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Primary ovarian insufficiency: update on clinical and genetic findings

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Primary ovarian insufficiency (POI) is a disorder of insufficient ovarian follicle function before the age of 40 years with an estimated prevalence of 3.7% worldwide. Its relevance is emerging due to the increasing number of women desiring conception late or beyond the third decade of their lives. POI clinical presentation is extremely heterogeneous with a possible exordium as primary amenorrhea due to ovarian dysgenesis or with a secondary amenorrhea due to different congenital or acquired abnormalities. POI significantly impacts not only on the fertility prospect of the affected women but also on their general, psychological, sexual quality of life, and, furthermore, on their long-term bone, cardiovascular, and cognitive health. In several cases the underlying cause of POI remains unknown and, thus, these forms are still classified as idiopathic. However, we now know the age of menopause is an inheritable trait and POI has a strong genetic background. This is confirmed by the existence of several candidate genes, experimental and natural models. The most common genetic contributors to POI are the X chromosome-linked defects. Moreover, the variable expressivity of POI defect suggests it can be considered as a multifactorial or oligogenic defect. Here, we present an updated review on clinical findings and on the principal X-linked and autosomal genes involved in syndromic and non-syndromic forms of POI. We also provide current information on the management of the premature hypoestrogenic state as well as on fertility preservation in subjects at risk of POI.

KEYWORDS

female hypogonadism, estradiol, estradiol replacement therapy, premature menopause, premature ovarian failure

1 Introduction

Primary ovarian insufficiency (POI) is characterized by impaired or intermittent ovarian follicle function before age 40 (1, 2), determined by diminished number of primordial follicles, accelerated follicular atresia, blocked follicle maturation or follicular dysfunction. The cut-off age of 40 years is used because it represents two standard deviations below the mean age of natural menopause. The definition and appropriate terminology of this condition have been debated for decades (3): the aforementioned definition of POI, which should replace the terminology of ‘premature ovarian failure (POF)’, has the advantage of clearly defining the ovarian origin of the condition, as is common practice in endocrinology. Moreover, the latter definition does not take into account the biological course of the condition, and is uninformative and stigmatizing for patients who may not experience the cessation of ovarian function at the time of diagnosis. POI should be intended as a wide clinical spectrum, with considerable variability of clinical presentation and its own natural history. It is a condition characterized by strong genetic susceptibility, occurring in up to 30% of cases in familial form, whose expression is modulated by various environmental factors (4, 5). It is a heterogeneous disorder, which can be acquired or congenital, although in 70–90% of cases it remains idiopathic (6), although more recent data suggest that, as a result of the effort made in identifying new genetic mechanisms, the percentage of idiopathic forms currently stands at 39% to 67% (2). Depletion or dysfunction of ovarian follicles leads to amenorrhea and subsequently to menopausal symptoms, infertility, and sexual dysfunction which adversely impact not only the physical and mental well-being of those affected but also their self-esteem and interpersonal relationships (7). Thus, the quality of life of women with POI is affected from a physical, psychological, and social point of view. The relevance of POI is emerging as the desire of women to conceive beyond the age of 30 grows, when the incidence of POI is the greatest, and life expectancy is extended, and, in turn, also the duration of hypoestrogenism. Considering the rising incidence of the condition in younger ages as well (8, 9), POI presents a growing challenge for women, as it interferes with their reproductive desires. At the same time, POI diagnosis, especially at younger ages, heightens the risk of associated morbidities and is expected to lead to early mortality, thereby having serious consequences on the health of those affected (10, 11). Therefore, gaining a deep understanding of POI is critical for its early diagnosis, development of an effective long-term management and patient counseling strategy. This would finally lead to improvements in the overall quality of life, including the physical and psychological well-being, reproductive health and primary life goals of the affected women.

2 Epidemiology

The Study of Women’s Health Across the Nation (SWAN) reported that approximately 1.1% of women under the age of 40 in the general population are affected by POI (12). However, a recent large-scale meta-analysis study estimated the global prevalence of POI to be 3.7% (13). The incidence of POI declines exponentially

with decreasing age. Specifically, the incidence rate ratios are 1:100 for women between 35 and 40 years old, 1:1,000 for women between 25 and 30 years old, and 1:10,000 for women between 18 and 25 years old (14). Interestingly, a nationwide Israeli study in women under 21 years of age, showed that the incidence rate of POI diagnoses doubled in the period of 2009–2016 compared to the period of 2000–2008 (8). Additionally, the results of a recent Finnish study suggest an increase in the incidence rate of the condition in adolescent girls, aged 15–19, from 2007 to 2017 (9). These results place emphasis on the discrepancy between the past and recent epidemiologic data, whilst indicating a rise in the incidence of POI amongst younger women, that could also reflect a change towards a more active approach to primary amenorrhea among adolescent women. The prevalence and incidence rates also differ across ethnicities. A multi-ethnic cross-sectional study conducted by Luborsky et al. (12) demonstrated significantly higher incidence rates in Hispanic and African American women compared to Japanese and Chinese women. Additionally, two population-based cohort studies on the Swedish and Iranian populations showed a prevalence of 1.9% and 3.5%, respectively (15, 16). Remarkably, first-degree relatives of women with POI have an increased risk of having POI themselves (9, 17, 18).

3 Etiopathogenesis

3.1 Genetic causes

Although POI negatively affects fertility, several studies have indicated that this condition has a strong heritable, and therefore genetic, component. A decade ago, Stolk and colleagues identified common loci associated with the age at menopause by a genome wide association study (19). However, the exact mechanisms underlying the heritability of this condition are not yet completely understood. The fact that mothers and daughters show a tendency of inheritance of the menopausal age supports the view of the inheritable susceptibility to POI, with a demonstrated high prevalence (31%) of familial POI in patients (18). Moreover, the even higher incidence of early menopause (EM) occurring within the same family group or among first-degree relatives also indicates a variable expression of the same genetic disease predisposition (20, 21). Two recent population-based studies further assessed the familial clustering of POI. In Finland, it has been estimated an odds ratio of 4.6 (95% CI 3.3–6.5) for POI in first-degree relatives of 129 women with POI (9). Whereas in a cohort of 396 cases from Utah, first-degree relatives demonstrated an 18-fold increased risk of POI compared with controls relative risk (RR, 18.52; 95% CI, 10.12–31.07), second-degree relatives demonstrated a 4-fold increase (RR, 4.21; 95% CI, 1.15–10.79), and third-degree relatives demonstrated a 2.7-fold increase (RR, 2.65; 95% CI, 1.14–5.21) (17). Hereditary disorders can affect the functioning of the ovaries and contribute to the development of POI: among the genetic conditions that have been associated with an increased risk of POI, there are X chromosome aneuploidies, together with polymorphisms and mutations in several causative genes, that are associated with either pleiotropic genetic syndromes or isolated cases (Tables 1–3).

3.1.1 Overview of genetic candidates and stages of folliculogenesis

In this section, the main genetic factors involved in non-syndromic forms of POI will be described, according to the biological process in which each gene participates, based on literature findings. See also [Figure 1](#) and [Tables 1–3](#) for details.

3.1.1.1 Primordial germ cells and oogonia formation

Human primordial germ cells (PGCs) originate from the extraembryonic mesoderm 3 weeks after fertilization and migrate to the developing gonadal ridges, the bipotential gonads that will differentiate into either ovaries or testis. Here, female PGCs differentiate into oogonia and start proliferating in clusters of germ cells called syncytia or germ cell nests, which are connected and synchronized by intercellular connections. At this stage, an active phase of mitosis ensues to establish adequate ovarian reserve. During this phase of rapid proliferation, PGCs uphold genomic stability by crucially depending on precise DNA replication and repair mechanisms, which are tightly regulated through cell cycle blockades. The maximum number of oogonia resulting from mitotic divisions occurs approximately during the 20th week of development, with the ovaries containing approximately 6–7 millions of germ cells. A recent study in knockout mice (KO) indicated that defects of *Fance* may act during rapid mitotic periods in PGCs, leading to impaired cell proliferation and genomic instability. Through mechanisms not completely understood, *Fance*^{-/-} mice showed reduced numbers of PGCs, decreased ovarian reserve, and infertility ([152](#)). In humans, previous studies have already shown that patients harboring biallelic pathogenic variants in genes such as *FANCA*, *FANCM*, *FANCD1*, *FANCU*, as well as those with monoallelic pathogenic variants in *FANCA*, *FANCD1*, *FANCL*, presented with gonadal dysfunction and infertility with or without other phenotypic features of Fanconi Anemia ([74](#)). During these early stages, mitotic oogonia expresses pluripotency-associated and germ cell-specific genes. Different groups identified *NANOS3* genetic variants in patients with POI ([124](#), [125](#)). The *NANOS3* gene is required for germ cell development coding an RNA-binding protein which functions by repressing apoptosis in germ cells. *ATG7* and *LIN28A* are other essential genes involved in female gametogenesis considered candidates for POI, however, no significant variations were found in POI cohorts yet ([153](#)). *ATG7* is an autophagy induction gene. Autophagy protects germ cells from over-loss in newborn ovaries. Loss of *Atg7* leads to subfertility with a dramatic decrease of the ovarian follicles pool in female mice ([154](#)). *LIN28A* together with *LIN28B* encode highly conserved RNA-binding proteins regulating microRNA biogenesis by promoting germ cell proliferation and inhibiting differentiation ([155](#)); the disruption of *Lin28a* affects germ cell development in mice ([156](#)).

3.1.1.2 Primordial to primary follicles transition

Around the 11th week of gestation, the upregulation of *FIGLA* drives the formation of primordial follicles. Female mice *Figla*^{-/-} exhibit impaired primordial follicle formation and infertility ([157](#)). Several deleterious variants of the *FIGLA* gene have been found in recent years by our group ([91](#)) and others ([92–94](#)). Each primordial follicle consists

of an oocyte surrounded by a single layer of flattened somatic pre-Granulosa Cells (GCs) enclosed by a basal membrane which enters meiosis. The mechanism beyond the meiotic initiation is still poorly known. During human fetal ovarian development, increasing *FMRI* expression marks the developmental transition from primordial germ cells expressing *LIN28* to meiotic germ cells ([158](#)). The presence of the premutated *FMRI* allele is frequently associated with ovarian dysfunction. *FMRI* premutation is one of the most frequent alterations involved in the pathogenesis of SA and POI. Meiosin and *Str8* germ cell factors interact to trigger meiotic entry via the retinoic acid-dependent pathway, acting as transcription factors ([159](#)). Both *STRA8* and *MEIOSIN* variants have been found to be associated with POI ([160](#)). Once meiosis proceeds, several genes are upregulated ([161](#)). Among these, *Dazl* protein mediates transcription of synaptonemal complex proteins ([162](#)). SNPs and rare genetic variants of this gene could associate with an earlier onset of menopause by impairing germ cells number ([163](#), [164](#)).

3.1.1.3 Meiotic phases

Key processes of prophase I are homologous chromosome pairing, synapsis formation, and repair of DNA Double Strand Breaks (DSBs) to enable recombination and crossover. The genetic disruption of either one of the meiotic genes leads to impaired meiosis progression and usually results in oocyte loss as shown in animal models thus making them candidates for human POI.

