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An update on primary ovarian insufficiency

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Primary ovarian insufficiency (POI) occurs in about 1% of female population under the age of 40, leading to reproductive problems, an earlier encounter with menopausal symptoms, and complicated diseases. There are three presumable mechanisms involved in the development of POI, namely apoptosis acceleration, follicular maturation blocking and premature follicle activation, through the following studied causes: (i) chromosomal abnormalities or gene mutations: mostly involve X chromosome, such as *FMR1* premutation; more and more potentially causal genes have been screened recently; (ii) metabolic disorders such as classic galactosaemia and 17-OH deficiency; (iii) autoimmune mediated ovarian damage: observed alone or with some certain autoimmune disorders and syndromes; but the specificity and sensitivity of antibodies towards ovary are still questionable; (iv) iatrogenic: radiotherapy or chemotherapy used in cancer treatment, as well as pelvic surgery with potential threat to ovaries' blood supply can directly damage ovarian function; (v) virus infection such as HIV and mumps; (vi) toxins and other environmental/lifestyle factors: cigarette smoking, toxins (e.g., 4-vinylcyclohexene diepoxide), and other environmental factors are associated with the development of POI. The etiology of a majority of POI cases is not identified, and is believed to be multifactorial. Strategies to POI include hormone replacement and infertility treatment. Assisted conception with donated oocytes has been proven to achieve pregnancy in POI women. Embryo cryopreservation, ovarian tissue cryopreservation and oocyte cryopreservation have been used to preserve ovarian reserve in women undergoing cancer treatments.

primary ovarian insufficiency, genetic aberrations, environmental factors, hormone replacement therapy, ovary preservation

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Primary ovarian insufficiency (POI), commonly referred to as premature ovarian failure (POF), is defined as the occurrence of amenorrhea (for 4 months or more) before the age of 40 in women, accompanied with an increase of serum FSH to menopausal level (usually over 40 IU L^{-1}, obtained at least 1 month apart), and estradiol levels less than 50 pg mL^{-1} (which indicate hypoestrogenism) [1]. Primary ovarian insufficiency is first brought to light by Fuller Albright in 1942, who emphasized that the end stage of ovarian function is the primary defect rather than abnormality in gonadotropin secretion [2], and avoided the discomforting and inaccurate stressing on "failure", like death-sentence for ovarian function and conception.

Menopause is a destined phase of women, which is expected to occur at around the age of (50±4) years in US women [3]. The age of 40 is two standard deviations below this average [4]. With an incidence of 1% in women under the age of 40, and 0.1% in women under the age of 30 [5], POI renders patients estrogen deficiency and anovulation, resulting in vasomotor symptoms (hot flashes and night sweats), atrophic vaginitis, dyspareunia, primary or secondary amenorrhea, and infertility. 76% of POI cases developed after normal puberty and establishment of regular menses [6]. Some of such conditions occur after stopping hormonal contraceptives intake, some occur as failure to resume menses after pregnancy, and some with prodromal menstru-

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al disorders. But, still 10% of patients present with primary amenorrhea. Even though presented with clinical findings similar to menopause, almost 50% of POI patients have varying and unpredictable residual ovarian function, and about 5 to 10% are able to accomplish pregnancy [7−10].

POI is far beyond a group of physical discomforts. Psychosocial and reproductive problems that come along as well as the long-term risks associated with POI need to be attentively evaluated and taken care of in an integrated management. Compared with women in general population, patients with POI are more like to have bone and cardiovascular diseases such as osteoporosis myocardial infarction and stroke [11,12].

There are no well-established diagnostic criteria yet, but differential diagnosis is needed to rule out pregnancy, and other underlying conditions causing secondary amenorrhea such as polycystic ovary syndrome, hypothalamic disorders, or uncontrolled diabetes mellitus [13]. Serum hormonal levels, anti-Müllerian hormone (AMH), antral follicle count (AFC) and ultrasonography of ovaries, together with age are traditional indicators to evaluate ovarian aging [14]. X chromosomal abnormalities and FMR1 premutations are most commonly known intrinsic causes of POI [6], but only a limited number of clear causal mutations (*FMR1*, *BMP-15*, *GDF-9*) are reported to have been identified and incorporated as diagnostic biomarkers. Moreover, antibodies screening still lacks specificity and sensitivity [15]. It is of importance that more candidate genetic aberrations, antibodies, and other reliable biomarkers are investigated and validated.

