ubiquitous expression in both oocytes and GCs. The possibility of a second hit from unidentified loci cannot be excluded as well. Further genetic evidence from larger-scale studies and in vivo experiments will be advantageous in unveiling the underlying mechanism.

Primordial follicle activation

The ovarian reserve gradually diminishes with aging as ordered activation of primordial follicles. Therefore, the speed of primordial activation is crucial for maintaining ovarian reserve and the length of female reproductive lifespan. Primordial follicle activation is regulated by the mTORC1, PI3K-AKT-FOXO3, and HIPPO-YAP signaling pathways (184, 185). TSC2 binds with TSC1 and exerts a negative regulatory effect on mTORC1 (186). Deletion of *Tsc2* in either oocytes or pregranulosa cells led to excessive activation of primordial follicles and premature depletion of the primordial follicle pool (187, 188). A recent study reported 5 heterozygous variants of *TSC2* in isolated POI (189). However, *TSC2* is ubiquitously expressed in somatic cells, and the heterozygous variants have been found to be responsible for dominant genetic disorders (190, 191). Therefore, the pleiotropic effect of *TSC2* variants on reproductive and somatic diseases requires further exploration in larger populations and extended follow-up.

Previous studies also reported 7 heterozygous mutations of *FOXO3* in patients with POI (192, 193). In mice models, deletion in *Foxo3* lead to overactivation of primordial follicles and accelerated follicle loss, indicating *FOXO3* mutation could induce POI by premature exhaustion of ovarian reserve (194). Moreover, there is different expression pattern of FOXO3 in mouse and human follicles. In the mouse ovary, *Foxo3* is primarily expressed in the oocytes from primordial follicles, which is localized in the nuclei and translocated to the cytoplasm when primary follicles are activated. Whereas, in the human ovary, *FOXO3* is expressed not only in oocytes but also in some GCs of certain follicles (195, 196). Furthermore, overexpression of *FOXO3* can induce apoptosis of human GC line (197). These findings suggest that FOXO3 is involved in the maintenance of human follicle pool by a stabilized expression both in oocytes and GCs.

AMH, which has been widely used as a biomarker of ovarian reserve in ART (198), is expressed in the GCs surrounding the growing follicles (199-201). It plays a pivotal role in inhibiting primordial follicle activation through interaction with the AMH receptor 2 (AMHR2) (202, 203). Association studies have shown that single nucleotide polymorphism (SNP) of *AMH* and *AMHR2* were related to POI (204, 205). Moreover, Li et al verified the variant p.I209N in *AMHR2* identified in patients with POI adversely affected AMH pathway (206). However, the frequency of SNPs in *AMH* and *AMHR2* was not significantly different between POI and controls in Korean and Chinese population (205, 207), suggesting the existence of ethnic disparities in the distribution of AMH SNPs and their contribution in POI pathogenesis.

Follicle development

The development of follicles occurs in 2 stages. The first stage is independent of gonadotropins and is primarily regulated by autocrine or paracrine factors, such as GDF9 and BMP15. Both of them are secreted from oocytes, and form a dimer to promote follicular development by stimulating GC proliferation (208, 209). *Gdf9*-null mice exhibited arrested follicular development at the primary follicle stage (210), while *Bmp15*-null mice experienced abnormal ovulation and decreased oocyte quality (211). To date, many researches have confirmed the causative role of *BMP15* and *GDF9* variants in human POI (212).

The second stage of follicle development relies on gonadotropins. The FSH receptor (FSHR) begins to be expressed in the GCs of primary follicles (213). The activity of FSHR controls follicle development by responding to FSH and thereby regulating steroid hormone synthesis. Aittomaki et al first identified a homozygous *FSHR* variant in patients with POI in the Finnish population, with ovarian biopsies revealing a lack of mature antral follicles in most patients (214). Interestingly, the mice model with FSHR haploinsufficiency presented with altered ovarian steroidogenesis, leading to accelerated follicle loss and subfertility (215). In the meantime, 1 study has reported that *FSHR* rs6166 polymorphism is significantly associated with POI in Asian populations (216), and 2 heterozygous *FSHR* variants have been identified to induce the disease through haploinsufficiency effect (217). Recently, the WES data from a Chinese cohort of POI further support the relationship between *FSHR* LoF variants and POI, especially for those patients with PA (67). Therefore, *FSHR* variants might induce POI through both dominant and recessive modes (95, 217-219). Notably, the possibility of a second variant synergizing with *FSHR* variants to cause POI cannot be ruled out. Notably, because several cases had age-appropriate AMH levels and antral follicle counts (217, 219), they are more likely to have undiagnosed resistant ovary syndrome rather than ovarian failure.

Steroid hormone synthesis and metabolism are crucial for the second stage of follicle development. The genes involved in the process have been well-known in POI, such as *STAR*, *HSD17B1*, *HSD17B4*, and *HSD17B12*. In a Chinese POI pedigree, compound heterozygous variants in *HSD17B12* were identified in the 2 daughters with POI, and confirmed that *HSD17B12* deficiency contributed to POI through a dosage-dependent effect as observed in the *Hsd17b12*$^{+/-}$ mice (220). Moreover, monoallelic LoF variants in *HSD17B1* were found to be enriched in patients with POI (67). The biallelic variants of *STAR* and *HSD17B4* have been reported respectively in lipoid congenital adrenal hyperplasia and Perrault syndrome, both of which are syndromes with ovarian failure as 1 symptom (221, 222). *WT1* encodes a transcriptional factor that regulates the proliferation and hormone synthesis of GCs. The heterozygous variants of *WT1* have been found in sporadic and familial POI (223, 224). Notably, the *WT1* variant carriers have history of full-term pregnancies, suggesting that monoallelic variants did not affect the quality of oocytes. Early identification of the

variants and giving reproductive counseling could improve their pregnancy outcomes. Considering that *WT1* variants increase the risk of Wilms tumor (225, 226), preimplantation genetic testing should be recommended to the carriers of *WT1* pathogenic variant.

During follicle development, there is a gradual increase in protein synthesis in the oocyte, suggesting that dysfunctional translation may disrupt follicle development. Both the variants in translation regulator *EIF4ENIF1* and *EIF2B* have been found to induce POI. However, their inheritance modes are different. EIF4ENIF1 binds to eIF4E, which is crucial for the initiation of cap-dependent translation. The *EIF4ENIF1* variant caused POI in a dominant pattern, as verified by family cosegregation analysis and *Eif4enif1*$^{+/-}$ mice demonstrating an accelerated follicle atresia with aging (227, 228). EIF2B controls eIF2 activity making it vital for cellular adaptation to various stresses (229). Biallelic variants in subunits of EIF2B, including *EIF2B2*, *EIF2B4*, and *EIF2B5* cause adult-onset leukoencephalopathy combined with ovarian dysgenesis (230-233). Among them, the homozygous variant *EIF2B2* p.Val85Glu was the most prevalent biallelic variant in sporadic POI, accounting for nearly 1% of the patients. Previous study demonstrated that *EIF2B2* p.Val85Glu led to decreased GDP/GTP exchange activity of the EIF2B protein (231). However, the mechanisms by which *EIF2B2* p.Val85Gl lead to ovarian dysgenesis have not been clearly investigated.

Follicle atresia

The length of reproductive lifespan is also influenced by the rate of follicular atresia. Recent studies have shown that genetic defects can accelerate follicle atresia through various cell death pathways, such as apoptosis, autophagy, and ferroptosis. TAp63α, a member of the p53 gene family, is specifically expressed in the oocytes of primordial follicles and acts as a quality control factor for oocytes (234-236). Recent study reported 6 gain of function variants in the C-terminal of *TAp63*, accounting for 0.78% of the POI cohort, constitutively activate oocyte apoptosis by upregulating the transcription of *PUMA*, *NOXA*, and *BAX* (237). Moreover, 2 variants of the autophagy-related gene *ATG7* induce POI by reducing autophagosome formation, leading to an unbalanced degradation and recycling of the long-lived proteins and cellular organelles in oocytes and GCs (238). Ferroptosis is a form of cell death resulting from disruptions in iron-dependent lipid oxidation metabolism. The variant *BNC1* p.Arg356Valfs*6, which was carried by 6 cases in a POI pedigree, was verified to induce oocyte ferroptosis by interfering with the NF2-Hippo pathway (239, 240). Interestingly, all the variants above accelerated oocyte death by dominant pattern.