3.1.1.3.1 DNA double strand breaks formation

The precise localization and formation of DSBs are essential for the accurate recognition and pairing of homologous chromosomes. *PRDM9* is a meiosis-specific histone H3 methyltransferase which catalyzes H3K4 trimethylation, binds chromosome axis by interacting with *CXXC1*, *HORMAD1*, *MEI4*, *REC114*, *ANKRD31* and *IHO1*, and together with *Hells* opens chromatin at hotspots, thus providing the access for the DSBs machinery. Subsequently, the endonuclease *SPO11*, along with *MEI1* and *TOPOVIB-Like* complexes, is recruited at *PRDM9*-binding sites where it generates chromosome breaks. Except for *Cxxc1* and *Hormad1*, the conditional KOs of the above-mentioned factors demonstrate female mice infertility with premature oocyte loss caused by impaired DSBs formation ([165](#)). A few pathogenic variants in *PRDM9* and *ANKRD31* ([83](#)) have been identified in patients with POI so far. Up to date, no causative variants of POI have been identified in the other meiotic DSBs genes which are rather associated with male infertility ([166](#)) or other female fertility issues different than POI, such as preimplantation embryonic arrest and recurrent implantation failure and female infertility ([167](#), [168](#)).

3.1.1.3.2 DNA double strand breaks processing

Following the formation of DSBs, DNA ends undergo a maturation process which requires the tight cooperation of the *MRE11-RAD50-NBS1* (MRN) complex. The relevance of the MRN complex in maintaining the primordial follicle pool has been demonstrated in animal models ([169–171](#)). In humans, biallelic nonsense mutations in the *NBS1/NBN* gene have been identified in compound heterozygosity in two siblings presenting the unique

TABLE 1 Syndromic forms of POI.

CHROMOSOMAL ABNORMALITIES						
Syndrome	Karyotype	Molecular Mechanism	Phenotypes	Frequency	Ref.	
<i>Turner Syndrome</i> (X monosomy)	(45,X/46,XX), mosaicisms	Short stature and other skeletal dysmorphism may associate to cardiac defects, hearing loss and hypothyroidism. Accelerated PmFs atresia with ovarian reserve reduction cause either SA or gonadal dysgenesis (with streak ovaries and elevated FSH levels since infancy)	X structural abnormalities, with partial/complete loss of one X chromosome due to deletion, translocation, inversion, or formation of an isochromosome. Possibly, chromosomal pairing fails during meiosis or dosage effect of X-linked genes escapes X inactivation	1:2500 live births; 4-5% of POI cases	(22-24)	
<i>Triple X Syndrome</i> (X trisomy)	47,XXX	Low AMH with increased FSH and LH. Occasionally longer legs, delayed language development, poor motor coordination and increased risk of POI or genitourinary abnormalities	Non-disjunction errors in meiosis I or II in oogenesis	1:1000 women (often undiagnosed due to modest symptoms)	(25, 26)	
<i>Xp and Xq deletions</i>		Large deletions associated with high POI incidence at a young age, but no simple relationship between phenotype and chromosomal loss. - Xp(del): Xp11 is the most common breakpoint for terminal deletions, leading to either PA (55%) or SA (45%). Deletion of the most telomeric portion (Xp22.3 - Xpter) does not result in amenorrhea. - Xq(del): Breakpoints cluster at Xq13 - Xq21 (balanced translocations) and Xq23 - Xq27 (interstitial deletions). Xq13del are associated with PA and absent secondary sexual development. Terminal deletions at Xq25 or Xq26 seem not linked to PA; more distal deletions have mild phenotypes	Disruption of gene expression balance	4%-12% of POI cases	(27-30)	
<i>X autosome translocations</i>		PA or SA; Turner stigmata if translocation occurs within the critical region Xq13-q26	Haploinsufficiency/disruption of critical genes, positional effect on contiguous genes or non-specific/defective meiotic pairing			
<i>Gonadal Dysgenesis</i>	46,XY	External female genitalia, bilateral streak gonads, minimal breast enlargement, propensity for malignant transformation of the gonads	Several genetic causes have been identified, including mutation in <i>NR5A1</i> , <i>SOX9</i> , <i>SRY</i> , <i>GATA4</i> , <i>WT1</i>	rare	(31)	
AUTOSOMAL POI SYNDROMES						
Pathology	OMIM	Gene	Gene Functions	Phenotypes	Inheritance (AD, AR)	Ref
<i>Pseudo-hypoparathyroidism type 1a</i>	#103580	<i>GNAS</i>	Ubiquitously expressed gene, but high levels in thyroid and brain. <i>GNAS</i> encodes for the α -subunit of the stimulatory GTP binding protein with key roles in several cellular responses triggered by receptor-ligand interactions	Resistance to parathyroid hormone, to thyroid-stimulating hormone, gonadotropins and growth-hormone-releasing hormone. Sometimes associated with short stature, skeletal anomalies, ectopic ossifications, obesity, mental retardation and	AD, maternally inherited. Parent-specific methylation and paternal protein	(32-36)

(Continued)

TABLE 1 Continued

AUTOSOMAL POI SYNDROMES						
Pathology	OMIM	Gene	Gene Functions	Phenotypes	Inheritance (AD, AR)	Ref
				hypogonadism with incomplete sexual maturation, delayed puberty, oligomenorrhea or SA	expression reduction	
<i>Blepharophimosis, ptosis, epicanthus inversus (BPES) type 1</i>	#110100	<i>FOXL2</i>	Expressed in the developing eyelids and in fetal/adult ovary. Role in GCs differentiation, folliculogenesis and postnatal maintenance of ovaries, estrogen production and steroidogenesis, repressing male sex determination	Bilateral eyelid dysplasia with small palpebral fissures, drooping eyelids and skin fold starting from the lower eyelid and running inward and upward, inherited with ovarian failure (PA or SA with absent or rare follicles). <i>FOXL2</i> (*605597) is occasionally described in isolated PA or SA with a prevalence of 1.0% – 3.2%	AD, AR	(37–42)
<i>Perrault Syndrome</i>	#614129	<i>CLPP</i>	Mitochondrial function	Mild to severe bilateral hearing loss and ovarian dysfunction, ranging from gonadal dysgenesis to SA, with streak, absent or small ovaries. In some cases, patients also present with variable neurological signs. <i>LARS2</i> (*604544) is occasionally described in non-syndromic SA	AR	(43–49)
	#617565	<i>ERAL1</i>				
	#614926	<i>HARS2</i>				
	*614917	<i>RMND1</i>				
	*609947	<i>PRORP</i>				
	#616138	<i>TWNK</i>				
	#615300	<i>LARS2</i>	Cellular metabolism			
	#233400	<i>HSD17B4</i>				
	*606982	<i>GGPS1</i>				
	*601498	<i>PEX6</i>	Mitochondrial large and small ribosomal subunit			
	*605810	<i>MRPS7</i>				
*611972	<i>MRPL50</i>					
<i>Progressive external ophthalmoplegia (PEO) A1</i>	#157640	<i>POLG</i>	Encodes for the catalytic subunit of the mitochondrial DNA polymerase	Progressive weakness/paralysis of the eye muscle, myopathy, sensory axonal neuropathy, ataxia, parkinsonism and delayed sexual maturation, associated in women to PA or SA (with diminished follicle reserve). Multiple mtDNA deletions triggers mitochondrial depletion <i>POLG</i> (*174763) is occasionally described in isolated SA	AD, AR in isolated SA	(50–52)

(Continued)

TABLE 1 Continued

AUTOSOMAL POI SYNDROMES							
Pathology	OMIM	Gene	Gene Functions	Phenotypes	Inheritance (AD, AR)	Ref	
Mitochondrial DNA depletion syndrome 11	#615084	<i>MGME1</i>	Mitochondrial genome integrity maintenance	PEO, respiratory insufficiency, emaciation, ptosis, gastrointestinal and skeletal abnormalities, dysphonia	AR	(53)	
Leuko-encephalopathy	Ovarioleukodystrophy	#603896	<i>EIF2B4</i>	Protein synthesis under cellular stress conditions; likely responsible of increased apoptosis of ovarian follicles	Unusual association of chronic and progressive neurological deterioration (brain white matter degeneration) and ovarian dysfunctions. <i>EIF2B2</i> (*606454) is occasionally described in isolated PA or SA	AR	(54)
		<i>EIF2B5</i>					
		<i>EIF2B2</i>					
	<i>LKENP</i>	#615889	<i>AARS2</i>	Mitochondrial alanyl-tRNA synthetase	Progressive loss of motor and cognitive skills with ovarian failure	AR	(55, 56)
Woodhouse-Sakati syndrome	#241080	<i>DCAF17</i>	Nuclear transmembrane protein that associates with ubiquitin ligase complexes	Hypogonadism, alopecia, and neurological defects	AR	(57)	
Prolyl endopeptidase-like deficiency	*609557	<i>PREPL</i>	Regulation of exocytosis of synaptic vesicles	Neonatal hypotonia, feeding difficulties, ptosis, neuromuscular and cognitive symptoms, growth hormone deficiency and hypergonadotropic hypogonadism	AR	(58)	
Cockayne Syndrome B	#133540	<i>ERCC6</i> (CSB-PGBD3)	Response to DNA damage	POI (principally PA) and neurological abnormalities	AD	(59)	
<i>XRCC4</i> -related Disorder	#616541	<i>XRCC4</i>	Double strand breaks (DSBs) repair	Short stature, microcephaly, developmental delay, neurological defects and gonadal failure (associated with SA)	AR	(60)	
Nijmegen breakage syndrome	#251260	<i>NBN</i>	Chromosomal stability	Facial dysmorphism, predisposition to cancer and POI. (PA or SA, with streak gonad, small ovaries). <i>NBN</i> (*602667) is occasionally described in isolated POI	AR	(61, 62)	
Ataxia telangiectasia	#208900	<i>ATM</i>	Check-point, cellular response after DNA damages. Ovarian age control	Cerebellar ataxia, telangiectasis, immune defects, and predisposition to malignancy. Associated to PA. <i>ATM</i> (*607585) is occasionally described in isolated POI	AR	(63)	
Retinal Dystrophy	#617175	<i>RCBTB1</i>	Ubiquitination processes	Retinal Dystrophy, with or without extraocular anomalies, such as POI	AR	(64)	
	*616618	<i>ACBD5</i>	Peroxisomal membrane protein			(65)	

(Continued)