1 Etiologic mechanisms of primary ovarian insufficiency

The pathophysiological development of POI remains unknown in most cases, and is yet to be fully studied. Possible underlying causes (Table 1) include chromosomal abnormalities, gene mutations, autoimmunity, metabolic disorders, infections, and iatrogenic treatments somehow leading to follicle dysfunction or follicle depletion [1]. The serum AMH level, which is correlated with remaining primordial follicle counts, can distinguish follicle dysfunction and follicle depletion. Altered rate of apoptosis, follicle maturation blocking and abnormalities in primordial follicle activation that result in reduced number of functional follicles or accelerated atresia are possible involved molecular mechanisms in one or more types of POI [16,17].

At a certain point of time, the majority of primordial follicles in the ovary rest in a quiescent state, avoiding premature follicular depletion, which could end up in POI. Adhikari *et al*. [18] demonstrated the function of tumor suppressor tuberous sclerosis complex 1 (Tsc1) in oocytes to prevent premature activation and therefore maintain the quiescence of primordial follicles, through negative regulation of mammalian target of rapamycin complex 1 (mTORC1) using mutant mouse models. They suggested that Tsc/Mtorc1 signaling pathway and PTEN/PI3K signaling pathway regulate the on-and-off of primordial follicles activation collaboratively, ensuring a normal reproductive lifespan. Meanwhile, novel concept has arisen to challenge traditional understanding of ovarian functions, stating that ovarian

Table 1 Classification of primary ovarian insufficiency by etiology[a)]

Etiology	Known risk factors	Diagnostic methods/features
Genetic	Chromosomal abnormalities	X monosomy, trisomy X, X chromosome mosaicism, deletions, or balanced X/autosomal translocations detected by karyotyping or FISH
	Mutated POI-related genes on X chromosome	Genetic screening for *FMR1*, *BMP-15*, etc.
	Mutated POI-related genes on autosome	Genetic screening for *GDF-9*, *FOXL2*, *FSHR*, *LHR*, *FSH-β*, *LH-β*, *INHA*, *GALT*, *AIRE*, etc.
Metabolic	Classic galactosaemia	Family history, symptoms, blood/urine/amniocentesis tests for enzyme levels, genetic screening for *GALT*
	17-OH deficiency	Symptoms, serum gonadal and adrenal sex hormones levels, Genetic screening for *17-hydroxylase*
Autoimmune	Accompanied with APS, dry-eye syndrome, myasthenia gravis, rheumatoid arthritis, or SLE, etc.	Serum ovarian antibodies, adrenal cortex antibodies, 3β-hydroxysteroid dehydrogenase (3β-HSD) autoantibodies, antibodies against FSH and LH receptors, anti-thyroid antibodies, anti-parathyroid antibodies, etc. Genetic screening for *AIRE*
Iatrogenic	Chemotherapy	High risks: alkylating agents Low risks: vinca alkaloids, anthracyclic antibiotics, and antimetabolites Age and dose dependent
	Radiotherapy	Age and dose dependent
	Surgical procedures	Esp. pelvic surgeries
Viruses	Mumps, HIV infection	Symptoms of corresponding infection, test for antibodies
Environmental/lifestyle	Toxins (e.g., VCD), cigarette smoking, nulliparity, lifelong irregular menstrual patterns	
Existing somatic diseases	e.g., epilepsy	

a) FISH, fluorescence *in situ* hybridization; APS, autoimmune polyglandular syndrome; SLE, systemic lupus erythematosus; VCD, 4-vinylcyclohexene diepoxide.

germ cells are capable of self-renewal over time [19]. Further studies are required to support such optimistic concept.

Approximately 10%–15% of POI cases have a positive family history [6,20]. Many genes have been reported to have association with familial POI. Davis *et al*. [21] looked into 41 cases of familial premature ovarian failure. Clear genetic association has been identified in 11 cases, and the investigation in siblings of the remaining 30 families revealed female sex preponderance, indicating that X chromosome defect is an important cause of familial premature ovarian failure. In 2008, Hunter *et al*. [22] compared women from 225 families with a history of fragile X syndrome with women from families in the general population, and reported significant familial aggregation of age at menopause with an estimated additive genetic variance of 0.55–0.96. Adjustment for *FMR1* repeat size and confounders is performed.