Follicle maturation and ovulation

Previous studies rarely found genes related to follicle maturation and ovulation involved in the pathogenesis of POI, as these gene defects predominantly lead to disorders of ovulation, oocyte maturation and embryo developmental. In recent studies, the LoF variants in those genes, such as *ZAR1*, *ZP3*, *H1-8*, *PPM1B*, *ALOX12*, and *MST1R*, have been found to be enriched in the patients with POI, suggesting their pleiotropic effects on ovarian function (67). For instance, ZP3, a crucial component of the zona pellucida starting to be consisted from primordial follicle, linked to both oocyte maturation defects and POI. *Zp3*-null mice exhibited a reduction in the number of preovulatory follicles, zona pellucida deficiency, and infertility, supporting its multifaceted role in follicle development (241). Intriguingly, only missense variants or in-frame deletions of *ZP3* have been reported in patients with empty follicle syndrome (242), whereas POI cases carried LoF mutations. Biallelic variant carriers showed the earliest onset of amenorrhea, underscoring the dosage effect of *ZP3* variants on ovarian dysfunction.

Mitochondrial Dysfunction and POI

The metabolism of glucose and lipids is crucial for ovarian function. In the oocytes, ATP is generated through mitochondrial oxidative phosphorylation (OXPHOS) to meet the energy demands of oocyte development, as well as subsequent fertilization and early embryo development (243). Under physiological conditions, a small amount of ROS is produced as a byproduct during oxidative phosphorylation. However, cells possess antioxidant mechanisms that can prevent the accumulation of ROS, maintaining their levels in a balanced state (244). During age-related ovarian dysfunction or pathological conditions, such as mutation induced mitochondrial dysfunction or DNA damage accumulation, there is an increase in ROS production and a deactivation of antioxidant pathways in oocytes, leading to ROS accumulation (245). Excessive ROS can damage multiple cellular organelles, inducing oxidative stress and accelerating follicle loss (246). Around the oocytes, mitochondrial function of GCs is also essential for follicle development since the pyruvate necessary for oocyte OXPHOS is generated from glycolysis of cumulus GCs and the steroid hormone necessary for oocyte growth is synthesized in the mitochondria of mural GCs (246, 247). Therefore, mitochondrial dysfunction within GCs may impede their proliferation and steroidogenesis, as well as impair the metabolic crosstalk between GCs and oocytes, compromising oocyte quality and precipitating ovarian aging (248).

POI is a pathological condition characterized by accelerated ovarian aging, exhibiting similar histopathological features to those observed in natural ovarian aging, including follicular atresia and interstitial fibrosis. Understanding of the mechanisms that drive physiological ovarian aging can give insights into the pathogenesis of POI. A recent single-cell transcriptomic landscape of ovaries from aged nonhuman primates found decreased expression of mitochondrial genes in early-stage oocytes and GCs. Additionally, inactivated antioxidative pathways, increased ROS, and apoptosis were observed in the GCs from aged women, indicating insufficient mitochondrial function contribute to ovarian aging (249). In the WES data of POI cohorts, the LoF variations in mitochondrial genes are significantly enriched (67), suggesting mitochondrial dysfunction also participate in the pathogenesis of POI. The proposed mechanisms of mitochondrial dysfunction driving ovarian aging include quantitative and qualitative dysfunction of mitochondrial DNA (mtDNA), impaired mtDNA translation, and unbalanced protein homeostasis (250).

Quantity and quality of mtDNA

In mammals, mtDNA encodes 37 genes, including 13 proteins for OXPHOS, 22 tRNAs, and 2 rRNAs (251). The copy number of mtDNA is increasing along with the generation of mitochondria during oogenesis, which is significantly higher in the mature oocytes compared to somatic cells, with a range of 100 000 to 600 000 copies (252). The quantity and quality

of mtDNA is essential for reproductive lifespan and pregnancy outcome. Quantitative mtDNA dysfunctions along with ovarian aging include decreased mtDNA copy number and mtDNA deletions in the oocytes. The lower mtDNA content has been observed in the women with POI, DOR, or physiological ovarian aging (253-257). Moreover, the decreased mtDNA contents affect the oocyte fertilization and embryo developmental competence, thus is an outcome indicator and treatment target of IVF. Therefore, elucidating the genetic factor influencing mtDNA contents is important for reproductive health studies. Interestingly, mtDNA is regulated by many genes that are not on mtDNA itself, such as autosomal gene *TWNK* and *TFAM*. TWNK is one of the core mtDNA helicase required for mtDNA replication (258). To date, there are 13 cases with POI were reported to carry biallelic *TWNK* variants, with the majority of carriers exhibiting Perrault syndrome (259). A recent study with WES data of over 100 000 women from the UK Biobank database found that the carriers of *TWNK* variants experienced menopause approximately 1.54 years earlier than the non-carriers (77). In addition, 2 cases with heterozygous deleterious variants of *TWNK* presented with isolated POI, further suggesting that monoallelic variants of *TWNK* also contribute to accelerate ovarian aging by haploinsufficiency effect (67). *TFAM* encodes a component of the mitochondrial replisome machinery that regulates mtDNA transcription and replication. One homozygous variant in *TFAM* has been identified in 4 patients with syndromic POI who presented with POI and somatic symptoms, such as seizures, intellectual disability, and hearing loss. Functional studies in the primary fibroblasts found *TFAM* mutation resulted in decreased mtDNA copy number, altered mitochondrial morphology and impaired oxygen consumption. The *tfam* mutant zebrafish exhibited decreased oocyte number and aberrant gonad morphology, supporting its pathogenicity in POI (260, 261).

The qualitative mtDNA dysfunctions include strand breaks and mutations. Unlike nuclear DNA, mtDNA lacks histone protection, which makes the mitochondrial genome more susceptible to the changes of metabolism and environment, leading to a mutation rate 25 times higher than nuclear DNA (262). Both the maternally inherited and acquired mtDNA mutations in humans are related to DOR (263, 264). The mechanism of acquired mtDNA mutations has not been elucidated clearly, but may result either from oxidative damage, or from the defective mtDNA polymerase gamma (*POLG*) (264). In the GWAS studies of ANM, more than 15 *POLG* variants were linked to POI (265). Furthermore, heterozygous LoF variants of *POLG* have been identified in 0.7% (7/1030) of the cases with isolated POI, among whom nearly half cases carried additional LoF variants in other POI causal genes (67). The presence of multiple heterozygous variants indicates a complex genetic mode of POI, and the variants in mitochondrial genes that induce overwhelmed mitochondrial capacity might act as a catalyst for mutation burden, potentially accelerating follicle loss (266).

Translation of mtDNA

Abnormalities in mitochondrial translation system can impair the synthesis of mtDNA-coded ETC components, thus affecting OXPHOS and ROS production. The translation of mitochondrial RNA relies on nuclear DNA encoded specialized protein translation machinery, including mitochondrial ribosomes, various aminoacyl-tRNA synthetases (mt-aaRS), and translation elongation factors (267). Of particular note are the mitochondrial ribosomal proteins *MRPS7* and *MRPS22*, involved in the assembly of the 28S small subunit, and *MRPL50*, contributing to the formation of the 39S large subunit. Variants in *MRPS7* and *MRPL50* have been linked to Perrault syndrome with POI as 1 symptom. Additionally, variants in *MRPS22* have been associated with isolated POI, with carriers of biallelic variants presenting with PA and monoallelic variants carriers had SA (67, 268, 269). These findings indicate that MRPS22 deficiency-induced mitochondrial dysfunction may affect ovarian function by a dosage-dependent mode.

The mt-aaRS attaches specific amino acids to their corresponding tRNA molecules, forming mt-aaRS complexes, which further participate in protein synthesis in mitochondria (270). Mutations in genes encoding mt-aaRS, such as alanyl-tRNA synthetase 2 (*AARS2*), leucyl-tRNA synthetase 2 (*LARS2*), and histidyl-tRNA synthetase 2 (*HARS2*), have been associated with central nervous system and reproductive system abnormalities following an autosomal recessive inheritance pattern (271). Although a carrier of biallelic variant in *LARS2*, which often cause Perrault syndrome, experienced isolated POI, the possibility of a syndromic phenotype remains due to the complexity of Perrault syndrome and variable ages of onset.