TABLE 1 Continued

AUTOSOMAL POI SYNDROMES							
Pathology		OMIM	Gene	Gene Functions	Phenotypes	Inheritance (AD, AR)	Ref
Premature aging (Progeria)	<i>Bloom syndrome</i>	#210900	<i>BLM</i>	Helicases involved in homologous recombination repair	Acceleration of aging process and highly variable somatic abnormalities, together with hypogonadism and SA, associated with increased follicular atresia. Ovarian aging may be influenced by abnormal epigenetic modifications (changes in methylation levels, histone modifications or non-coding RNA expression) in germ cells and early embryos may influence	AR	(66)
	<i>Werner syndrome</i>	#277700	<i>WRN</i>			AR	(67)
	<i>Hutchinson-Gilford</i>	#176670	<i>LMNA</i>	Key component of the nuclear lamina		AD	(68)
<i>Rothmund-Thomson syndrome type 2</i>		#268400	<i>RECQL4</i>	DNA helicase	Poikiloderma, telangiectasia, photosensitivity, skin atrophy, congenital bone defects and increased risk of osteosarcoma/skin cancer together SA and gonadotropin resistance	AR	(69)
<i>Acromesomelic Dysplasia (Demirhan syndrome)</i>		#609441	<i>BMPR1B</i>	Gonadal and skeletal development	Chondrodysplasia characterized by short stature and hand/foot malformations, associated with PA, hypergonadotrophic hypogonadism and genital anomalies. <i>BMPR1B</i> (*603248) is occasionally described in isolated SA	AR, AD or AR in isolated POI	(70)
<i>Proximal symphalangism (SYM1)</i>		#185800	<i>NOG</i>	BMP4 and BMP7 ligand with roles in cartilage and ovarian development	Skeletal abnormalities (fusion of interphalangeal joints and carpal/tarsal bones) sometimes associated with hearing loss and SA	AD	(71)
<i>GAPO syndrome</i>		#230740	<i>ANTXR1</i>	Actin assembly, cell adhesion and matrix build-up	Growth retardation, alopecia, failure of tooth eruption and progressive optic atrophy, sometimes associated with SA and follicle depletion	AR	(72, 73)
<i>Fanconi Anemia</i>		#227650	<i>FANCA</i>	DNA repair after crosslinking damage (maintenance of genome stability)	Developmental defects, early-onset bone marrow failure and high predisposition to cancer. Impairment in follicular development due to defective oocyte meiosis and abnormal germ cell development with PA or SA. <i>FANCA</i> (*607139), <i>FANCL</i> (*608111), <i>FANCM</i> (*609644), <i>FANCU</i> (*600375), <i>FANCD1</i> (*600185) are occasionally described in isolated POI (principally SA)	AR, AD or AR isolated POI	(74, 75)
		#227645	<i>FANCC</i>				
		#614083	<i>FANCL</i>				
		#605724	<i>FANCD1/BRCA2</i>				
		#617247	<i>FANCU/XRCC2</i>				
		#614082	<i>FANCG/XRCC9</i>				
Adrenal Hyperplasia		#201710	<i>STAR</i>	Steroid hormone biosynthesis	Adrenogenital syndrome, insufficient cortisol production, atypical genitalia, altered growth	AR	(76)
		#202110	<i>CYP17A1</i>				(77)

(Continued)

TABLE 1 Continued

AUTOSOMAL POI SYNDROMES						
Pathology	OMIM	Gene	Gene Functions	Phenotypes	Inheritance (AD, AR)	Ref
<i>Aromatase deficiency</i>	#613546	<i>CYP19A1</i>	Androgen aromatization to estrogen	Pseudohermaphroditism in female infants, delayed bone maturation during childhood and adolescence, puberty with primary amenorrhea, failure of breast development, virilization, and hypergonadotropic hypogonadism	AR	(78)
<i>Congenital Disorders of Glycosylation</i>	#212065	<i>PMM2</i>	Glycans or oligosaccharides synthesis and processing	Encephalopathy, psychomotor and growth retardation, cardiomyopathy, liver dysfunction, hypothyroidism associated with PA. <i>PMM2</i> (*601785) occasionally described in isolated PA or SA	AR	(79)
<i>Galactosemia</i>	#230400	<i>GALT</i>	Galactose metabolic pathway	Intellectual disability; developmental delay, PA with streak ovaries or few immature follicles	AR	(80)

AD, Autosomal Dominant; AR, Autosomal Recessive; PA, Primary Amenorrhea; SA, Secondary Amenorrhea; POI, Primary Ovarian Insufficiency. The symbol # before OMIM entry number indicates that it is a descriptive entry, usually of a phenotype, and does not represent a unique locus. The symbol * before an entry number indicates a gene.

clinical symptom of fertility defects and POI (172). Then, the MRN complex recruits EXO1, an exonuclease which contributes to DSBs resection and formation of recombinant DNA structures and participates in mismatch repair. Inactivation of Exo1 in mice causes dynamic loss of chromosome chiasmata during the first meiotic prophase, leading to POI (173). Recently, WES performed in 50 sporadic patients with POI with PA identified in *EXO1* gene one heterozygous missense variant impairing homologous recombination (HR) (146).

3.1.1.3.3 Synapsis generation

The 5' to 3' exonuclease activity of Exo1 generates long 3' single-stranded tails, which serve as substrates for assembly of DMC1 and RAD51 recombinases. Both are necessary for strand invasion during synapsis formation (165). KO mice for *Dmc1* show meiotic arrest at prophase I with ovaries devoid of follicles. Moreover, *DMC1* genetic variants have been described in POI (87, 174). Recently, a report described a family with a homozygous frameshift mutation as causative for both non-obstructive azoospermia and diminished ovarian reserve, suggesting that *DMC1* could be dispensable in human oogenesis (88). Contrarily, the lack of *Rad51* in mice results in embryo lethality. WES in 50 sporadic patients with POI with PA identified a missense variation in *RAD51* impairing the nuclear localization of this factor (146).

The nucleation and stabilization of RAD51 at DSBs are mediated by direct interaction with BRCA2 and BRCA1-BARD1 complexes (175). *BRCA1/2* act as tumor suppressor genes known to predispose the heterozygous carriers of deleterious mutations to breast, ovarian and other types of cancers (176) Conditional *Brca2*-deficient mice exhibit infertility due to defective follicular development and oocyte degeneration, whilst *BRCA2* transcript may be found downregulated in human POI oocytes (177). A few genetic studies contributed to the identification of pathogenic biallelic variants of *BRCA2* in patients with POI in absence of cancer or Fanconi Anemia trait (75, 178), thus supporting *BRCA2* haploinsufficiency as a possible mechanism leading to isolated POI (179). A tendency to accelerated decline of ovarian reserve, oocyte aging, and POI was also observed in patients carrying *BRCA1* germline variants as well as in *Brca1* mouse model (180).

Other regulating factors of RAD51-DMC1 are HOP2/PSMC3IP and MND1. They function as heterodimer which enhances strand exchange on homologous DNA or containing a single mismatch (181). Aberrant synapses and DSBs repair result from the loss of this complex (182). Both the ovarian phenotype displayed by KO mice and the identification of variants in patients corroborates their key role in oogenesis and POI pathogenesis (120, 149, 150, 183). *Meiob* and *Spata22* form a complex recruited to induce DSBs. Inactivation of *Meiob* and *Spata22* induces meiotic arrest and leads to infertility in mice (184). Variants of *MEIOB* and *SPATA22* associated with POI are rare, with only 3 cases reported so far for *MEIOB* (117, 118) and only one for *SPATA22* (151).

3.1.1.3.4 Homologous recombination

The heterodimeric complex MSH4-MSH5 stabilizes the interaction between parental chromosomes during DSBs repair (185). Disruption of either *Msh4* or *Msh5* genes in female mice

TABLE 2 Classic candidate genes for POI.

Gene	OMIM	Ovarian Phenotype (PA, SA, OD); other phenotypic anomalies	Inheritance (AD, AR, XLD)	Prevalence	Ref.
<i>AMH</i>	*600957	SA	AD	0.2% - 2.0%	(81, 82)
<i>AMHR2</i>	*600956	SA	AD	0.8% - 2.4%	(81, 82)
<i>ANKRD31</i>	*618423	SA	AD	0.3%	(83)
<i>BMP15</i>	*300247	PA, SA	XLD (dominant or recessive)	0.4% - 12%	(81, 84)
<i>BMPRI1A</i>	*601299	SA	AD	unknown	(85)
<i>BMPRI2</i>	*600799	PA, SA	AD	1.4%	(81, 86)
<i>DMC1</i>	*602721	SA, DOR	AR	2.4%	(87, 88)
<i>ESR1</i>	*133430	SA	AD	unknown	(89, 90)
<i>FIGLA</i>	*608697	PA, OD	AR	0.3-2.5%	(91-96)
<i>FMRI</i> premutation (55 to 200 CGG repeats)	*309550	Intellectual and developmental disabilities associated with ovarian dysfunction; Fragile X-Associated Primary Ovarian Insufficiency (FXPOI)	XLD	2% in sporadic cases 14% in familial cases	(97)
<i>FOXO3A</i>	*602681	PA, SA	AD	2.2%	(98)
<i>FSHR</i>	*136435	OD, PA, SA with pubertal disorder, oligomenorrhea	AR, AD	0.1% - 42.3%	(81, 82)
<i>GDF9</i>	*601918	PA, SA, delayed puberty	AR, AD	0.2% - 4.7%	(81, 99)
<i>HFM1</i>	*615684	PA, SA	AR, AD	0.8-4.2%	(100-105)
<i>INHA</i>	*147380	OD, PA, SA	AR, AD	0% - 11%	(82)
<i>LHCGR</i>	*152790	Delayed or absent menarche, SA	AR, AD	unknown	(106, 107)
<i>LHX8</i>	*604425	Primary infertility, SA	AD	0.7% - 1%	(53, 108, 109)
<i>MCM8</i>	*608187	PA, SA	AR, AD	1.25-2%	(104, 110-112)
<i>MCM9</i>	*610098	OD, PA, SA	AR, AD	1.6-8%	(53, 111, 113-116)
<i>MEIOB</i>	*617670	SA	AR	unknown	(117, 118)
<i>MEIOSIN</i>	n.d.	SA	AD	rare	(119)
<i>MND1</i>	* 611422	OD, PA, SA	AR, AD	unknown	(120)
<i>MRPS22</i>	*605810	SA, delayed puberty	AR	unknown	(121)
<i>MSH4</i>	*602105	OD, PA, SA, DOR	AR	1.2%	(81, 121, 122)
<i>MSH5</i>	*603382	SA	AR	0.6%	(81, 123)
<i>NANOS3</i>	*608229	SA	AR, AD	0.5-2.5%	(124, 125)
<i>NOBOX</i>	*610934	PA, SA (with or without delayed puberty)	AD, AR	1.2% - 9%	(81, 126, 127)
<i>NOTCH2</i>	*600275	PA, SA	AD	0.04%	(99, 128)
<i>NR5A1</i>	*184757	PA, SA, delayed puberty	AR, AD	0.3% - 2.3%	(10, 81)
<i>PGRMC1</i>	*300435	SA	XLD	2.0%	(53, 81)
<i>REC8</i>	*608193	SA	AR, AD	1.25%	(114, 129)
<i>SMC1B</i>	*608685	PA, SA	AD	2%	(53, 129)
<i>SOHLH1</i>	*610224	PA, SA	AD, AR	0.2% - 2.2%	(81, 130, 131)
<i>SOHLH2</i>	*616066	SA	AD	1.9%	(53, 132)
<i>STAG3</i>	*608489	OD, PA	AR	unknown	(53, 105, 133-136)

(Continued)

TABLE 2 Continued

Gene	OMIM	Ovarian Phenotype (PA, SA, OD); other phenotypic anomalies	Inheritance (AD, AR, XLD)	Prevalence	Ref.
<i>SYCE1</i>	*611486	SA	AR, AD	<2%	(101, 113, 137–139)
<i>TP63</i>	*603273	OD, PA, SA	AD	3.75%	(140–143)

AD, Autosomal Dominant; AR, Autosomal Recessive; DOR, Decreased Ovarian Reserve; OD, Ovarian Dysgenesis; PA, Primary Amenorrhea; SA, Secondary Amenorrhea; POI, Primary Ovarian Insufficiency; XLD, X-Linked Dominant.