In fact, a majority group of POI cases arise spontaneously, alone or together with a series of systemic syndromes. If no causes are found after thorough evaluation, they are classified as idiopathic or spontaneous ovarian insufficiency. Abnormality on X chromosome account for a portion of spontaneous insufficiency, while karyotypically normal cases have been reported to be associated with premutation of *FMR1* gene [23], autoimmune response to steroidogenic cells, or some kinds of syndromes.

1.1 Genetic causes

Genetic causes are considered the main factor in determining age at menopause in general population, and are reported in 7% of POI cases [6,24]. The chromosomal and genetic aberrations mostly involve X chromosome, yet increased findings of autosomal involvement are reported. Even though a large number of related genes have been found, with some understanding of their pathogenesis, the precise genetic mechanisms are often unclear. Generally, these aberrations may impair meiosis through reduced gene dosage and non-specific chromosome effects, therefore decrease the reserves of primordial follicles, and accelerate atresia of follicles [15]. Involved genes have various biological functions including regulation of the hypothalamic-pituitary-ovarian (HPO) axis, regulation of oogenesis, coordination of development of germ cell to primordial stage (*GDF9*, *BMP15* and *NGF*), regulation of development of further stages (*FSH* and *LH*), and participation in systemic endocrinal functions [25,26].

1.1.1 Chromosomal abnormalities

X chromosomal abnormalities have been described in both familial and non-familial POI patients. Almost all kinds of defects are involved, including X monosomy (Turner's syndrome), trisomy X, X chromosome mosaicism, deletions, and balanced X/autosomal translocations [8,15,27]. However, very limited cases of POI are reported to have association with translocation within autosomes [28–30]. In X monosomy, the depletion of great number of oocytes may be associated with haploinsufficiency for loci on the X chromosome, or a nonspecific meiotic breakdown, as the solitary X is unable to pair.

1.1.2 POI genes on X chromosome

The Fragile X mental retardation 1 gene (*FMR1*) is located in Xq27.3 [15]. Mutations of *FMR1* can lead to the expansion of a polymorphic CGG repeat in the 5′ untranslated region, which can become unstable and expand in length from generation to generation [22]. According to the count of repeats, alleles are classified in four types, normal range (26–34 repeats), intermediate (35–54 repeats), premutation (55–199 repeats), and full mutation (greater than 200 repeats) [31]. When there is a full mutation, the gene is silenced by methylation, resulting in the absence of FMR protein (FMRP) expression, which causes mental retardation. Premutations of *FMR1* gene, especially those with ~80–99 repeats, are the most common discovered genetic cause of spontaneous 46, XX POI, and the resultant POI is named the fragile X-related primary ovarian insufficiency (FXPOI) [6,17,22,32]. Premutation alleles remain unmethylated, and lead to increased *FMR1* transcription and decreased levels of FMRP [22]. Premutation alleles occur in ~7% of sporadic POI and ~21% in familial POI, significantly higher than in general population [33,34]. Furthermore, evidence suggests that women with premutation tend to have decreased ovarian function along a continuum of severity, dependent on CGG repeat length and environmental factors, even not yet met the criteria of POI. Full mutation, however, is not associated with POI [35]. Increased repeat size might play a role in the pathogenic process of POI throughs elevated level of mRNA transcript level [36,37]. Bretherick *et al.* [37] considered the *FMR1* gene as a possible indicator for age at menopause. Clinics already establishing the detection of *FMR1* premutation as a routine biomarker to screen potential patients with POI.