Novel Tu translation elongation factor, mitochondrial (*TUFM*) is a nuclear-encoded mitochondrial protein translation elongation factor. Previous studies have reported a close relationship between *TUFM* variants and syndromic mitochondrial diseases such as encephalopathy (272, 273). Carriers of *TUFM* variants often exhibit severe mitochondrial dysfunction and early mortality, thus its role in the reproductive system has been overlooked. Recently, Zhang et al reported a case with isolated POI carried biallelic *TUFM* variant in a consanguineous family (274). The mice model with the homologous variant exhibited decreased ovarian reserve and severely impaired fertility, hinting at *TUFM's* potential role as a causative gene for POI. Nevertheless, the lack of reproductive phenotype descriptions in cases with *TUFM* variant-induced syndromic mitochondrial diseases leaves open the possibility that *TUFM* variants might contribute to syndromic POI.

In addition to the mitochondrial translation machinery mentioned above, the leucine-rich pentatricopeptide repeat containing protein (LRPPRC) can also bind to mitochondrial mRNA to promote high-fidelity translation and protein synthesis efficiency (275, 276). LRPPRC is encoded by nuclear DNA and plays multifunctional roles in vesicular transport, cytoskeletal composition, and regulation of mtDNA and nuclear DNA transcription and translation (277). Mutations in *LRPPRC* lead to the occurrence of recessive inherited Leigh syndrome, which has a high mortality rate. Female patients who survival to adulthood exhibit features of POI characterized by PA or delayed secondary sex characteristics, with ultrasound showing small ovaries and absence of follicles (278). Due to the pleiotropic effects of LRPPRC protein, the pathogenicity of *LRPPRC* variants identified in patients with POI should be interpreted cautiously.

Mitochondrial protein homeostasis

Human mitochondria contain 1000 to 1500 proteins (279). The protein homeostasis is collectively regulated by mitochondrial

chaperones, proteases, and the ubiquitin–proteasome system. They assist in protein folding and degrade damaged or mislocalized proteins by upregulating caseinolytic peptidase *P* (CLPP) and caseinolytic peptidase B (CLPB) (280). Disruption of mitochondrial proteostasis often results in a syndromic phenotype, including ovarian dysfunction. To date, 5 biallelic variants in *CLPP* have been reported in the patients with Perrault syndrome, who developed POI after puberty (261, 281-284). *CLPB* variants might induce POI in recessive and dominant modes, which also cause syndromes with metabolism abnormalities, impaired nervous system, and hematopoietic system symptoms (285). Functional studies have found that these variants affect mitochondrial function through both "gain of function" and "loss of function" effects, suggesting that mitochondrial proteostasis must be balanced to regulate cell survival, including oocytes (286).

Beside genetic defects, lifestyle and environmental factors, such as smoking, alcohol, and exposure to chemicals or bisphenol A, have been associated with oxidative stress, which in turn is linked to accelerated ovarian aging and POI (287-290). Advanced glycation end-products, which are increased in the patients with diabetes, also promote chronic oxidative stress. Therefore, the endogenous mitochondrial dysfunction induced by genetic defects or primary disease and exogenous environmental factors might cumulatively affect ovarian function and contribute to POI pathogenesis.

Monogenic and Polygenic Inheritance Patterns of POI

POI is characterized by remarkably high heterogeneity, both in clinical manifestations and genetic etiology, with correspondingly variable and complicated modes of inheritance, our understanding of which continues to expand (1). Furthermore, growing evidence from WES studies in POI cohorts from around the world (291, 292), as well as GWAS studies on ANM in the general population (8), together suggest that the pathogenicity of monogenic variants in POI is more complex than we thought. Importantly, POI also exhibits characteristics of oligogenic or polygenic inheritance, where common variants cumulatively influence the age of menopause, especially for ANM down to age 34 years, contributing to the overall genetic landscape of POI (8).

Most of the POI causal genes were identified by WES in POI pedigrees, and the majority of these genes have a recessive mode of inheritance. However, several WES studies on large-scale cohorts of sporadic POI have found that deleterious biallelic variants were carried by less than 6% of unrelated patients (292-294). Most of the variants identified in sporadic POI cases are heterozygous. Some of them cause POI through a dominant mode, which has been confirmed by family cosegregation analysis or the diminished ovarian function observed in the heterozygous mouse models. However, the pathogenicity of those heterozygous variants in traditionally recessive POI genes remains controversial.

Taking together the amenorrhea types of the heterozygous variant carriers and the ovarian phenotypes of the respective mouse models, it seems like that monoallelic variants may have a dosage-dependent effect on ovarian function. This hypothesis could be raised from 2 phenomenon: (1) certain genes responsible for syndromic POI in the biallelic state could induce isolated POI by monoallelic defects (eg, *FANCA* (115) and *FANCL* (112)); and (2) the monoallelic variants in recessive POI genes were associated with a milder phenotype, such as DOR or poor ovarian response. For instance, although biallelic variants of *BRCA2* have been reported in POI cases, some previous, well-designed prospective cohort studies have confirmed that carriers of *BRCA2* heterozygous variants exhibit decreased levels of AMH (295), lower primordial follicle densities (296), and early menopause (8). Therefore, these studies thus suggest the possibility that monoallelic variants in recessive genes could be responsible for a potentially measurable contribution to POI incidence.

Furthermore, because stringent criteria in the American College of Medical Genetics and Genomics (ACMG) guidelines may result in exclusion of a proportion of variants that were predicted to be potentially deleterious in silico but lack experimental validation, as well as the technical limitations in identifying noncoding variants and structural variants may lead to omission of deleterious variants that cannot be detected by WES (220); those monoallelic variants in recessive genes may contribute to POI by combining with another unrecognized variants in recessive mode. These limitations indicate that monoallelic variants in recessive POI genes identified by WES deserve further investigation to avoid overlooking potentially pathogenic variants.

Despite the high heritability estimates of menopausal age, multiple studies over a decade of extensive research found that monogenic inheritance only accounted for a low proportion of POI cases, indicating the involvement of non-Mendelian inheritance in POI (297, 298). Indeed, many diseases originally thought to be caused by highly penetrant Mendelian alleles actually comprise a spectrum from Mendelian to complex (299, 300). In fact, previous WES studies of POI have suggested the oligogenic or polygenic inheritance (269). Moreover, the recent population-based study involving 104 733 women from the UK Biobank found that the heterozygous high-confidence protein-truncating variants have limited penetrance for POI (77). Although there were limitations, such as only 113 women were clinically defined as patients with POI, homozygous or compound heterozygous variants or cytogenetic abnormalities have not been assessed, as well as the splice site and stop gain variants near the end of proteins had not been analyzed for true loss of function effects, those findings suggested monogenic variants could not explain the majority of the cases. Future studies should address on the genetically complex trait of POI.

Recently, some oligogenic models have been reported in other diseases. For instance, Gifford et al described an oligogenic combination of *MRTFB*, *MYH7*, and *NKX2-5* in the pathogenesis of congenital heart disease (301). In this case, a rare missense *NKX2-5* variant acts as a genetic modifier, together with missense mutations in myocardin-related transcription factor *MKL2* and sarcomeric protein *MYH7*, contributing to the left ventricular non-compaction. Additionally, Wang et al reported the cases with Müllerian duct anomalies carrying dual deleterious mutations, whose synergistic effect had been verified by animal models, revealing the digenic inheritance of Müllerian duct anomalies (302). Although the oligogenic or polygenetic mode in POI remains theoretically speculative, this is a pivotal direction for future research. Considering the technical limitations of WES in recognizing novel POI causal genes and detecting pathogenic variants in known POI genes, as described above, future studies with WGS and advanced pathogenicity