The symbol * before an entry number indicates a gene.

results in infertility due to impaired and aberrant chromosome pairing, followed by apoptosis (186, 187). In the last years, WES in several POI pedigrees reported the contribution of *MSH4* and *MSH5* variants in the pathogenesis of POI. The recent identification of a digenic heterozygous variant in *MSH4/MSH5* suggested that a dysfunctional interaction or cumulative haploinsufficiency of both heterodimer subunits, may disrupt HR during meiosis, finally causing POI (81).

MCM8 and MCM9 proteins form a hexameric ATPase/helicase complex which mediates HR repair (188). HR results impaired in both *Mcm8* and *Mcm9* KO mice, also presenting genome instability and being predisposed to develop tumors, suggesting a role in cancer development as tumor suppressor genes (189). Evidence for an association between variants in either *MCM8* or *MCM9* comes forth in genetic studies in POI families and worldwide cohorts of patients (110). Importantly, oncologic screenings are recommended in mutations' carriers for prevention and early diagnosis (190).

Another helicase gene involved in the realization of crossing over is *HFM1*. In line with the observed phenotype of the *Hfm1*^{-/-} mice, variations in the human gene can be causative for sporadic

POI (100–105). Instead, variants in helicase genes, *RECQL4* and *BLM*, which also participate in HR repair, have been identified in both Bloom and Rothmund-Thomson syndrome.

3.1.1.3.5 Synaptonemal complex and cohesins

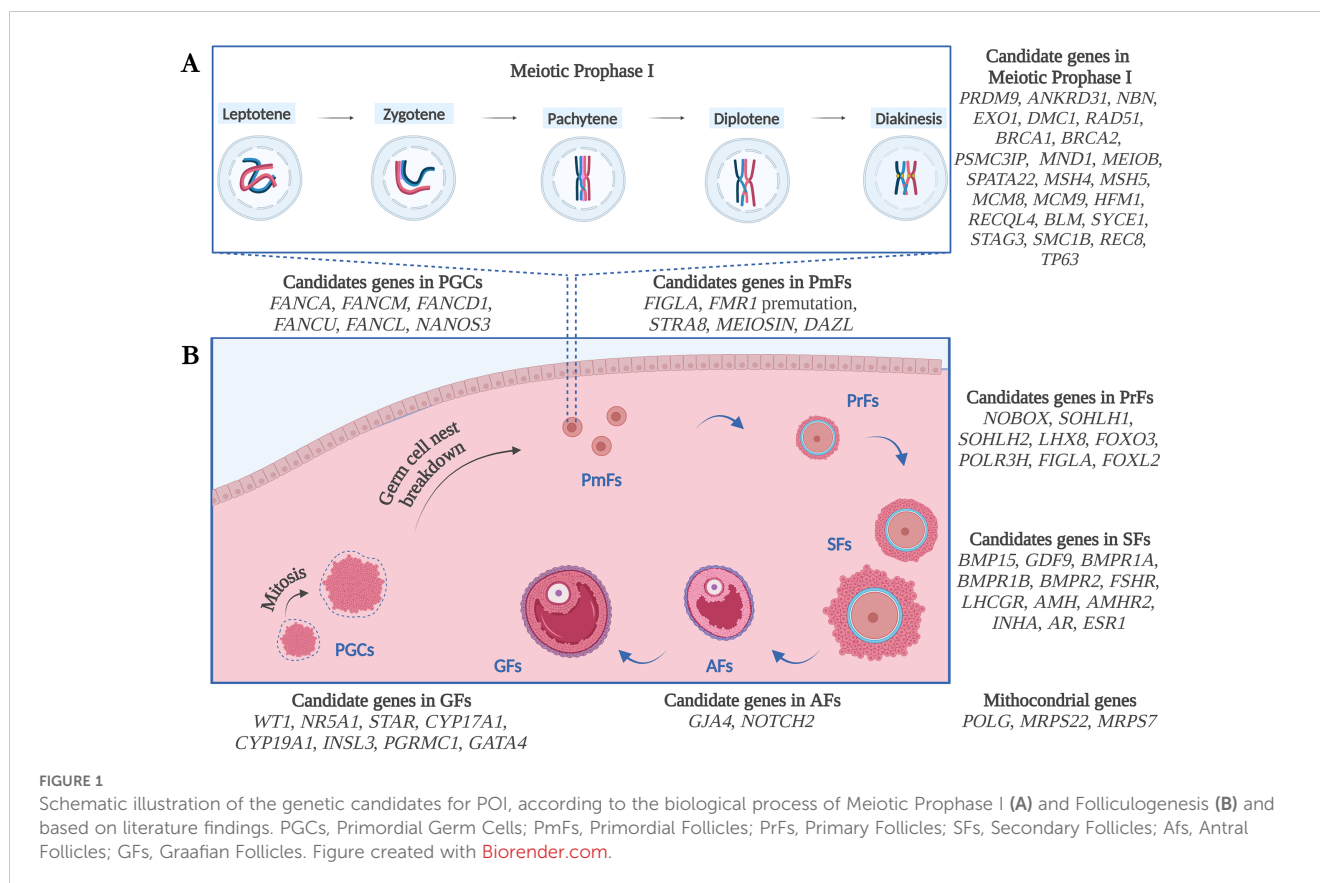
The synaptonemal complex (SC) is a protein complex that forms a zip-like structure between homologous chromosomes during meiotic prophase I. Its primary function is to uphold the pairing of homologous chromatids, thus ensuring crossing over. The central structure of SC consists of transverse filaments, constituted by *Sycp1*, and central elements, including among others *Sycc1*. Whereas *SYCP2* and *SYCP3* form the parallel lateral elements of SC. In patients with POI, except for variants identified in *SYCE1* (101, 113, 137–139, 191, 192), no causative variations have been identified so far, although infertility has been described in animal models. Cohesins are proteins that directly associate with SC and ensure cohesion between sister chromatids. Some cases of POI have been associated with defective chromosomal cohesion due to variants in components of the ring-shaped protein structure made of cohesins. Cohesins core

TABLE 3 Proposed candidate genes for POI with still uncertain pathogenic roles.

Gene	OMIM	Ovarian Phenotype (PA, SA, OD); other phenotypic anomalies	Inheritance (AD, AR, XLD)	Prevalence	Ref.
<i>AR</i>	*313700	PA, SA	XLD	0.03%	(144)
<i>BRCA1</i>	*113705	SA	AD	1.8%	(145)
<i>EXO1</i>	*606063	PA	AD	2%	(146)
<i>FANCM</i>	*609644	SA	AR	rare	(53)
<i>GATA4</i>	*600576	PA	AR	0.1%	(53, 113)
<i>GJA4</i>	*121012	SA	AD	unknown	(53, 147)
<i>INSL3</i>	*146738	PA	AR	0.02%	(53)
<i>POLR3H</i>	*619801	PA, delayed puberty	AR	1.5%	(53, 148)
<i>PRDM9</i>	* 609760	SA	AD	0.4%	(53, 83)
<i>PSMC3IP</i>	*608665	OD, PA, SA	AR	unknown	(120, 149, 150)
<i>RAD51</i>	*179617	PA	AD	2%	(146)
<i>SPATA22</i>	*617673	SA	AR	0.1%	(151)
<i>STRA8</i>	*609987	PA	AR	rare	(119)
<i>WT1</i>	*607102	PA, SA	AD, AR	0.5%	(82)

AD, Autosomal Dominant; AR, Autosomal Recessive; OD, Ovarian Dysgenesis; PA, Primary Amenorrhea; SA, Secondary Amenorrhea; XLD, X-Linked Dominant.

The symbol * before an entry number indicates a gene.



subunits may be meiosis-specific, such as *STAG3*, *RAD21L*, and *SMC1B*, or generic, such as *SMC3* and *REC8* (193). Pathogenic homozygous or compound heterozygous variants in *STAG3* gene have been found in several POI pedigrees. Up to date, 22 variants in *STAG3* have been reported in association with ovarian dysgenesis and PA, mostly with a predicted loss of function effect (53, 104, 105, 133–136). Variants in other cohesin genes have been firstly found for *SMC1B* and *REC8*, in heterozygosity, by a targeted NGS in 100 sporadic patients with POI (129). Accordingly, female mice KO for these cohesins are sterile with premature oocyte exhaustion and higher risk of developing ovarian tumors (*Stag3^{-/-}*) (194) and early meiotic arrest (*Smc1b^{-/-}* and *Rec8^{-/-}*) (195, 196).

3.1.1.3.6 Dissolution of joint DNA intermediates

The dissolution of the SC takes place in the diplotene stage of prophase I, when recombined homologous chromosomes start separating except for the sites of crossovers. The joint DNA intermediates dissolution is executed by *BLM* helicase in complex with topoisomerase III alpha and other subunits. Genetic defects in this complex cause Bloom syndrome. Oocytes are then maintained at the diplotene stage for a prolonged period by high concentrations of cAMP inside the oocyte. During meiotic arrest, p63, a member of p53 transcription factor family, acts in maintaining the female germ line integrity. The alpha isoform is particularly expressed in oocytes of primordial and primary follicles in response to DNA damage and mediate apoptosis (197). The p63+/ΔTID transgenic female mice, in which the transactivation inhibitory domain of the protein is deleted, show rapid oocyte depletion through apoptosis after birth

(198). Several variants located in the C-terminal region of the human *TP63* gene have been found. Recently, our group contributed to identify an intragenic duplication paternally inherited in two sisters diagnosed with ovarian dysgenesis and PA (140). A few nonsense and missense variants were then reported in literature in isolated or syndromic POI families (141, 142, 199). More recently, heterozygous pathogenic single nucleotide variants and intragenic copy number variations of *TP63* have also been described in sporadic patients with POI (143). All the identified variants are supposed to enhance oocyte apoptosis leading to premature depletion of the ovarian reserve, but further researchers may better elucidate the mechanism and pathways involved. Thereafter, through a still undeciphered mechanism, primordial follicles undergo growth and maturation, thus entering the growing pool of primary follicles (200).

3.1.1.4 Follicular growth and maturation

The primordial follicle cohort may have different fates: some remain quiescent and constitute the ovarian reserve, while the majority undergo atresia, either directly or after an initial recruitment and growth, but a smaller portion is activated and then develops until ovulation. In physiological conditions, during transition from primordial to primary follicles, the oocyte resumes meiosis and gradually increases in size, while the surrounding pre-GCs enters a proliferative and differentiated state (201). However, in some pathological situations and after exposure to chemotherapy or environmental chemicals, primordial follicle depletion may accelerate thus leading to POI (202).