Region Xq13 is critical for ovarian maintenance, as nearly all terminal deletions originating in this region are associated with primary amenorrhea and ovarian failure [25]. Xq13.3-21.1 is designated as premature ovarian failure 2 (POF-2). Region Xq 21.3-Xq27 is labeled premature ovarian failure 1 (POF-1). Despite of lower significance than POF-1 genes, mutations in POF-1, specifically at Xq25 or 26, often result in secondary amenorrhea [25,38,39]. Other potential POI genes located on X long arm: (i) *Diaphanous homolog 2* (*DIAPH2*), associated with cytoskeleton and involved in oogenesis; (ii) *Dachshund homolog 2* (*DACH2*); (iii) POF1B, mapped to distal POF2, on Xq21, associated with non-muscle myosin, which plays a pivotal role in cell division; (iv) the *X-inactivation gene* (*XIST*), mapping to Xq13. Associated with haploinsufficiency of vital ovarian developmental genes; (v) *X-propyl aminopep-*

tidase 2 (*XPNPEP2*), mapping to critical region Xq25; (vi) *FSH primary response homologue 1* (*FSHPRH1*), mapping to Xq22, expressed in the developing ovary [15,25].

Growth differentiation factor 9 (GDF-9) and Bone morphogenetic proteins 15 (BMP-15, GDF-9B) are two growth factors that are present in follicles during most stages of folliculogenesis. They share a coincident primary structure and spatio-temporal expression pattern in ovary [40]. The roles of the two proteins in follicle growth and development can be co-operative but with species-dependent granulosa cell responses [41]. *GDF-9* is located on an autosome [25], and will be discussed in detail later. *BMP-15* gene is located at Xp11.2 within the Xp POF critical region [42,43]. *BMP-15* null males have intact fertility, but *BMP-15* knockout female mice were subfertile, with reduced litter size. The first *BMP-15* mutation associated with primary ovarian insufficiency was detected in 2004 [44], being an A-G transition at base pair 704 of *BMP-15* gene, resulting in a non-conserved substitution of Y235C. It was a heterozygous mutation in *BMP-15* found in two sisters, acting in a dominant negative fashion. Many other mutations in *BMP-15* gene are later on identified in women with primary ovarian insufficiency [44–47]. Research on different sheep breeds uncovered several point mutations on *BMP-15* gene that could result in ovulation variability, indicating the role of BMP-15 in ovulation, but there were no significant relevancy between *BMP-15* gene SNPs and dizygotic twinning [48]. Impaired posttranslational proprotein processing of the BMP-15 and/or GDF-9 proteins results in reduced mature protein levels, and is associated with increased ovulation rate and litter size. Therefore, their mutations might result in a limited period of enhanced ovulation and fertility in early phase of reproductive age, increasing possibility of dizygotic twins as well as premature drain of ovarian reserve [49].

Other potential POI genes located on X short arm: (i) *Ubiquitin-Specific Protease 9* (*USP9X*), also known as *Drosophila fat facets related X-linked gene* (*DFFRX*), mapping to Xp11; (ii) *Zinc Finger X* (*Zfx*): *Zfx* null mice are characterized by diminished germ cell number in ovaries and testes and impaired fertility [15,25].

1.1.3 Autosomal POI genes

GDF-9 is an oocyte-secreted growth factor, which influences differentiation of oocyte, granulosa and theca cells [50,51]. *GDF-9* gene is located on chromosome 5 (5q31.1) [25]. According to a research using *GDF-9* null mouse model, while a complete loss of *GDF-9* does not impact male fertility, homozygous females were infertile [52]. Homozygous *GDF-9* null female mice present significantly smaller ovaries than wild type, probably because the granulosa cells lost mitotic ability and the follicle growth is blocked at the primary one-layer follicle stage [40,53]. Eight SNPs were uncovered across the coding region of *GDF-9* gene [54,55], in which GDF-9^{S77F} and GDF-9^{S109R} were directly associated with sterility phenotype in ewes [54–56]. GDF-9^{P103S} mutation is identified both in patients with non-syndromic primary ovarian insufficiency and in mothers of dizygotic twins indicating polyvulatory feature [57,58].

Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) is an autosomal dominant condition caused by *FOXL2* mutation. BPES is classified into two types according to the presence of POI. Type I BPES is complicated with POI [15]. Pisarska *et al*. [59] used coimmunoprecipitation and kinase assays to demonstrate that LATS1 is coexpressed with FOXL2 in granulosa cells of small and medium follicles in ovaries in mice. LATS1 phosphorylates FOXL2 at its serine residue, and promotes FOXL2's repressive activity on the StAR promoter, which is involved in granulosa cell differentiation. Mutant *FOXL2* or its dysregulation by LATS1 may result in inappropriate rate of granulosa cell differentiation and follicle maturation, potentially causing POI.