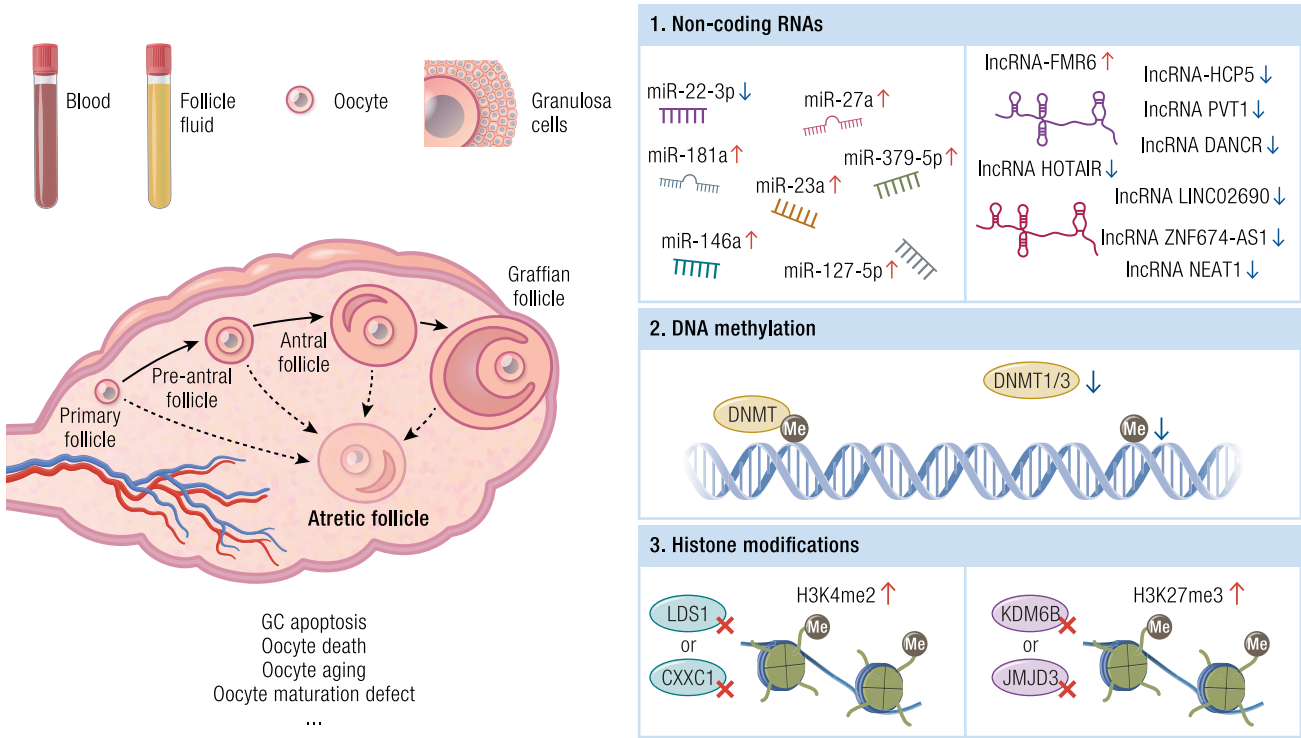


Figure 2. Epigenetic factors involved in ovarian aging and POI. Through epigenomic profiling of peripheral blood, follicular fluid, oocytes, and granulosa cells (GCs) from patients with POI or females of advanced age, numerous epigenetic markers associated with ovarian function have been identified. Multiple noncoding RNA (ncRNA), such as microRNA (miRNA) and long ncRNA (lncRNA), primarily regulate the expression of genes essential for ovarian function, inducing POI through GC apoptosis and follicular atresia. Downregulation of DNA methylation is a feature of germ cell aging. Ovarian function decline is correlated with high densities of hypomethylated CpG-rich regions in GCs, and the expression of DNA methyltransferase (DNMT) in MII oocytes is decreased as ovarian aging. Histone modifications play a critical role in follicle development. The histone 3 lysine 4 (H3K4) methylation is involved in primordial follicle formation, follicle atresia, and germinal vesicle breakdown. Disruption of H3K4me2 demethylase LSD1 in oocytes or H3K4me3 regulator CXXC1 in GCs leads to increased follicle atresia. Moreover, deletion of H3K27me3 demethylase KDM6B and JMJD3 in GCs affects the nuclear–mitochondrial genomes and leads to subfertility, indicating their potential role in POI occurrence.

evaluation system for variants, will facilitate establishing a comprehensive genetic architecture of POI.

Epigenetic Etiology of POI

During folliculogenesis, the orderly activation and inhibition of mass genes are under the synergistic control of diverse modifiers through genetic and epigenetic events (21). Epigenetic modification, such as noncoding RNA expression, DNA methylation, and histone modification, may change chromatin structure without affecting the DNA sequence to regulate gene expression and functions, and is considered as a hallmark of aging. Over the past few decades, substantial progress has been made in studies of epigenetic alterations during germ cell development. There is increasing evidence that epigenetic modifications are involved in the occurrence and progression of POI (303). Here, we introduced these alterations through noncoding RNA, DNA methylation, and histone modifications perspectives (Fig. 2).

Noncoding RNAs

Noncoding RNAs (ncRNAs) are not capable of protein translation, yet they regulate gene expression by interacting with nucleotide sequences or proteins, and participate in follicle development (304, 305). Recent studies have demonstrated that microRNAs (miRNAs) and their target genes play an important role in the pathogenesis of POI by inhibiting GCs proliferation, promoting apoptosis, and impairing genomic integrity. Dang et al identified miR-22-3p was significantly downregulated in the plasma of patients with POI compared to age-matched controls and was negatively associated with serum FSH levels (272). Chen et al reported the upregulation of miR-146a in the plasma and GCs from patients with POI, which contributed to GCs apoptosis by targeting IRAK1 and TRAF6 via the caspase cascade pathway (274). Elevated serum levels of miR-23a and miR-27a in the patients with POI also have been found to promote GCs apoptosis via the FasL-Fas pathway (306). Conversely, another upregulated miRNA, miR-181a, found in the blood of POI cases, has been shown to inhibit GCs proliferation by suppressing the expression of activin receptor ACVR2A (307). Moreover, miR-379-5p (308) and miR-127-5p (309) were identified to be upregulated in the GCs from patients with biochemical POI (bPOI, defined as serum FSH between 10 and 25 IU/L). These miRNAs may promote the progression of POI by inhibiting the proliferation and DNA repair capacity of GCs through targeting PARP1and XRCC6, and HMGB2, respectively.

In addition to miRNAs, long ncRNAs (lncRNAs) are also regulators of the specification and proliferation of GCs and contribute to the pathogenesis of POI. Fragile X-associated POI (FXPOI) is 1 type of POI induced by *FMR1* premutation (an expansion of CGG repeats within the 5′ UTR of the *FMR1* gene). Recent study found that lncRNA-FMR6, an antisense lncRNA

produced by the 3′ UTR of *FMR1*, in the cumulus GCs was negatively related to the number of oocytes (310). In vitro experiments found overexpression of lncRNA-FMR6 inhibited the proliferation of GC cells, impairing follicle development (311), confirming the *FMR1* RNA toxicity is a potential mechanism of FXPOI. Moreover, lncRNA HCP5 (312), lncRNA PVT1 (313), lncRNA LINC02690 or GCAT1 (314), lncRNA ZNF674-AS1 (315), lncRNA HOTAIR (316), lncRNA DANCR, and lncRNA NEAT1 were identified to be downregulated in the GCs of patients with POI, which contribute to follicle atresia by GCs apoptosis (317, 318).

Moreover, Zhou and colleagues investigated the expression profiles of circular RNAs (circRNAs) in the GCs from patients with bPOI. They demonstrated that upregulated hsa_circ_003785 and hsa_circ_103903 were positively correlated with serum FSH, while the downregulated hsa_circ_008389 was positively correlated with AMH level and antral follicle counts (AFCs). They further constructed a circRNA-miRNA network and found the miRNA-targeted genes predominantly enriched in the FOXO signaling and cellular senescence pathway, suggesting that circRNAs may be involved in the pathogenesis of POI via circRNA–miRNA-targeted gene regulation (319). In addition, a recent study found circBRCA1 was decreased in the serum and GCs of patients with POI. Further study found circBRCA1 upregulated FOXO1 expression by sponging miR-642a-5p. CircBRCA1 insufficiency could aggravate mitochondrial dysfunction and induce GCs senescence through miR-642a-5p/FOXO1 axis, confirming the role of circRNAs involving in the pathogenesis of POI (320).

Notably, multiple studies have revealed that ncRNAs are also involved in the occurrence of drug-induced POI. Cisplatin and tripterygium glycosides promote cytotoxicity, senescence and apoptosis of GCs by upregulation of miR-125a-5p and miR-15a, respectively (321, 322). Cyclophosphamide upregulates the expression of miR-15b, leading to the reduced ability of mouse GCs to induce autophagy and ROS scavenging (323). Meanwhile, cyclophosphamide defers GCs proliferation and promotes POI by inducing lncRNA-Meg3 expression (324). Understanding the molecular mechanism underlying drug-induced POI is of great significance for protecting ovarian function prior to medication administration.