3.1.1.5 Primary follicles development

In mammals, early follicular progression is carried on through PI3K/AKT/mTOR activation and PTEN inhibition: multiple players in these pathways have been identified although complete comprehension of these processes is still very limited, particularly in human (203, 204). In the oocyte, key events that trigger the development of primary follicles seem to be the activation of specific transcription factors, such as *NOBOX* and *SOHLH1/SOHLH2* together with *LHX8*. KO mice of these genes present with hypergonadotropic hypogonadism: in female *Nobox*^{-/-} fibrous tissues replace follicles (205), while in female *Sohlh1*^{-/-} and *Lhx8*^{-/-} infertility is respectively caused by gonadal dysgenesis (206), and early oocytes loss (207). Studies in mouse indicate that *NOBOX*, *SOHLH1/SOHLH2* and *LHX8* are co-expressed and cross-regulate each other, either directly or indirectly, thus controlling oocyte development during early follicular progression and therefore their mis-regulation leads to infertility (95). Differently to *NOBOX* and *SOHLH1/SOHLH2*, *LHX8* and *FOXO3* maintain primordial follicles quiescent and inhibit follicular development (208). *FOXO3* is a substrate of *AKT*. In mice, *Foxo3* deficiency prematurely activates dormant follicles in the pubertal ovary, while its constitutive expression delays oocytes and follicles development (209). *NOBOX* gene is considered one of the major genetic causes of POI (126), whose variations have a high incidence in woman from sub-Saharan Africa (210), while *SOHLH1*, *SOHLH2*, *LHX8* and *FOXO3* variants are rather uncommon (98, 105, 108, 130, 132, 211). Recent WES data in a cohort of women with infertility and oocyte maturation arrest, however, report the identification of 5 novel heterozygous loss of function *LHX8* variants that produce truncated proteins (109). In turn, *Foxo3a* expression results diminished in mice with a homozygous point mutation in the *Polr3h* gene and characterized by delayed pubertal development. Remarkably, a pathogenic mutation in the *POLR3H* gene is described in two unrelated POI families, thus highlighting a new player in ovarian function and a new candidate gene (148). The continuous oocyte expression of *FIGLA* regulates the zona pellucida (ZP) genes, necessary for the production and assembly of an extracellular coat of glycoproteins which surrounds and separates the oocyte from the adjacent GCs, but allows the exchange of second messengers or small molecules through gap junctions (161, 212). At this stage, the ovarian follicle is defined a functional syncytium, that allows bidirectional communication between oocytes and GCs, and defects of ZP genes may results in female infertility in mice and humans (213). To support oocyte maturation, GCs first become cubically shaped and tight junctions appear. Then, GCs further enlarge and become stratified into multiple columnar cells, that progressively differentiate into internal cumulus cells (CCs) and external mural granulosa cells (MGCs), characterized by different metabolomes (214). *FOXL2*, a pleiotropic transcription factor with key roles throughout ovarian development, is critical in promoting differentiation and maintenance of GCs identity (215). Conditional loss of *Foxl2* in mouse adult ovaries causes GCs reprogramming into testicular cells (216), and human *FOXL2* variants have been associated with POI (81, 217). However, follicles result histologically mostly abnormal and atretic in POI,

characterized by a partial or complete absence of GCs and, therefore, an important challenge today is to identify new players in GCs development.

3.1.1.6 Secondary follicles growth

Primary to small antral follicle transition depends on the oocyte production and secretion of two members of the transforming growth factor beta (TGFβ) family, *GDF9* and *BMP15*. Evidence in natural and experimental animal models provide insight into their roles and demonstrate their oocyte-specific co-expression as cumulin (218). In particular, it has been reported that *BMP15* is more relevant in mono-ovulating species (such as sheep and human) than in the poly-ovulating ones (mice) (5). In humans, mutations in *BMP15* have been first found in association with hypergonadotropic ovarian failure characterized by ovarian dysgenesis (219) and from then on other variants have been identified worldwide (220–226). *BMP15* maps on the Xp, in a locus critical for ovarian reserve determination, where several TS traits are located, including ovarian failure (227, 228). *BMP15* as synergic heterodimer with *GDF9* interacts with a tetrameric receptor complex on GCs formed by the kinase receptor *BMPR2* and the *ALK3* and *ALK6* co-receptors, respectively *BMPR1A* and *BMPR1B*. *BMPR2* variants are described in potential functional association with POI (106). A variant in *BMPR1A* was found to alter downstream signaling, possibly causing POI (85), whereas mutations in *BMPR1B* have been associated with some cases of non-syndromic POI, besides those with Demirhan syndrome (99). Upon binding receptors, cumulin triggers SMAD proteins phosphorylation cascade and promotes the transcription of GCs proliferation genes (229). One of the known downstream targets of cumulin is *FSHR*, which expression is essential for follicle growth and later estrogen secretion (230). Mutations in *BMP15* or *GDF9* may negatively affect the FSH signaling, arresting folliculogenesis and causing POI (231). *FSHR* genetic defects frequently alter ovarian development in women with highly variable POI clinical manifestations (PA to SA), depending on the degree of resistance to FSH action in granulosa cells (27). *FSHR* mutations lead to POI when both alleles are affected and represent the first genetic cause that was linked to POI in the Finnish population (232). Other TGFβ-like growth factors produced by GCs have instead inhibitory roles on follicles development, such as *AMH* and *INHA*. *AMH* is a secreted factor that can either interact with its receptor *AMHR2*, mainly expressed in the adjacent mesenchyme, or circulate and play a role in controlling the gonadotropin-releasing hormone (GnRH) in the hypothalamus (233). *Amh* mutant female mice show accelerated ovarian primordial follicle recruitment, despite morphologically normal ovaries, suggesting a suppressor role in regulating germ cell development. *AMH* expression in developing follicles is highly dynamic: it starts in primary follicles, increases in preantral and small antral follicles, and then decreases in pre-ovulatory follicles, but not in CCs. Polymorphisms in this gene are associated with the age at menopause (234) but are rarely described in patients with POI, similar to mutations in *AMHR2* (235–237). *INHA* inhibits FSH production in the pituitary gland and genetic screenings in POI series revealed variations potentially associated (114, 238). Theca cells (TCs) originate from the ovary

stroma, develop a blood supply and surround the follicle. TCs further differentiate into theca *externa* and *interna*, which develops LHCG receptors and provide androgen hormone secretion. FSHR and LHCG receptors are targets of the gonadotropins FSH and LHCG, respectively, both produced and released by the pituitary gland upon the hypothalamic stimulus. In turn, gonadotropin-dependent development allows the formation of antral and ovulatory follicles (239). *LHCGR* was among the first genes for which variations were related to POI (240), but its involvement in the pathogenesis of POI is rare. Female mice *Lhgr*^{-/-} are infertile with decreased estradiol and progesterone levels (241); however, after WT ovary transplantation, they can be fertilized (242). Women carrying homozygous pathogenic *LHCGR* variants usually exhibit normal secondary sex characteristics but may have delayed or absent menarche; however, heterozygous mutations might contribute to POI phenotype if combined with other genetic variants (106). Interestingly, infertile women carrying mutated *LHCGR* variants, coding for proteins with absent cell surface localization and signal transduction abilities, achieved successful oocyte retrieval and high-quality embryos leading to live births, indicating that *LHCGR* defects disrupt late folliculogenesis events and ovulation but have no effect on fertilization or embryo development (107).

Steroid hormone receptors, *ESR1* and *AR*, are positive regulators of follicular maturation. *ESR1* is a nuclear receptor expressed by TCs and GCs at this stage of follicular development, regulating growth and maturation to antral stage. *Esr1*^{-/-} mice present folliculogenesis blocked before antral formation or fail to ovulate and are infertile (243). Polymorphisms in *ESR1* have been associated with increased risk of POI (89, 244). *AR* is present in GCs and its deficiency in female mice may lead to dysregulation of important genes involved in folliculogenesis causing a POI-like phenotype (245), but few mutations of this gene have been linked to POI so far (144, 246).

3.1.1.7 Antral follicles formation

Endocrine and paracrine factors from the hypothalamic-pituitary axis together with precise interactions among oocytes and GCs/TCs act in concert for antral follicle formation. Pre-antral follicles continue to extend their diameter, stimulated by FSH action and by the oocytes production of cumulin, and develop a fluid-filled cavity (antrum) with the oocyte eccentrically located in it. Simultaneously, oocyte further increases its volume, with cytoplasmic synthesis and accumulation of proteins, mRNAs, glycogen granules, ribosomes, mitochondria, and vesicles (161). Communication between the oocyte and GCs are facilitated by gap junctions, through which ions and small molecules pass mediated by Connexins, and filopodia-like structures with adherens junctions, where ligand-receptor interaction transduce the signal (i.e. KIT/KIT-ligand and Notch/Jagged) (247). Among connexins, *GJA4* has a role in ovarian follicle development, and disruption of this gene in mice results in female infertility due ovarian folliculogenesis arrest at the preantral stage (248), but few variations have been reported in patients with POI so far (147). KIT-Ligand, a NOBOX target (249), activates the

phosphatidylinositol 3-kinase/AKT pathway by interacting with its receptor (250). Variations in KIT/KIT-ligand cause ovarian insufficiency in rodents, but their role has yet to be elucidated in women affected by POI (53). Notch signaling regulates GCs proliferation (251): Jag1 ligand on oocyte interact with Notch2 and Notch3 receptors on GCs to activate the expression of target genes (i.e. Hey transcriptional repressors) (252). *NOTCH2* variants have been identified through WES in patients with POI (99, 128), while the role of other Notch genes in POI is still unclear. antral follicles are the most susceptible to atresia and may degenerate after GCs programmed death throughout apoptosis, autophagy (253), and ferroptosis (254). Increased circulating FSH levels and a fine balance of stimulatory and inhibitory growth factors, such as IGF1 and TGFβ family members, direct follicles to either atresia or development until ovulation (4). In monovulatory species, after puberty, just one dominant follicle, although several antral follicles are recruited, undergoes final development and maturation during each reproductive cycle, in response to cyclic hormonal changes (255, 256). Growing evidence suggests roles of miRNA in gonadal development, regulating genes involved in folliculogenesis, ovulation and steroidogenesis (257), although their functions and regulatory mechanisms remain inadequately understood (258).