As part of the hypothalamo-pituitary-ovarian axis, FSH and LH pathway are pivotal for normal ovarian functions. *FSH-β* is located at 11p13, and mutations in this gene are reported in two women primary amenorrhea [60]. FSH receptor is crucial for recruitment of ovarian follicles and follicular maturation from and beyond the preantral stage [15,25]. *FSHR* gene maps to 2p21−p16. The missense mutation C566T (Ala566Val) was found in many families of women with 46,XX primary or secondary amenorrhea in Finland, but seemed to be uncommon elsewhere [61]. Nine different loss-of-function mutations have been identified in six POI patients [6], and there are also reports about mutations of *FSHR* associated with resistant ovary syndrome [15]. Polymorphisms have no known significance to ovarian function so far [62]. Women with POI are found to more commonly have *LH-β* subunit variants than controls [63], and a homozygous *LH-β* mutation was found in a woman who experienced secondary amenorrhea as well as her two hypogonadal male siblings [64]. LH receptor is necessary for follicle ovulation. *LHR* maps to 2p21, near the locus for *FSHR* [15,25]. *LH receptor* (*LHR*) mutations in 46,XX may cause gonadal dysgenesis or premature ovarian failure. A homozygous C544→X mutation was found in a 22-year-old 46, XX female with primary amenorrhea. All of her three siblings (46,XY), sharing the same mutation, had a reversed sexual phenotype and Leydig cell hypoplasia, and her female sibling experienced anovulation [65].

Inhibin has dual actions on FSH secretion by the pituitary and gametogenesis. There is a strong association between POI and variants in the *inhibin-α subunit gene* (*IHNA*) (e.g., G769A missense mutation) in female population in India and New Zealand [66,67]. The *INHA* G769A mutation, with prevalence from 0−11% in different population [15], results in normal production of dimeric inhibin A and B, but impaired bioactivity of inhibin B, which may be related to POI

development [66]. Low serum inhibin B level has been reported to have association with reproductive aging, diminished ovarian reserve, and POI [68–70].

Galactose 1-phosphate uridyl transferase (*GALT*) gene, located at 9p13, can cause galactosemia, a rare autosomal recessive disorder [15]. Galactosemia is a metabolic cause of POI, and will be discussed in detail in the following part in this article. *GALT* heterozygotes appear to be at no increased risk of POI. Human homozygotes and *GALT* knockout mice do not obligatorily have POI, and those who have POI seem to present with varied severity, possibly due to redundant bypass [25,71].

AIRE gene maps to 21q22.3. Mutations of the gene are responsible for autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome. Up till now, more than 40 mutations have been identified [15,39]. Discussion is continued in the following part with regards to autoimmune mediated mechanisms.

A genome-wide study on ovarian reserve in reproductively normal women with regular cycles aged 25–45 years (232 Caucasian and 200 African American) was performed, reported to be the largest study on this issue. Scientists analyzed genetic variants across the genome associated with FSH and AMH, and identified one SNP approaching genome-wide significance and several nominal SNPs nearby and within the *MYADML* (*myeloid-associated differentiation marker-like*) gene, which were associated with FSH levels. They also found that several variants associated with AMH or FSH map to the same genomic regions of 12p13.1–13.2 and 13q12.13, which may be a hot spot for causative alleles linked with ovarian reserve. As none of the variants were within or close to known ovarian genes, the study provided excellent candidate genes for further approach to possible genetic causes of POI [72].

Apart from the above genes, other genes involved, or potentially involved in POI in women include: *fragile mental retardation 2* (*FMR2*), *newborn ovary homeobox protein* (*NOBOX*), *factor in the germline-α* (*FIGLα*), *forkhead box O3* (*FOXO3*), *estrogen receptor-α* (*ERα*), *estrogen receptor-β* (*ERβ*), *splicing factor 1* (*SF1, NR5A1*), *Eukaryotic initiation factors 2B* (*EIF2B*), *Noggin*, *POLG*, *Wilm's tumor suppressor gene-1* (*WT1*), *Ataxia telangiectasia mutated* (*ATM*), *mitochondrial DNA polymerase-γ*, *connexin 37*, *CYP-19*, *G-protein coupled receptor 3* (*GPR3*), *LIM homeobox 8* (*LHX8*), *NANOS3*, *17-hydroxylase* (*CYP-17*) [15, 39,73,74]. Further studies are required before their use in genetic diagnosis for POI.