Recently, some ncRNAs have been investigated as potential biomarkers and pharmaceutical targets for ovarian reserve decline. For instance, miR-22-3p in exosomes derived from umbilical cord stromal cell (325), miR-369-3p in exosomes derived from human amniotic fluid stem cell (326), miR-644-5p (327), and miR-144-5p (328) in exosomes derived from bone mesenchymal stem cell (MSC) have been found to attenuate the apoptosis of GCs. lncRNA nuclear enriched abundant transcript 1 (NEAT1) and melatonin could block GCs autophagy by inhibiting the expression of miR-654 and miR-15a-5p, respectively (329, 330). Moreover, miR-126-3p and miR-21 could downregulate LATS1 to reduce the phosphorylated LOXL2 and YAP levels and ultimately promote estrogen secretion in GCs (331, 332). However, most of the studies were performed in the mice models, their application in clinical practice still needs more evidence.

DNA Methylation

DNA methylation patterns of germ cell change mainly along fetal age and abnormal DNA methylation is a feature of germ cell aging (85, 87, 333). A genome-wide DNA methylation study was conducted in human ovarian GCs and found the ovarian function decline correlated with high densities of hypomethylated CpG-rich regions (334). That might result in the decreased expression of genes essential for the maintenance of ovarian function, such as AMH, result in DOR and response to gonadotropins (334). Recently, Lu and colleagues integrate the DNA methylation profile of human GCs and the transcriptomic data from patients with POI, and found that majority of the 240 differentially expressed and methylated genes were enriched in oxidative stress pathways (335). They also found the top hub genes hypomethylated in in exon regions and the 3′ UTRs correlated with abnormal metabolism, providing insights into the pathological mechanism of POI and potential therapeutic targets. Studies from murine models found deficiency of Tet methylcytosine dioxygenase 1 increases the DNA methylation levels of a subset of meiotic genes in the oocytes, subsequently decreases their expression, leading to abnormal synapsis induced oocyte apoptosis and ovarian reserve decline (336, 337). Additionally, the expression levels of DNA methyltransferase (DNMT) 1/3a/3b/3L and DNA methylation levels in MII oocytes were decreased significantly as aging (338). Upregulating the expression of DNMTs by drugs or allografting brown adipose tissue could improve the DNA methylation status of ovarian tissue, thereby enhancing the quantity and quality of oocytes (339, 340). However, how to use the methylation data for ovarian function assessment or how to develop the treatment strategies of POI still face many challenges.

Histone Modifications

Although there is currently little direct evidence addressing the association between histone modifications and POI, histone modifications have been indicated to play a critical role in follicle development (341). The histone 3 lysine 4 (H3K4) methylation (H3K4me1/2/3) is mainly related to gene transcriptional activation and is involved in primordial follicle formation, follicle atresia, and germinal vesicle breakdown. Disruption of H3K4me2 demethylase LSD1 in the oocytes (342, 343) or H3K4me3 regulator CXXC1 in GCs (344-346) lead to increased follicle atresia, indicating a potential role of them in ovarian aging and POI.

The H3K9 methylation modification (H3K9me1/2/3) primarily represses gene transcription, playing an important role in epigenetic reprogramming of PGCs (88) In females, it mainly affects the number of germ cells after birth and their potential of differentiating into growing oocytes (347). Lysine demethylase 6B (KDM6B) specifically catalyzes the demethylation of H3K27me3, playing a crucial role in coordinating the nuclear–mitochondrial genomes, which is essential for maintaining ovarian function and female fertility. Conditional deletion of *Jmjd3*, another H3K27me3 demethylase, in GCs leads to a significant reduction in mtDNA content, a decrease in the total number of healthy follicles, disruption in the estrous cycle, and increased follicular atresia, ultimately leading to subfertility and premature ovarian failure (348).

Other histone modifications also have different degrees of influence on follicle development. Histone deacetylases (HDACs) participate in maintaining primordial follicles in a dormant state by regulating the mTOR-KITL signaling pathway (349). Overexpression of HDAC6 in mice increased the number of follicles, especially secondary and antral follicles,

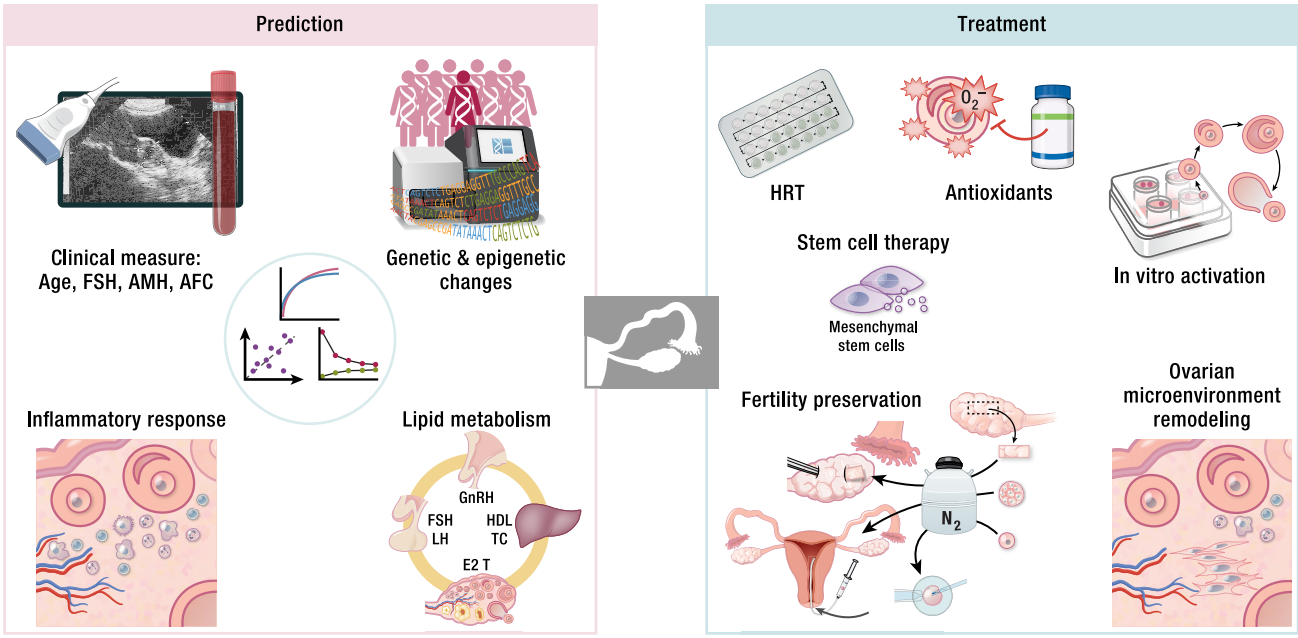


Figure 3. Early prediction and treatment of POI. Since ovarian reserve decline is irreversible, early prediction and intervention of POI are prioritized. The ovarian reserve assessment model has been developed using clinical measures such as age, AMH, FSH, and antral follicle counts (AFCs). With advances in the genetic and epigenetic etiologies of POI, combined with ovarian aging-related biomarkers in inflammatory response and lipid metabolism, a multidimensional prediction model for POI will be generated. Moreover, besides individual treatments with HRT and antioxidants, advances in bioengineering promote the development of promising strategies, such as fertility preservation, ovarian microenvironment remodeling, and stem cell transplantation, in the treatment of POI.

reduced H3K9me3 levels, and prolonged the reproductive lifespan (350). In addition, the histone ubiquitination/deubiquitination system plays a vital role in meiotic and mitotic processes (351). DCAF13 is a part of the Cul4-RING E3 ubiquitin ligase complex, which participates in the processing of 18S rRNA in growing oocytes (352). Deficiency of DCAF13 in oocytes inhibits follicle development, resulting in defective chromatin condensation, premature ovarian failure, and female sterility (353, 354).

These studies suggest that dysregulation of histone modification may be a cause of insufficient establishment of the primordial follicle pool and accelerated follicle loss, providing new insights into the epigenetic etiology of POI. Notably, ordered histone modification also is essential for oocyte maturation, fertilization, and early embryo development through maternal-zygotic transcription and zygotic genome activation (355). Therefore, defects in histone modification could result in other reproductive disorders besides POI, such as oocyte maturation defects, embryonic developmental arrest, and recurrent implantation failure.