3.1.1.8 Ovulation and steroidogenesis

Ovulation is the fine-tuned remodeling process that ensures the follicle rupture when the uterus is receptive for embryo implantation. The dominant antral follicle rapidly grows to reach preovulatory stage (Graafian follicle) and produces higher levels of estradiol, that positively feedback to the hypothalamic-pituitary axis in a response required both for its further ovulatory process and for subordinate follicles growth inhibition after FSH levels lowering (259). Both FSH and estradiol signaling leads GCs to acquire LH receptors, thus the properly timed preovulatory LH surge from the pituitary gland activates the Graafian follicle and triggers a sequence of events that lead to ovulation: cAMP levels decrease in the oocyte with subsequent nuclear maturation (meiotic resumption), CCs mucificate and, at the end, oocyte-cumulus complex is released for fertilization while the remaining TCs and GCs of the ovulated follicle undergo dynamic transformation to become the corpus luteum, a progesterone producing structure needed for pregnancy (260). Conversely, inappropriate luteinization would impair follicle growth, reduce both the estradiol production in response to FSH and the negative feedback on ovary (261, 262). Previous studies provided evidence for the presence of luteinized Graafian follicles in the ovaries of women with karyotypically normal POI: in contrast with control population, in these cases a poor correlation between follicle diameter and serum estradiol levels and a failure in subsequent achievement ovulatory serum progesterone levels were found, suggesting that premature luteinization may be a major pathophysiological mechanism compromising follicle function in POI (263). However, the molecular mechanism underlying these pathophysiological processes are still unknown. The occurrence of luteinized Graafian follicles is the major source of the cyclic secretion of ovarian estrogens in women of reproductive age, in a joint two-cells system between TCs (that produce progesterone and

precursor androgens under the control of LH signaling) and GCs (where FSH signaling regulates estradiol synthesis starting from androgens) (258). A recently identified player regulating this process of steroidogenesis is *Epg5*; its underproduction blocks autophagy in murine GCs and results in the accumulation of *Wt1* transcription factor that finally leads to infertility (264). In humans, WES identified a rare *WT1* loss-of-function variant in a non-syndromic POI patient (265), and *NR5A1* is reported as a fundamental steroidogenic factor, whose variants were associated also with POI (81), either alone or in combination with other genetic variations (91). *NR5A1* regulates the expression of *STAR*, *CYP17A1*, and *CYP19A1* (266), whose variations have been reported in syndromic POI. Another player with a role in estrogen production, *INSL3*, has been identified as mutated in a Brazilian patient with PA (164); *Insl3* mouse KO promotes follicle atresia and disruption of female cycle (267). Similarly, targeted *Pgrmc1* deletion in GCs suppresses antral follicles development and increased atresia (268) but its variations are rarely found in patients with POI and more research is needed (269, 270). *In vitro* studies point to a role of *GATA4* in ovarian steroidogenesis by impairing estradiol synthesis (271), and conditional knockdown of *Gata4* in mice showed female infertility. Variation of this gene has been found in two patients (99, 164). Recent data report that ovulation is initiated in mice by Progesterone receptor induction in GCs, which cooperate with *RUNX1* to reprogram chromatin accessibility and alter gene expression (272). Noteworthy, the first *in vitro* model of GCs has been generated from human induced pluripotent stem cells (hiPSCs) after overexpression of *NR5A1* and either *RUNX1* or *RUNX2*; the procedure highlights the role of these transcription factors in folliculogenesis and is a central starting point in modelling several key ovarian phenotypes (273).

3.1.1.9 Mitochondrial contribution

Oocyte viability and follicle maturation notably rely on mitochondrial biogenesis and bioenergetics (274, 275) and are the central sites for steroid hormone biosynthesis. Their swelling has been linked to GCs apoptosis and follicles atresia and, consistently, variations in genes involved in mitochondrial functions are responsible for POI (276), mainly syndromic cases. Mitochondrial defects due to mutations in the polymerase β domain of the nuclear *POLG* gene predispose to Progressive external ophthalmoplegia (PEO) associated with POI (50, 277). Variants in *MRPS22* and *MRPS7* are respectively reported in isolated POI and in a patient with failure of pubertal development and hypogonadism (121, 278). We previously reported that the premature impairment of the ovarian reserve is associated with a significant decrease in the number of copies of the mitochondrial DNA (mtDNA) in blood cells and could then be considered a form of anticipated aging in which the ovarian defect may represent the first manifestation (279). The quantification of mtDNA in the peripheral blood could be used as a non-invasive biomarker for POI risk prediction (279, 280). The role of mitochondrial DNA content and of nuclear and mtDNA genes related to mitochondrial functions should be deepened with further investigations in larger populations, and with additional studies in model organisms.

3.2 Autoimmune causes

It is reported that autoimmune cover between 4 and 30% of POI cases (6, 281), however recent data suggest that number is closer to 4 to 15% (2, 282, 283). Dysimmune diathesis can be responsible for polyglandular diseases or result in oophoritis alone. Association with autoimmune diseases can be frequently found among women with POI (282, 284). The exact mechanism involved in the abnormal recognition by the immune system remains unknown, but both genetic and environmental factors are required for initiating the autoimmune response. The proofs for an autoimmune etiology are presence of lymphocytic oophoritis and associated autoimmune disorders (285), but this is not feasible in the clinical context. There are several reported target antigens involved in autoimmune oophoritis; importantly, among them, adrenocortical and steroidogenic autoantibodies, and in particular circulating 21-hydroxylase enzyme (21-OH-Ab), are recognized as the best markers of autoimmune POI (286, 287). A clear association between serum adrenal cortex autoantibodies and the presence of histologically confirmed autoimmune oophoritis was demonstrated (281). Between 2.5 and 20% of patients with POI result positive for adrenal autoantibodies, i.e. directed against the adrenal cortex (steroid cell adrenal antibodies, SCA-Ab) or the 21-OH-Ab (285). The other way round is also true, i.e. 10-20% of patients with Addison's disease develop POI (6, 288). However, these antibodies are usually found in POI associated with autoimmune Addison's disease, but they are not a frequent occurrence in non-adrenal autoimmunity or in isolated idiopathic POI (289). Anti-ovarian antibodies (AOAs) are found in 24-73% of patients with confirmed POI (285, 290), however, sources conflict in the accuracy of these findings and the exact prevalence remains unclear. Their role as a marker for POI is of no value due to the low specificity of existing tests leading to a high rate of false positive results and lack of validation (290). Autoimmune thyroiditis (defined as isolated finding of autoantibodies anti-thyroperoxidase and/or anti-thyroglobulin) appears to be the most frequent pathology associated, with a percentage of patients suffering from clinical and subclinical hypothyroidism of 8-20% and up to 24% of POI cases, respectively (291). However, the prevalence of autoimmune thyroiditis in the female general population results nevertheless high, varying from 8.6% to 17.3% with prevalence increasing with age (292). Moreover, it is worth mentioning that a recent case-control study in 4302 euthyroid women with normal ovarian reserve and low ovarian reserve, had shown that among the whole population thyroid autoimmunity was not associated with low ovarian reserve but was significantly associated with overt POI in woman with TSH > 2.5 mUI (293). Women with diabetes mellitus are also at higher risk of developing POI with an estimated prevalence of 2.5%. Therefore, fasting blood sugar or glycosylated hemoglobin can be recommended (2). POI has also been associated with numerous other disorders including rheumatoid arthritis, Crohn's disease, myasthenia gravis, systemic lupus erythematosus, and multiple sclerosis (294). The different glandular diseases may then combine into different clinical and/or subclinical clusters, i.e. Autoimmune Polyglandular Syndromes (APS). In the specific case,

patients with POI may fall into APS type 1, type 2 or type 3A in approximately 3% of cases (295). The APS type 1 typically develops in pediatric patients and is characterized by the presence of mucocutaneous candidiasis, Addison's disease and hypoparathyroidism; auto-antibodies anti-steroidogenic cells can lead to lymphocytic oophoritis in 60% of cases. Type 2 APS is associated with Addison's disease, type 1 diabetes mellitus, hypothyroidism (or Graves' disease) and less frequently with POI (296). However, the causal association between autoimmunity and ovarian insufficiency remains difficult to establish, and the presence of autoimmunity (either clinically or biochemically) does not necessarily imply the autoimmune origin of the condition, also in view of the relatively broad prevalence of autoimmune disorders and the low specificity of autoantibody measurement. The autoimmune etiology of the POI can be considered substantiated in such case as the presence of adrenocortical and/or steroidogenic cell antibodies and autoimmune Addison's disease (APS type 1 or 2), possible or probable in case of presence of autoantibodies and/or autoimmune disease other than autoimmune Addison's disease (297). Interestingly, in terms of phenotype, it has been described that autoimmune oophoritis presents as a distinct clinical entity compared to women with idiopathic POI: the former were found to have significantly larger, and possibly multifollicular ovaries in association with elevated inhibin B values (281, 298).

3.3 Iatrogenic causes

Iatrogenic causes account for 6-47% of POI cases (2); they can in turn be distinguished into surgical forms, post-chemotherapy, or following radiotherapy (whether local or external, with exposures greater than 1 Gray). Also, common iatrogenic causes that lead to POI in the process of treating non-malignant gynecological diseases include uterine artery embolization and pelvic surgery for ovarian cysts, endometriosis, and ovarian torsion; in particular, it has been shown that excision of bilateral endometriosis can lead to POI in 2.4% of cases (299). Female survivors of childhood, adolescent, and young adult cancer, have an increased risk of POI, with a cumulative incidence of approximately 8% by age 40 years (300, 301). The effects of chemotherapy depend on the type, previous ovarian reserve, dosage, and age at administration (302, 303). Treatments with evidence of causing POI include alkylating agents in general, cyclophosphamide, procarbazine, and radiotherapy to which the ovaries were potentially exposed, in a dose-dependent manner (300, 304). Indeed, for at-risk pre- and peripubertal survivors the monitoring of growth and pubertal development and progression is strongly recommended. Whereas, for postpubertal women who were treated with alkylating agents and/or radiotherapy to which the ovaries were potentially exposed, is strongly recommended detailed menstrual history and physical examination, with specific attention paid to POI symptoms (300). Laboratory assessment should be performed only on the basis of clinical indication or when the patient desires valuation of potential future fertility, at least annually (300).

3.4 Other acquired causes

In 1% of the cases, POI may be related to toxic, metabolic or infectious causes (2). Regarding POI associated with a history of infectious diseases, there is some evidence to suggest that women affected with HIV experience menopause at an earlier age (305) and, although gonadal function is relatively understudied, data found that HIV-positive women were more likely to have lower levels of AMH, largely explained by lower CD4 counts (306). The parotitis virus that causes mumps and results in mumps oophoritis can lead to ovarian failure in 2-8% of cases; however, this tends to be transient in most affected women and normal ovarian function resumes after recovery (299). Anecdotal reports described other viral and microbial infections, such as tuberculosis, varicella, cytomegalovirus, malaria and shigella as causes of POI (2). Association with environmental and toxic causes is also described. Exposure to phthalates and bisphenol-A present in plastic production and other environmental pollutants has been suggested as a possible risk factor POI; these toxins have been shown to increase follicular depletion and accelerated atresia of preantral follicles resulting in an earlier onset of menopause (307). A 2024 meta-analysis described that environmental pollutants pose a serious threat to human and animal reproduction. Such substances, including persistent organic pollutants, heavy metals, phthalic acid esters, polycyclic aromatic hydrocarbons, cosmetic and pharmaceutical products and cigarette smoke, are indeed significant risk factors for POI, with pooled OR of 2.331 (308). Also, preclinical studies speculated that environmental pollutants lead to POI via improper hypothalamic-pituitary-gonadal axis functioning, changed follicular mRNA/hormones, reduced ovarian volume and obvious follicle atresia (308). Moreover, a relation between cigarette smoking and early menopause has been described, although no direct causal relation has been confirmed (295). However, women who are prone to POI should be advised to stop smoking (309).