1.2 Metabolic disorders

Classic galactosaemia is an inherited inborn disease caused by GALT deficiency. Severe phenotypes lead to lethal toxic syndrome and cognitive and motor abnormalities [75]. 17%–67% galactosemic women are reported to have POI [71,76], and studies show that classic galactosaemia leads to varied level of ovarian dysfunction in different individuals [77]. Almost all women with homozygous mutation in the *GALT* gene present POI sooner or later in their lives [71]. FSH is often elevated as early as from infancy (4 months–4 years). It has been reported that neonatal ovaries have normal morphology, number and folliculogenesis [78]. However, histological examination on ovaries in young women suffering from classic galactosaemia revealed severely decreased number of primordial follicles with normal morphology, without intermediate or mature follicles. Ovaries of patients in their teens and twenties have been found to be hypoplastic and streak-like. These findings, suggesting mature arrest, have also been observed in patients with *FSHR* inactivating mutations and other genetic diseases affecting the ovary [77]. Although girls with classic galactosaemia are often believed to be infertile, fluctuating POI course and spontaneous pregnancies have been reported, even with low AMH, latter being the indicator for poor ovarian reserve [79,80]. Mechanisms and timing of follicle development disturbance are still unclear. It have been hypothesized that the accumulation of galactose and its toxic metabolites (galactose-I-phosphate and galactitol) after birth (since toxic metabolites in fetus should be cleared rapidly by maternal enzymes) leads to direct ovarian damage. Apart from this, hypoglycosylation of glycoproteins or glycolipids, oxidative stress and activation of apoptosis could result in FSH dysfunction [15,75,81]. Gubbels *et al.* [75] compared the FSH isoform patterns between 5 galactosaemia patients, one PMM2-CDG (a primary glycosylation disorder) patients, and 5 naturally postmenopausal women, finding that less acidic isoform of serum FSH due to hypoglycosylation is not significantly related to the development of POI. Autoimmune mechanisms might also be involved, but no antibodies have been reported yet. Although classic galactosaemia is strongly associated with POI and infertility, correct interpretation of pregnancy chance at different time is needed.

17-OH deficiency has also been reported to have caused POI [39].

1.3 Autoimmune causes

A study of a cohort of 357 consecutive patients presenting with POI showed that 14.3% of cases are clinically and/or biologically associated with autoimmunity [6]. The prevalence of autoimmune diseases reported in other studies varied from 10%–20% to 55% [15].

POI is associated with a series of autoimmune diseases and syndromes, such as Addison's disease and Autoimmune polyglandular syndrome, dry-eye syndrome, myasthenia gravis, rheumatoid arthritis, or systemic lupus erythematosus [15,82–85]. A study of 266 women with 46,XX spontaneous premature ovarian failure showed a clear association between histologically-confirmed autoimmune oophoritis and serum adrenal cortex antibodies [10]. Autoimmune oo-

phoritis is characterized by mononuclear cell infiltration into the theca layer of antral follicles. Steroid cell autoimmunity primary ovarian insufficiency (SCA-POI) is caused by autoimmune destruction of theca cells, yielding elevated concentrations of inhibin, but there is still a preserved pool of functioning follicles [84,86].

Several ovarian autoimmunities may be responsible for primary ovarian insufficiency, and the breakdown of immunological tolerance can be provoked by either genetic or environmental factors [87,88]. However, specificity and pathogenic importance of ovarian antibodies are questionable [15]. Therefore, diagnosis of autoimmune-mediated POI is still a challenging task. Non-ovarian antibodies potentially mediating autoimmune damage in POI include: autoantibodies to steroid producing cells, 3β-hydroxysteroid dehydrogenase (3β-HSD) autoantibodies, antibodies against FSH and LH receptors, anti-thyroid antibodies, anti-parathyroid antibodies, autoantibodies to a zona pellucid 3 epitope, etc. [10,15]. Apart from autoantibodies, alteration of T-cell subsets and T-cell-mediated injury, decrease in number and activity of natural killer cells may also be responsible for autoimmune ovarian damage [39].