Intervention of POI

Because ovarian reserve decline is irreversible, there is currently no effective method to restore the ovarian function of patients with POI. Therefore, early detection, early diagnosis, and early intervention during the development of the disease are prioritized. Elucidating the pathogenic mechanisms of POI could facilitate timely identification of the females with high-risk of POI. With the early reproductive counseling and comprehensive health management, they may have improved pregnancy outcome and life quality in the future. In this section, we will introduce the potential prediction and treatment strategies to improve the long-term health and reproductive outcomes of the patients with POI (Fig. 3).

Prediction and Early Warning of POI

Recent clinicians recommended that POI should be considered when women present with new-onset irregular menses or amenorrhea and possibly vasomotor, depressive, or anxiety symptoms (1). Women with elevated FSH and low estradiol levels measured on 2 occasions 1 month apart should be diagnosed with POI. Moreover, declining serum AMH, inhibin B, and AFC are also used to evaluate ovarian function. However, diagnosing POI still faces many challenges, including heterogeneous phenotypes, diverse diagnostic criteria, and the limitations of laboratory tests, resulting in prolonged time to diagnosis and treatment. Most patients when diagnosed with POI would face a low chance of spontaneous pregnancy due to significantly reduced ovarian reserve. Therefore, there is an urgent need for the development of a tool to predict POI at an earlier stage.

The understanding of genetic factors associated with natural and pathological menopause has been expanded through large-scale GWAS and WES studies, enabling genetic prediction of POI. Perry and colleagues calculated a polygenic score (PGS) for ANM using GWAS data from 108 840 women of European ancestry and found that the PGS performed well in predicting the risk of POI. Women at the top 1% of the PGS had equivalent POI risk to those with *FMR1* premutation (8, 356). Notably, the common variants associated with ANM

may vary due to ethnic and regional differences, and the predictive efficiency of the PGS for women with menopause onset before age 34 remains unclear. For these women, genetic prediction of POI may be facilitated by WES to identify pathogenic variants in POI causal genes, and the accuracy is expected to be improved with advances in WGS.

In addition, an increasing number of studies have endeavored to develop models capable of predicting ovarian reserve by integrating multidimensional clinical, biochemical, and imaging metrics. As early as 2010, Younis et al employed logistic regression analysis to identify 8 independent factors associated with low ovarian reserve, defined as 3 or fewer retrieved oocytes, in the women undergoing IVF treatment. They subsequently developed a multivariate scoring system and found that a cumulative score greater than 14 was more accurate than independent variables, such as age, basal FSH, and AFC, in predicting low ovarian reserve, with a sensitivity of 88% and a specificity of 69% (357). However, the use of this score to predict POI is inappropriate because the study was conducted with infertile women without diagnosed POI. Venturella et al generated a generalized linear model incorporating factors, such as AMH, basal FSH, E2, AFC, ovarian volume, vascular index, and flow index of ovary, to predict the ovarian age (named OvAge model) in 652 healthy fertile women and 29 patients with POI (358). The results showed that the predicted ovarian age of patients with POI (mean 50.63 ± 3.80 years) was significantly higher than their chronological age (mean 37.90 ± 3.31 years), suggesting that the model could identify depleted ovarian reserve in patients with POI, analogous to that observed in women ANM onset. Furthermore, machine learning methods have advanced the development of predictive models for ovarian reserve. Through retrospective cohort studies, Qiao and colleagues generated 3 mathematical models, including AA (AMH and Age), AFA (AMH, FSH and Age), and AAFA (AMH, AFC, FSH, and age), to predict ovarian reserve using the number of retrieved oocytes as outcome variables (359, 360). Based on the 3 models, they established an ovarian aging curve to predict the time to menopause (OvaRePred) (9). While, the viability of above models in predicting the risk of POI still needs to be validated by prospective cohort studies.

Moreover, the effects of iatrogenic and environmental factors also should be considered when predicting POI. Using training data from 7891 females in the Childhood Cancer Survivor Study and validation data from 1349 females in the St Jude Lifetime Cohort, Im et al developed age-specific risk prediction models for POI (failure to enter puberty or menopause before 40 years old) in childhood cancer survivors (361). Factors such as increased pelvic radiation, use of alkylators, hematopoietic stem cell transplantation, and younger age at cancer diagnosis are predictors of POI. They developed a risk prediction model for POI with the area under the receiver operating characteristic curve at 0.88 to 0.95. In addition, the polygenic risk predictor enhanced the average positive predictive value of the model from 0.76 to 0.87, suggesting that a comprehensive tool incorporating clinical and genetic data could improve the accuracy and generalizability of POI prediction models in clinical practice.

With the application of multiomics techniques in the study of reproductive aging, increasing potential biomarkers for POI would enhance the viability of POI prediction models. The combined analysis of single-cell RNA sequencing and spatial transcriptomics in human ovaries identified FOXP1 as a protective factor for ovarian aging (362). Silencing FOXP1 in GCs results in POI-like phenotype in mice, indicating its potential role in predicting POI. Pei et al also found the activation of the AP1 pathway within the ovarian microenvironment of humans and nonhuman primates is a feature of the premenopausal to postmenopausal transition (363). Furthermore, single-cell transcriptomic studies of nonhuman primates ovaries revealed various genes associated with ovarian senescence, including antioxidant genes that are specifically downregulated in oocytes and GCs during the early stages of ovarian senescence, such as *GPX1*, *GSR*, *GPX4*, and *PON1* (249). In addition, Harasimov et al analyzed proteostasis in mice ovaries and found 352 extremely long-lived protein in the oocytes and surrounding somatic cells, which functioned in mitochondria, cytoskeleton, chromatin, and proteostasis. Among them, those proteins sharply decreased with aging, which involved in DSBs repair, telomere function and zona pellucida pathway, as well as those increased proteins involved in inflammatory response, retinoic acid synthesis, and oxygen-related pathway, are likely to participate in ovarian aging (364). These increasing data enhances our understanding of the molecular mechanisms underlying both physical and pathogenic ovarian aging. The mechanisms by which these ovarian aging–related proteins influence ovarian function and their potential role in POI prediction are still needed to be investigated. Clinical studies are also needed to clarify the predictive accuracy and reliability of these markers in different populations, as well as the applicability of incorporating these markers into the predicative models of POI.

Hormone Replacement Therapy

Although the decline in ovarian reserve is irreversible, appropriate HRT is crucial for alleviating vasomotor and vulvovaginal atrophy symptoms and for optimizing long-term cardiovascular and bone health (365-367). HRT should be individualized based on age, clinical characteristics, and patient needs. In the absence of contraindications, patients with primary amenorrhea at puberty should be treated with low-dose estradiol (0.05-0.07 μg/kg/day transdermally or 0.3-0.5 mg/day orally) to mimic the physical tempo of puberty, with gradual dose escalation to adult levels over 2 to 3 years to induce puberty with optimal breast development. When adequate endometrial development is observed by ultrasound or vaginal bleeding occurs, or after 2 years of estrogen treatment, progesterone should be added cyclically, using micronized progesterone 200 mg or medroxyprogesterone 5 mg daily for 14 days, to protect the endometrium (368). For adult women with POI, physiological HRT to replace premenopausal levels of ovarian hormones until natural menopause is recommended. This includes oral estradiol (1-2 mg/day) or transdermal estradiol (50-100 μg/day), followed by progesterone (200 mg/day) or norethisterone (1-5 mg/day orally or 0.25 mg/day transdermally) for 10 to 14 days cyclically (369). Compared with combined oral contraceptive pills, physiological HRT is reported to be more effective in maintaining bone and cardiovascular health in young women with POI (367, 369-371). Furthermore, the transdermal or transvaginal routes for estradiol are preferred because they reduce the first-pass effect on the liver and the risk of venous thromboembolism (372-374).