4 Clinical presentation and diagnosis

Typically, POI may present as menstrual irregularities or secondary amenorrhea, associated with infertility and hypoestrogenism symptoms, such as hot flushes and night sweats, vaginal dryness and dyspareunia, diminished libido and sleep and mood disorder. They generally are more pronounced than those typical of climacteric, especially in acquired forms with sudden onset. In those cases with early onset it may occur as primary amenorrhea with varying degrees of pubertal development, eventually associated with gonadal dysgenesis. Associated symptoms and clinical findings can be variable due to intermittent production of ovarian hormones. In fact, it is worth emphasizing that it may be associated with intermittent resumption of ovarian activity in over 25% of women (310, 311). Estimates of the likelihood of spontaneous pregnancy vary widely in the literature, but from the available data it appears that about 5% of

women with POI will conceive naturally. Most of these conceptions will occur within a year of diagnosis, but pregnancies have been reported many years later (312). Despite the clinical marks, studies report that up to 70% of women with POI have ovarian follicles remaining in the ovary (262, 263), one-half demonstrated ovarian follicle function and, remarkably, 16% of these women achieved an ovulation (263). From a biochemical point of view, POI results in hypergonadotropic hypogonadism, which represents the diagnostic cornerstone. European Society of Human Reproduction and Embryology (ESHRE) guideline recommended that in case of oligo/amenorrhea for at least 4 months diagnosis is confirmed by two elevated FSH tests (>25 U/L), 4–6 weeks apart (309), performed on precocious follicular phase (day 2–3 of the cycle) if menstrual flows are still present. Elevated FSH must be associated with low estradiol level, to rule out the possibility of gonadotropins pre-ovulation peak. In addition, another useful marker is represented by the serum anti-Mullerian hormone (AMH) levels. It is a hormone produced by granulosa cells of growing follicles (<8 mm in diameter) (313, 314), whose concentration reflects the number of follicles remaining in the ovary (315). It has emerged as the current best biomarker of the primordial follicle pool constituting the ovarian reserve (316), and it is known that AMH declines before the menopause in advance of elevated FSH concentrations (317). AMH generally results in low/undetectable (318–320), although there are still no defined cut-offs for diagnosis (6). A small number of studies that have investigated the value of AMH in the diagnosis of POI, demonstrating a progressive decline in women across the stages of deteriorating ovarian function to POI, although data estimated that AMH is detectable in approximately 6% of the POI population (321–323). The largest study to date suggested that an AMH of ≤ 0.25 ng/ml (1.78 pmol/l) was diagnostic of POI with high sensitivity and specificity (323). Furthermore, it was reported that AMH concentrations were lower in women who experienced primary amenorrhea than in those with secondary amenorrhea (324). A transvaginal ultrasound scan can also be helpful in estimating ovarian status. The ovaries can be found to be compact and small, and up to 50% of primary amenorrhea cases may have gonadal dysgenesis with “streak” ovaries. However, as mentioned above, it is not uncommon to detect evidence of ovarian function (262) (pre-antral, antral follicles or pre-ovulation follicles and/or ovarian corpus luteum). Thus, ultrasound findings can be misleadingly reassuring regarding ovarian function and fertility prognosis (325), but may also be useful in revealing any remaining ovarian activity. Ovarian reserve can be assessed sonographically by antral follicle count (AFC), that would be expected to be low in POI and usually correlate with AMH levels. Occasionally relatively normal AFCs are seen despite low AMH levels, however, AMH appears to be a stronger predictor of ovarian response (316). Unfortunately, because of the above, when the biochemical criteria of POI are met, the ovarian reserve is found to be already substantially reduced or follicular dysfunction is present with impaired responsiveness to FSH (262, 263), consequently, the chances of fertility preservation are severely diminished (323). For this reason, the identification of early diagnostic markers to identify women at high risk of developing POI, enabling effective fertility planning, is of great interest.

However, while it has been postulated that AMH may be of value in assessing family members of a proband with POI (326), current evidence showed low discriminatory performance of AMH in menopause prediction in young women (316, 322, 327). Once the diagnosis of POI has been confirmed, it is important to carry out investigations to establish the origin of POI. After ruling out possible acquired causes by means of a thorough medical history, autoimmune and genetic causes should be sought in the first instance. ESHRE guidelines recommend routine screening for the presence of thyroid autoantibodies and 21OH-Abs in every case of POI. Screening for anti-ovarian antibodies is not recommended. Screening beyond Hashimoto’s and Addison’s diseases is not routinely performed (309). On the other hand, in patients with multiple autoimmune diseases or Addison’s disease it should be advisable to consider screening for early detection of POI. Also, measurement of fasting blood glucose or glycosylated hemoglobin levels should be performed (2).

4.1 Genetic diagnosis

Turner Syndrome (45,X), mosaicisms of X chromosome, the partial loss of critical terminal regions of the long arm of the X, and X-autosomal translocations are well-known chromosomal abnormalities causing POI that could lead to either primary or secondary amenorrhea (328). Besides, one of the major genetic alterations implicated in POI is being a carrier for the FMR1 gene premutation. In women, this condition defines a higher risk ($>20\%$) of developing the premature exhaustion of ovarian function, which can also be associated with other symptoms (i.e. ataxia, psychomotor developmental disorders, and cardiovascular pathologies). Additionally, premutated alleles are mitotically and meiotically unstable and could lead to the expansion to full mutation allele during the maternal transmission and cause the Fragile X syndrome in male offsprings of the next generation. The prevalence of premutated FMR1 allele in the general female population is estimated to be around 1:250 and even higher among different ethnic groups (329). Investigating the FMR1 premutation is of primary importance in patients with POI because the chance of evolving to the full mutation (>200 repeats) in the subsequent generation is close to 100% for expansions >100 repeats (330). Fragile X syndrome is characterized by dysmorphism, severe intellectual disability and autism in males. Therefore, first-level tests for the clinical and genetic evaluation of POI are high-resolution karyotype (that we suggest as first-line genetic test in PA and in SA cases <30 years of age) on 2 independent cultures by analyzing at least 30 metaphases (at 400–550 band resolution), according to the International System of Chromosome Nomenclature 2020 (ISCN 2020) (331), which can be extended to 100 in case of mosaicism and eventually replicated on a cutaneous biopsy, and the molecular analysis of the FMR1 gene; its involvement is highly unusual in PA cases while more frequent in SA cases >25 years of age. In case of negative or uncertain results for both FMR1 and karyotyping, Comparative Genomic Hybridization arrays could be performed to identify undetected chromosomal duplications/deletions or low level mosaicism ($<10\%$). The further genetic screenings should be guided

by the presence of clinical features suggestive of a specific syndrome. In the absence of any syndromic phenotype, *ad-hoc* target Next Generation Sequencing (NGS) panels of candidate genes can be used to identify single nucleotide variants potentially pathogenic. Within the NGS strategies, the analysis of families with POI and large POI series through whole exome sequencing or whole genome sequencing can be used to identify new variants and novel genes involved in the pathogenesis of the disorder and their application is considerably improving our understanding of the molecular basis of ovarian functions and dysfunctions (332). NGS has shed light on the role of oligogenicity as a significant contributor to the genetics of POI (105, 332). Discerning true oligogenicity from digenicity or rare, potentially deleterious variants associated with POI remains a significant challenge. Oligogenicity refers to the involvement of multiple genes in a phenotype, while digenicity specifically involves interactions between two genes. In the context of POI, understanding these genetic complexities is crucial for accurate diagnosis and counselling. Another significant challenge in the genetic diagnosis of POI is the huge number of variants of unknown significance that emerge from NGS. It is likely that several heterozygous VUS can predispose to POI in the context of an oligogenic or multifactorial origin. In the future, efforts should be directed toward a more precise genotype-phenotype correlation and the resulting causative relevance. These challenges are further complicated by the complex gene network involved in POI, as well as the environmental component. Further, in the same family, the occurrence of members affected by POI or early menopause could be observed, due to incomplete penetrance. Investigating the genetics of the pathogenesis of POI is essential to deepen ovarian physiology and to solve the pathogenic mechanisms involved. As we uncover novel pathogenic variants, genetics can serve as valuable tools for precise diagnosis, predicting POI risk in families, and furnishing improved genetic and reproductive counselling that help women to plan their fertility.

5 Clinical management and long-term consequences

POI has a multisystem impact with profound physical and emotional implications; as such, its optimal management should be handled by a multi-disciplinary team. Of course, the effects of the condition on quality of life depend on the age of onset, the underlying cause and inter-individual variability. Age at menopause has been shown to have an additive effect on all-cause mortality and an independent predictor of subsequent cardiovascular outcomes (333–336). In particular, regardless of etiology, POI increases the long-term risk for cardio-metabolic disease (337): in this meta-analysis emerges that compared to women with menopause at age >45 years, women with POI had a higher risks of type 2 diabetes (RR: 1.32, 95% CI: 1.08–1.62), hyperlipidemia (RR: 1.21, 95% CI: 1.05–1.39), coronary heart disease (RR: 1.52, 95% CI: 1.22–1.91), stroke (RR: 1.27, 95% CI: 1.02–1.58) and total cardiovascular event (RR: 1.36, 95% CI: 1.16–1.60). In fact, hypoestrogenism exerts several deleterious effects on many contributor factors, including lipid profile, insulin resistance,

centripetal obesity, chronic inflammation, hypertension, vasoconstriction, endothelial dysfunction, and autonomic nervous system dysfunction. It is interesting to note that in this large Chinese study (338) the Authors found that POI increased the risk of total and cancer-specific mortality (HR (95%CI): 1.29 (1.08–1.54) and 1.38 (1.05–1.81), respectively), while decreasing incidence of breast cancer (OR (95%CI): 0.59 (0.38–0.91)), but they didn't find any statistically significant association of POI with either mortality or morbidity related to CVD. Similar results were observed when HRT users were excluded from the analysis. Nonetheless, in many of the reported studies women who used or had used HRT were excluded from analysis or data on HRT use was not available. Thus, data are lacking to demonstrate whether the results were independent of HRT. However, cardiovascular protection seems to be related to exposure time (339), with the greatest reduction in CVD incidence in women who used HRT for at least 10 years and within 1 year of diagnosis (336), and type of HRT (340). Given the well-characterized cardiometabolic and bone impact of POI, optimal management of this condition should include baseline assessment of insulin resistance and lipid profile. Monitoring of these parameters should be dependent on comorbidity, personal and family history; however annual assessment of cardiovascular risk markers may be appropriate, although evidence on cost-effectiveness is currently lacking (6).

Women with POI have a significantly lower bone mineral density (BMD) (341–343) and a 1.5-fold greater risk of fracture compared to women who experience menopause at the typical age (344), with an estimated prevalence of osteoporosis of approximately 8–27% (342, 345, 346), mainly due to insufficient acquisition of peak bone mass (in those with primary amenorrhea or early onset) and increased bone resorption associated with estrogen deficiency (347), with greater loss of trabecular bone than cortical bone. Identified risk factors for low BMD included young at onset of irregular menses and delay in diagnosis greater than one year and/or lack of compliance with HRT. Indeed, the most important risk factors contributing to BMD loss in POI are the degree and duration of estrogen deficiency. Also, it may contribute the presence of comorbidities and risk factors related to the specific etiology, e.g. women with Turner Syndrome have additional contributors to bone loss, skeletal fragility and falls risk; including genetic abnormality, coeliac disease, hearing impairment and visuo-spatial abnormalities (348, 349) while autoimmune conditions associated with POI may also directly contribute to bone loss. Dual-energy X-ray absorptiometry (DEXA) examination should be performed at diagnosis in all young patients with amenorrhea lasting more than 6 months as a result of hypoestrogenism (309). The frequency of bone densitometry should be evaluated according to the presence of other risk factors for osteoporosis, BMD at baseline, and its change with time (6), however in women with POI with low BMI, and treatment initiated, a repeat DEXA scan in 2–5 years to monitor response is recommended (309, 348). Nevertheless, DEXA has some limitations in the context of patients with POI: it can generally not be used until peak bone mass has been achieved; it does not differentiate between cortical bone and trabecular bone; it does not provide any information on bone quality or geometry; it underestimates BMD in women with short stature, such as Turner syndrome (TS) (345, 350). However, it has been

proposed that Z score < -2 should be used to define low bone mass in pre-menopausal women, though, maintaining the use of T- score < -2.5 to diagnose osteoporosis in young adults suffering from chronic disorders known to affect bone metabolism (351). In the absence of more specific tools, trabecular bone score (TBS) could be a promising adjunct to DEXA for guiding the evaluation of POI-related bone health (343).