1.4 Iatrogenic causes

Chemotherapy and radiotherapy, potentially lifesaving therapies for several neoplastic diseases and thalassemia major undergoing bone marrow transplantation, is responsible for a portion of primary ovarian insufficiency [89,90]. The effect of chemotherapy and radiotherapy are dependent on types of drugs, location of radiation field, dose and age [15,91]. Ovaries of young women appear to be relatively resistant to these two forms of gonadotoxicity.

Alkylating agent cyclophosphamide (CYC) is a non-cell-cycle-specific drug that is cytotoxic even to resting cells [91], and results in up to 40% risk of ovarian failure at childbearing age [92]. Alkylating agents are reported to be of high risk of gonadotoxicity, while vinca alkaloids, anthracyclic antibiotics, and antimetabolites are of relatively low risk [93]. Histological examination of ovaries in patients after treatments with alkylating agents, antimetabolites, anthracycline antibiotics, vinca alkaloids, or prednisolone showed cortical fibrosis, blood vessel damage, and reduced follicle numbers [94,95]. Anticancer drugs are presumed to interrupt essential cell processes, arrest cell proliferation and therefore cause ovarian follicular and stromal damage [93]. Chemotherapy does most harm to mature ovarian follicles during treatment, by inducing apoptosis in granulosa cells. But the extent of effects on primordial and dormant follicles needs further studies. A meta-analysis by Clowse *et al.* [92] reached a conclusion that the adoption of GnRHa during chemotherapy appears to prevent ovarian damage and help improve ovarian function and increase pregnancy chance. Although some scientists believe that 65%–70% cases of POI are reversible after stopping medication, the long-term impairment of fertility is still a concern [93].

26% of patients who received whole abdominal irradiation at mean age of 3.45 years developed POI at an average age of 23.5 years [91]. Although best efforts are made to shield the gonads from radiation during cancer therapy, it is hard to preserve intact ovarian function. Even cranial irradiation could affect ovulation and fertility by disrupting hypothalamic-pituitary-ovarian (HPO) axis. Direct radiation damages the ovaries in similar ways to chemotherapy, possible mechanisms being increased activation of follicles and resultant accelerated atresia [93].

Surgeries, especially those in pelvic region, such as hysterectomy [96], may also cause POI by affecting blood supply to ovaries or causing local inflammation [97]. Laparoscopic ovarian drilling (LOD) in women with PCOS does not necessarily end in diminished ovarian reserve or POI according to existing literature [98].

1.5 Viruses

Several cases of mumps oophoritis have been described as the presumable cause of POI [99,100]. A multicenter U.S. study of 1139 HIV seropositive and 292 seronegative women showed that HIV seropositive women were three times more likely to have prolonged amenorrhea (for at least 1 year) than HIV seronegative women [101]. A prospective pilot study in France evaluated ovarian function of 78 HIV-seropositive women using markers including the antral follicular count (AFC), follicle-stimulating hormone (FSH), inhibin B and antimüllerian hormone (AMH). The four markers all showed high rate of abnormal values, being 63%, 36%, 57%, 23% respectively for AFC, FSH, inhibin B and AMH [102]. These results indicate that HIV infection or the corresponding antiretroviral therapy may impair ovarian functions and fertility, and end in POI.

1.6 Toxins and other environmental/lifestyle factors

4-vinylcyclohexene diepoxide (VCD) is an ovotoxic occupational chemical. Repeated doses of VCD can accelerate apoptotic process of atresia, and selectively destruct primordial and primary follicles in rats and mice. Molecular studies using cultured whole neonatal rat ovaries showed that VCD specifically interacts with and inhibits autophosphorylation of c-kit receptor, which is a key molecule in a critical signaling pathway associated with cell growth, and thus disturbs normal oocyte growth. Women with exposure to VCD are therefore considered at risk of POI [103–106].