Furthermore, concerns have been raised about the increased risk of hormone-sensitive cancers, such as breast and ovarian cancer, associated with HRT use. The clinical evidence of HRT not increasing the risk of those cancers before the age

of natural menopause remains insufficient. Notably, due to the high risk of ovarian and breast cancer in carriers of FA and BRCA mutations (375-377), HRT should be carefully considered for POI cases with these mutations. To date, 11 clinical studies have evaluated the effect of HRT on breast cancer risk in BRCA mutation carriers. Most studies found that short-term HRT use did not increase the risk of breast cancer after risk-reducing salpingo-oophorectomy (RRSO) (378-382). However, some studies have indicated that different agents and timing of hormone exposure may alter the risk. In a prospective cohort study with a 10-year follow-up, Kotsopoulos et al observed that the cumulative incidence of breast cancer was significantly lower in patients treated with estrogen-alone HRT than in those treated with estrogen plus progesterone HRT. This suggests a potentially detrimental effect of HRT regimens that include progestins on breast cancer (383). Furthermore, Michaelson-Cohen et al found that short-term post-RRSO HRT use was associated with a threefold increased risk of breast cancer in BRCA mutation carriers who received HRT after age 45, indicating that the effect of HRT on breast cancer risk is age-related (384). The Clinical Practice Guidelines in Oncology (Version 2.2021) recommend prophylactic RRSO after the completion of childbearing and the use of HRT for less than 5 years based on postmenopausal symptoms, which does not appear to increase cancer risk in gene mutation carriers (385). Due to varying criteria for subject inclusion, limited sample sizes, unclear routes and dosages of HRT drugs, and recall bias in retrospective studies, future prospective studies are needed to refine personalized treatment for patients with specific genetic characteristics.

Besides estrogen and progesterone, the inclusion of dehydroepiandrosterone (DHEA) in the HRT regimen has shown potential in enhancing ovarian function with limited data. DHEA is an endogenous steroid secreted by the female adrenal cortex and ovarian theca cells, involved in estrogen synthesis and folliculogenesis. Because testosterone supplement has potential risks of excess hair, acne, weight gain, even deepened voice and clitoral enlargement in high dosage, the routine use is not recommended in the guidelines. Since 2005, several observational studies have showed that supplementation with DHEA could improve ovarian response and pregnancy outcomes in patients with POI or DOR (386-391). However, a randomized controlled trial found that women with POI receiving 25 mg of DHEA 3 times a day for 16 weeks did not show significant changes in serum AMH and FSH levels, although higher AFC and ovarian volume were observed in the DHEA group at 12 and 20 weeks, respectively (392). Therefore, more clinical trials with larger sample-size are needed to verify the effect of DHEA in the treatment of POI, especially focus on the dosage, duration, and safety.

Prolong Reproductive Lifespan by Remodeling Ovarian Microenvironment

The development, atresia, and ovulation of follicles are influenced by the dynamic mechanical forces surrounding them, interactions between oocytes and somatic cells, as well as angiogenesis and immune cell infiltration within the ovarian microenvironment (14, 249, 393). Studies on reproductive senescence suggest improving ovarian microenvironment is a promising strategy to prolong reproductive lifespan, providing potential targets for POI intervention (249, 362-364).

Multiomics studies in murine models (11, 12) suggest that alterations in the extracellular matrix and vasculature regulate ovarian aging. Transplantation of stromal cells from young mice or inhibiting neovascularization can prolong the reproductive lifespan of aged mice (394, 395), potentially by decelerating primordial follicle activation due to altered mechanotransduction signals and nutrient transfer. Recent spatial transcriptomics studies in human ovaries identified 3 GC subtypes and 5 subtypes of theca and stromal cells involved in ovarian aging (362). Additionally, long-lived proteins related to ovarian aging were found to be expressed in oocyte, ovarian stromal cells, GCs, and theca cells, confirming that ovarian senescence was driven by both oocytes and surrounding somatic cells (364). Therefore, treatments targeting at these stromal cell components and proteins hold promise for extending ovarian function in patients with POI.

Moreover, inflammatory factors (eg, TNF-α, IL-1, NLRP3 inflammatory vesicles, etc.) and immune cell differentiation (eg, macrophages, T-cells, B-cells, etc.) contribute to ovarian aging by disrupting the immune balance within the ovarian microenvironment (10, 396-400). Zhou et al observed that macrophages activated through the pyroptosis pathway remolded the ovarian immuno-microenvironment, promoted stromal cell senescence, and accelerated ovarian function decline. In contrast, inhibition of the pyroptosis pathway via knockout of GSDMD (a key executor of pyroptosis) or through the use of disulfiram (a known pyroptosis inhibitor) could partially increase the number of retrieved oocytes from aged ovaries, suggesting the potential role of these strategies in treating ovarian aging (10). Another study confirms that in the aged ovaries, inflammation-induced upregulation of NADase CD38 significantly reduced NAD+ levels, accelerating ovarian aging. In that study, a small molecule CD38 inhibitor enhanced oocyte quality and fertility by countering age-related gene expression changes and intercellular communication alterations (396). These studies provide novel insights into intervention strategies aimed at delaying POI progression.

Fertility Treatments

The spontaneous pregnancy rate in patients with POI is below 5%. Most patients achieve their fertility goals through the use of donor oocytes and IVF treatment. However, the clinical pregnancy rate among patients with POI undergoing ART remains below 10% (401). Recent studies have indicated that antioxidants, stem cells, and IVA may improve the reproductive outcomes of the patients.

Antioxidants

Oxidative stress induced by various factors can lead to elevated ROS level and inflammatory factors in the ovaries, resulting in reduced ovarian function (249). Antioxidants and molecules that affect antioxidant signaling pathways have the potential to improve follicle quality by modulating these mechanisms. Coenzyme Q10 (CoQ10) has been reported to positively impact ovarian function due to its antioxidant properties that enhance mitochondrial function. In primate oocytes, the expression of enzymes responsible for CoQ10 production, such as PDSS2 and COQ6, declines with aging. However, the age-related ovarian reserve decline could be mitigated by CoQ10 administration (402). Furthermore, in mice models of POI or POF (FSH > 40 IU/L) induced by

VCD or cyclophosphamide, oral administration of CoQ10 at 150 mg/kg/day for 14 days or 22 mg/kg/48 hours for 21 days reduced serum ROS levels and partially reversed ovarian failure (403, 404). Another well-known antioxidant, melatonin, has been demonstrated to protect the ovary from chemotherapy by preventing primordial follicle activation through the PTEN/AKT/FOXO3a pathway (405-409). Additionally, antioxidants such as resveratrol (410) and N-acetyl-L-cysteine (411) have also been found to alleviate GC injury by enhancing autophagy or inhibiting apoptosis.

Based on foundational studies, antioxidants have been employed in managing ovarian aging, including in women with DOR or advanced age. A meta-analysis encompassing 20 randomized clinical trials involving 2617 participants found that the addition of antioxidants, such as CoQ10, melatonin, inositol, vitamins, resveratrol, acetyl L-carnitine, N-acetyl-L-cysteine, and a-lipoic acid, could increase the number of retrieved oocytes and clinical pregnancy rates during IVF treatment (412). CoQ10 is more effective than other antioxidants, with a dosage of 30 mg/day for 3 months prior to controlled ovarian stimulation proving optimal for improving pregnancy rates, particularly in those under 35 years of age with DOR (412). However, the effects of these antioxidants on reproductive outcomes in women with POI remain unclear. Furthermore, the recently identified antioxidant spermidine, which may improve the quality of aged oocytes, could also represent a potential therapeutic strategy for enhancing reproductive outcomes in POI cases (11). Therefore, the clinical application of these antioxidants in the reproductive management of POI, particularly biochemical POI, requires further high-quality clinical trials to determine optimal dosages and assess potential adverse effects.

Stem cell therapy

Transplantation of MSCs and their exosomes has been shown to be a promising strategy to improve follicular development and reproductive outcome in the murine models of POI (413-419). The MSCs used in treatment include human umbilical cord–derived MSCs (hUC-MSCs) (414-416), human adipose–derived MSCs (418), and bone marrow–derived MSCs (419). These treatments exhibit anti-inflammatory and antioxidant effects, remodel the immune microenvironment around follicles, and promote GC proliferation, thereby reduce the speed of ovarian reserve decline and activate primordial follicles (420). However, clinical trials are limited. Aghdami and colleagues conducted a nonrandomized clinical trial of transplanting autologous human adipose–derived MSCs into the ovaries of 9 patients with POI. They observed resumption of menstruation and decreased serum FSH level in 4 cases, while the pregnancy outcome had not been followed (421). Wang's team conducted a clinical trial of hUC-MSCs in 61 patients with POI. Among them, 15 patients received oocytes retrieval for in vitro fertilization and 4 patients delivered normally developed babies. Moreover, they found that patients with POI with shorter durations of amenorrhea (<1 year) or better ovarian conditions appeared to achieve better outcomes after stem cell therapy (422). Sun's team found that transplantation of hUC-MSCs on a collagen scaffold into the ovaries of patients with POF (FSH > 40 IU/L) could promote follicle activation compared to transplantation with isolated hUC-MSCs. Two cases conceived naturally in the study, but 1 case induced labor at 24 weeks due to fetal trisomy 21 syndrome (420). Although microsatellite loci analysis showed that the fetus was genetically related to the mother but not to the donor hUC-MSCs, the safety of stem cell transfer still should be considered. Recently, utilization of MSC-derived exosomes offers a cell-free option that retains the reparative properties of MSCs while overcomes tumorigenesis and immunogenicity of stem cells (423-425). Furthermore, MSCs and MSC-derived exosomes improve ovarian function via paracrine of cytokines and ncRNAs. These paracrine factors are promising targets for the treatment of POI as well.

Previous studies have demonstrated that human amniotic epithelial cells (hAECs) can restore ovarian function in the POI mouse model by inhibiting GC apoptosis and promoting angiogenesis (426-428). Recently, Lai and colleagues conducted a single-arm, phase 1 clinical trial to assess the safety and efficacy of allogenic hAECs in treating POF (FSH > 40 IU/L) (429). The researchers transplanted hAECs via the ovarian artery in 35 cases, finding that endometrial thickness, ovarian size, sex hormone levels, and menopausal symptoms were temporarily improved without serious adverse events during the 5-month follow-up period. Despite the clinical trial demonstrated positive short-term outcomes, long-term follow-up data on ovarian function and offspring remain unavailable. Therefore, the safety of clinical treatments involving stem cells must be thoroughly assessed, and randomized controlled trials with extended follow-up periods and larger sample sizes are necessary.

In vitro activation of early follicles

In recent years, IVA of early follicles has emerged as a promising fertility treatment for patients with POI. It is initially used to stimulate the residual primordial follicles in women with DOR through interruption of Hippo signaling pathway and stimulation of PI3K/AKT pathway (184, 430). Clinical studies found 40%–60% of the patients with POI with residual follicles showed follicle growth after treatment, resulting in 6 birth of healthy infants, even for those retransplanted with cryopreserved ovarian tissues (184, 431-433). Moreover, because some drugs such as AKT stimulating drugs or PTEN inhibitors could induce morphological abnormalities and DNA repair defects of oocytes (434, 435), IVA has been evolved into a medication-free process that is adequate to stimulate the growth and maturation of follicles (436, 437). In addition, there exist several issues with IVA that demand attention, such as lacking imaging techniques to localize residual follicles, low success rate of developing primordial follicle into growing follicles, and limited developmental potential of the obtained oocytes. Therefore, ongoing modifications is needed to enhance the safety and efficacy of IVA, thereby accelerating the clinical translation of this technology.

Fertility Preservation

The options for fertility preservation depend on the women's ovarian condition and pubertal status. Postpubertal patients with POI with visible antral follicles can undergo standard assisted reproductive technologies, including controlled ovarian stimulation and oocyte cryopreservation or embryo cryopreservation. For prepubertal girls at high risk of POI, such as those who will receive chemotherapy, pelvic radiotherapy or ovarian surgery for malignant disease, as well as those with Turner syndrome, ovarian tissue cryopreservation (OTC) is recommended (438, 439). For adolescents and

women with sex hormone–sensitive cancer or the treatment cannot be postponed, OTC is also optimal (440-442).

Ovarian tissue cryopreservation and transplantation

Transplantation of cryopreserved ovarian tissue has been shown to restore physiological sex hormone cycles and fulfill patients' fertility desires. Approximately 95% of the patients receiving ovarian tissue transplantation (OTT) have spontaneous menstruation, but the duration of ovarian function maintenance is approximately 2 to 5 years. To date, over 360 cases of OTT have been reported, with more than 140 live births resulting from these procedures. The use of OTC and OTT in clinical practice remains limited due to significant follicle loss (443, 444).

After OTT, functional vasculature is reestablished around 10 days and aerobic metabolism appears to be stabilized around 18 days (445). During that time, nearly 50% to 90% of the follicles in the grafted tissue are lost (443). This burn-out phenomenon is induced in 2 ways: (1) hypoxia occurring before revascularization and excessive ROS induced by reperfusion promote apoptosis of oocytes and somatic cells in growing follicles (446); and (2) a large number of primordial follicles are activated by hypoxia-related signaling such as VEGF and the PI3K/AKT pathways, leading to a more rapid depletion of ovarian reserve in grafted tissue (447).

To mitigate follicle loss after OTT, investigations focus on enhancing revascularization to minimize grafted tissue injury. Several strategies have been explored in murine models with encouraging results, including growth factors and antioxidants such as superoxide dismutase (448), N-acetylcysteine (449), and melatonin (450). However, data on their effectiveness in human OTT are lacking. Administration of stem cells has achieved promising results due to their roles in revascularization and follicle survival. Adipose-derived-MSCs have been shown to enhance neovascularization by secreting VEGF and differentiating into endothelial-like lineages. Treatment involving the encapsulation of hAD-MSCs in a fibrin scaffold and grafted 2 weeks prior to OTT into the peritoneal transplantation site increased oxygenation and vascularization rates, as well as follicle survival rates of the grafted ovarian tissue (451). Techniques combining stem cells and biomaterials are promising for preserving follicles after OTT.

Bioengineered artificial ovary

In patients with hematological malignancies, such as leukemia, lymphoma, and myeloproliferative or myelodysplastic diseases, OTC and OTT increase the risk of reimplanting malignant cells (443, 444). To mitigate this risk, researchers have investigated alternative approaches, including dissociating follicles from ovarian tissues and generating a 3D matrix to encapsulate the isolated follicles for transplantation, which is called an artificial ovary. The key factors influencing the survival rate of artificial ovary transplantation include the quality of isolated follicles and the characteristics of biomaterials that support follicle development and hormone secretion. The follicle isolation process prioritizes maintaining the integrity of the follicle basal membrane (452) and washing follicles to remove malignant cells (453). To enhance the 3D matrix, investigations have been conducted into the integration of ovarian stromal cells (454) and endothelial cells (455) into the artificial ovary, which can reestablish communication between follicles and surrounding stromal cells and promote vascularization post-transplantation. Additionally, both natural biomaterials, like decellularized ovarian tissue and fibrin, and synthetic materials, like hydrogel, offer promising strategies to address critical issues of stem cell homing, grafting efficiency, and histocompatibility during implantation (456-459). The biomaterial suitable for encapsulating isolated human follicles and cells has been explored based on its characteristics, such as stiffness, elasticity, biosafety, biodegradability, and biocompatibility. For instance, although alginate hydrogels have been used for in vitro maturation of follicles, due to its high rigidity and limited plasticity, it is not easily remodeled by ovarian cells and does not support vascular penetration, rendering it unsuitable for creating an artificial ovary (460). In contrast, fibrin matrix is an elective choice for construction of an artificial ovary, because it is more readily degraded by ovarian somatic cells, resembling physiological ovarian rigidity at certain concentration and maintaining follicular development through adaptive structural changes (461-463).

Future Perspectives for POI Diagnosis and Treatment

It should also be acknowledged that clinical diagnostics of POI may not immediately benefit from the identification of those pathogenic genetic and epigenetic factors, and that further studies are needed to rigorously and definitively establish a causal relationship between genotype and phenotype. At the same time, it is clear that criteria for defining causal genetic variations should also evolve to accommodate a broader scope of inheritance modes and phenotypic manifestations, which requires medical geneticists, clinical reproductive endocrinologists, and epidemiologists working in concert to avoid overlooking genetic factors that may be clinically relevant but do not meet classical diagnostic criteria.

Moreover, with the discovery of a growing number of ovarian aging biomarkers, it is possible to establish multimodal predictive models for POI. However, validation through clinical studies is essential. Further exploration of the mechanisms through which microenvironmental can alter ovarian function, along with ongoing refinement of therapeutic safety and effectiveness of the established strategies (eg, MSC transplantation and fertility preservation) through prospective clinical trials, will collectively facilitate the development of comprehensive intervention strategies for POI.

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The authors have nothing to disclose.

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