Cigarette smoking was reported to have adverse fertility and pregnancy outcomes, and was associated with premature menopause and increased risk of idiopathic POI [72,107,108]. Limited studies suggested that smoking is associated with elevated FSH levels, and certain changes in AFC or AMH levels, but further validations with larger

population base are needed [109,110]. Tobacco toxins may affect ovarian reserve by accelerating follicular atrophy and atresia via increased apoptosis in primordial germ cells [72,107]. For example, polycyclic aromatic hydrocarbons (PAHs), toxic chemicals in tobacco, induce aromatic hydrocarbon receptor (Ahr)-driven expression of Bax in oocytes, followed by apoptosis [111].

Sharara *et al*. [112] reviewed that environmental toxicants, including endocrine disruptors, heavy metals, solvents, pesticides, plastics, industrial chemicals, and cigarette smoke, were associated with adverse reproductive outcomes and ovarian failure in animals. However, the underlying mechanisms were not yet fully elucidated and conflicting results were found in human about these toxicants.

Klein *et al*. [113] reported that women with epilepsy were at higher risk for developing POI than general population. Whether education level and other sociodemographic characteristics are associated with risks of POI is inconsistent among different literatures. Nulliparity and lifelong irregular menstrual patterns are also reported risk factors of primary ovarian insufficiency [114].

Environmental and lifestyle factors [115], as well as existing somatic diseases are considered minor causes of POI, and among them many still require further investigation and validation for their negative effects and underlying mechanisms. However, these are the factors that are easily exposed to yet often ignored in daily life. Professional advices upon more standard studies are in demand to eliminate avoidable risks.

2 Management

Unexpected diagnosis of POI affects a woman's physical and emotional well-being. Therapeutic strategies to POI are hormone replacement therapy (HRT), infertility rescue, and concern about maintenance of bone health and emotional health as well.

2.1 HRT

Long-term HRT is needed for relief of menopausal symptoms (including vasomotor instability, sexual dysfunction, mood, and fatigue) and to prevent long-term health sequel of estrogen deficiency, such as osteoporosis. A wide range of HRT preparations are available, although no studies have directly compared various hormonal therapies for POI women [116–118]. Evidence supports that transdermal estradiol has little effect on hemostatic factors, and has been associated with a lower risk of venous thromboembolism than has oral estrogen. Normally a dose of 100 μg of estradiol per day administered by transdermal patch is recommended to achieve average serum estradiol levels in this range and effectively treat symptoms. However, dose of estrogen regimen required by young women may be higher than that used in an older age group. To date, no data are available to evaluate the impact of treatment on risk factors, such as the development of breast cancer, endometrial cancer, or of cardiovascular events.

2.2 Infertility

It has been clearly established that many young women with spontaneous POI have remaining ovarian follicles that may function intermittently and developing pregnancy even years after the diagnosis. Pregnancy may occur while a woman is taking estrogen and progestin therapy, suggesting that this might be a method to improve fertility in these women. Approximately 95% of women with spontaneous POI have serum LH levels above normal for the mid-follicular phase. Inappropriate premature luteinization of a growing follicle would thus be expected to impair follicle growth, reduce estradiol production, and impair ovulation. It has been demonstrated a dose of 100 μg of estradiol per day, administered by transdermal patch, achieves average serum estradiol levels [9]. Theoretically estrogen replacement therapy might improve ovulation rates in women with spontaneous POI by reducing the associated chronically elevated serum LH levels to normal. A strategy to provide appropriate physiological negative feedback and maintain LH levels in the normal range might avoid inappropriate luteinization of the few remaining follicles that women with POI have in their ovaries [119].

Assisted reproductive technique with donated oocytes has been used to achieve pregnancy in women with POI, and it remains the only means for fertility treatment in POI that carries high success rate. Cryopreserved embryos have also been employed for ovum donation in POI with a high pregnancy rate of 30% per transfer.

2.3 Recommends

Unexpected infertility is a life-altering diagnosis for many women. Emotional support should be addressed to maintain their health being. A positive and optimistic lifestyle should be encouraged to maintain, including engaging in regular weight-bearing exercise, maintaining an adequate intake of calcium (1200 mg daily) and vitamin D (at least 800 IU daily), eating a healthy diet to avoid obesity. Regular screening for bone loss and cardiovascular risk factors is also recommended.

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