Mental health sequelae can be explained primarily by estrogen deficiency, along with the denial or difficulty faced by diagnosed women in accepting the loss of fertility (312, 352). It has been demonstrated major prevalence of anxiety and depression in women with POI (353). Such psychological distress may not only negatively influence the treatment outcomes of these patients, but it can also cause social life disruption and issues in the affective and relational area and even social isolation (354, 355).

The inadequate levels of estrogen present in POI also result in symptomatic vulvovaginal atrophy and urinary incontinence, collectively defined as genitourinary syndrome of menopause (GSM). GSM is associated with symptoms such as dryness, itching, burning, irritation, decreased discharge, dysuria, urinary frequency and urgency, and recurrent urinary tract infections (356). Furthermore, women with GSM report low sexual desire, reduced orgasmic function and dyspareunia (357, 358). Sexual dysfunction and hypoactive sexual desire disorder (HSDD) can be attributed as well as the synergistic effect of estrogen and androgen deprivation related to reduced stimulation of sexual responses (359)). Personal, family, and psychosocial factors may further determine the severity of sexual impairment (360). In women diagnosed with POI, GSM and HSDD have a more detrimental effect on sexual function, body image and overall quality of life compared to women who experienced physiologic menopause (361, 362). However, some evidence showed that the arousal and lubrication domains are the most influential factors of sexual function among women with POI, while the desire domain played the lowest role. Additionally, GSM-related symptoms have a greater impact on quality of life compared to vasomotor symptoms, likely due to the fact that genitourinary symptoms deteriorate if not treated whereas vasomotor symptoms usually improve over time (363).

Education on a well-balanced diet with adequate physical activity in order to maintain an adequate weight, avoiding smoking and minimizing alcohol consumption is particularly important (6). Calcium and vitamin D supplementation are equally important. Women with inadequate dietary intake should take supplementary elemental calcium intake (diet and supplements) is approximately 1200 mg/day (350).

5.1 Hormonal replacement therapy

Women with POI experience symptoms due to low estrogen levels; however, whereas in the case of women who have gone through menopause at a physiological age HRT is aimed at alleviating symptoms due to hypoestrogenism, in women with POI HRT's fundamental purpose should be to restore physiological estrogen levels, in line with patients' age. Indeed, women should be informed that HRT may play a role in primary

prevention of long-term consequences (309, 340, 364, 365). Estrogen replacement therapy has, therefore, multiple goals: to induce the development of secondary sexual characteristics (including uterine growth) in prepubertal girls with primary amenorrhea, alleviate typical vasomotor symptoms (VMS), urogenital problems due to vulvovaginal and bladder atrophy, mood/cognitive problems, reduced energy levels and musculoskeletal pain, and, finally, reduce long-term complications such as cardiovascular disease and osteoporosis. To optimize the achievement of the therapy, the choice of treatment regimen is therefore crucial. Among available formulations, hormone preparations based on 17 β -estradiol are preferable because they are more physiological, safe, and effective than those based on ethinyl-estradiol and conjugated equine estrogens (366), especially when administered transdermally. The primary advantage of transdermal administration is that it bypasses the hepatic first-pass effect, reducing liver exposure to supraphysiologic doses of estrogen and the resulting increase in pro-coagulant factors, SHBG, triglycerides, and markers of inflammation (367), worsen insulin resistance, particularly in obese women who have an increased risk profile at baseline (368). Unfortunately, there are no products specifically designed for the long-term treatment of young women with POI, thus formulations marketed for the treatment of climacteric disorders in postmenopausal women or estrogen-progestin combinations for contraceptive purposes (COCs) are commonly used. The still widespread use of COCs (367) could certainly offer the advantage of greater patient acceptance, however, mounting evidence shows that its use has a less favorable impact on bone and cardiovascular health, as well as on uterine development. More physiological regimens should therefore be preferred, and synthetic estrogen-containing formulations should be avoided (328, 340, 366, 369, 370); even though the use of COCs containing estradiol valerate as HRT in POI is also off-label and requires further research. However, it must be recognized that much of the current evidence on HRT is not gained from studies specifically conducted on women with POI, but comes from extrapolations on data available for physiological menopausal women or from non-randomized controlled studies. Treatment with 17 β -estradiol should be continuous to avoid periods of hypoestrogenism (371). Recommended doses should be generally higher than those used in postmenopausal replacement therapy (6), with the rationale of restoring estrogenic values typical of childbearing women, as a dose-response effect of estrogen regarding cardiovascular and bone benefits has also been suggested (340, 372, 373). HRT maintains or increases BMD at the lumbar spine, femoral neck and total hip, with the magnitude of response dependent on the POI etiology or HRT regimen used, being physiological estradiol more beneficial than synthetic estrogens (346, 374, 375). In particular, in the only one long-term, prospective, double-masked, controlled study on HRT in women with POI data showed that physiologic HRT (estradiol patch 100 mcg/d and cyclical oral medroxyprogesterone acetate 10 mg/d for 12 days of month) restored bone mineral density to normal over three years, being well tolerated and increasing estradiol levels to those of a control group of women with normal ovarian function (376). Higher estrogen doses (2 mg oral or 100–150 mcg/d transdermal estradiol) have been found to be superior in

increasing BMD compared with lower doses or COCs (369, 377). In addition, transdermal estradiol was found to be associated with a better impact on BMD than oral estradiol (378, 379). However, to date studies available on the optimal regimen for women with POI are still lacking and future properly designed trials should aim to compare results to the validated regimens (376). HRT regimens must be individualized, carefully balancing benefits, risks, and side effects. It may be necessary to start with lower doses to test tolerance and increase the dose until the optimal dosage is reached. Examples of the dosages to be used are given in Table 4.

Treatment with progestin is necessary in women with uterus to prevent endometrial hyperplasia and minimize irregular bleeding. Micronized natural progesterone, taken orally or vaginally, has demonstrated greater safety than traditional synthetic progestins (such as medroxyprogesterone acetate) regarding breast cancer risk, metabolic impact, and thromboembolic events (380, 381) and, therefore, is the first choice recommended by the most recent guidelines. Dihydrogesterone, commonly used in oral preparations in fixed combination, has similar metabolic and mammary benefits.

HRT regimen can be either combined sequential, with the introduction of progesterone in the second phase of each cycle (for 12 to 14 days), or combined continuous, with progesterone taken at lower doses but throughout the entire month. In the former, if the estrogen dose is sufficient to thicken the endometrial mucosa, there are menstrual-like flows induced upon discontinuation of progestin. The continuous combined scheme results in almost complete atrophy of the endo-uterine mucosa resulting in absence of bleeding in most cases. Endometrial protection seems to be greater for continuous administration (382), however, the risk of breast cancer appears to be increased with the latter in postmenopausal women (383). The choice between the two types of administration also depends on the patient's preference. It is worth mentioning that it should be advisable to opt for a sequential combined regimen if the woman plans a pregnancy or if fertility treatment with egg donation is planned before long. It is also important to be aware that if doses of estrogen higher than standard are prescribed it may be necessary to adjust the progestin dosage using higher doses, depending on the clinical findings and the pattern of bleeding. Finally, the use of levonorgestrel-medicated intrauterine device (IUD) can be suggested (in combination with transdermal or oral estrogens), especially if contraception is needed or in cases of irregular vaginal bleeding. It provides durable endometrial protection, with the advantage of resulting in negligible systemic concentrations of progestin and, therefore, fewer side effects than systemic therapy

(384). The use of COCs should be considered if the patient is likely to have residual ovarian reserve and desires contraception. COCs provide contraception, menstrual cycle control and relief from VMS and other symptoms. Occurrence of VMS during the use of ethinylestradiol COCs that may be alleviated switching to an estradiol-containing COCs. VMS in the pill-free week can be managed by eliminating the placebo (385). In recent years, an estetrol-based contraceptive has also become available, appearing to have more favorable effects on metabolism and blood pressure (386). Women can transition toward HRT if contraception is no longer required, opting for a combined sequential therapy. However, these regimens do not suppress ovulation, therefore women with enduring ovarian function may frequently experience symptoms of estrogen excess including mastalgia and erratic bleeding due to their underlying ovarian function (385). COCs therapy can be also switched when the risk of an unwanted pregnancy is highly unlikely, typically >2 years after diagnosis (6). It is worth mentioning that some Authors proposed that, taking into account that inappropriate follicle luteinization due to the tonically elevated serum LH levels is recognized to be a key mechanism of follicular dysfunction (262, 263), a trial of physiologic HRT, by reducing LH levels, may improve follicle function and increase the chance of ovulation and spontaneous pregnancy in some women with POI (387).

Concerning patient with primary amenorrhea, puberty should be induced or progressed with 17 β -estradiol, preferably in the transdermal form, starting at the age of 12 with a low dose of approximately 10% of the adult replacement dose and increased every 6 months over a 2 to 3-year period (309, 328, 388, 389). After about 2 years of unopposed estrogen, or if more than one episode of significant breakthrough bleeding occurs, it is necessary to introduce a progestin to induce withdrawal bleeding. The progestin should not be added until there is substantial breast development, because premature initiation of progestin therapy can compromise ultimate breast growth, other than uterine maturation (328). Indeed, uterine maturation is a prerequisite for patients who want to carry on a pregnancy. Unfortunately, more than half of the patients with hypogonadism undergone to pubertal induction were found to have a suboptimal uterine outcome (390), and the risk appears to be greater in girls who had received pelvic irradiation (fibrotic damage to the uterine structure) or with Turner's Syndrome (96). Emerging data showed that progestins, hampering further changes in uterine volume and breast development, should be introduced only in the presence of a concomitant adequate 17 β -estradiol dose and an appropriate clinical response (96). Overall, the approach must be

TABLE 4 Formulations and regimens for hormone replacement therapy.

Estrogen therapy		Progestin therapy		
Formulations	Doses	Formulations	Sequential regimens*	Continuative regimens**
Estradiol valerate mg (tablets)	2 - 4	Micronized progesterone mg (caps)	100+	200+
Estradiol mcg/24 (patches)	50 - 150	Dydrogesterone mg (tablets)	5+	10+
Estradiol/Estradiol emiidrate mg (gel)	1 - 3	Medroxyprogesterone acetate mg (tablets)	2.5+	5+

*given for 14 day per month, **given every day.

individualized, depending on the specific characteristics, circumstances and desires of patients. When hypogonadism is diagnosed late, or it develops after spontaneous pubertal start, estrogen dosing regimens can progress more rapidly, especially for those in which final height is not a concern (389, 391, 392). Guidelines (309, 328, 393) recommend that replacement therapy continue at least until the average age of menopause (51 years). Thereafter, the risk-benefit ratio and individual symptomatology should be evaluated on an individual basis. However, it should be taken into account in clinical practice that a number of women with POI have received inadequate treatment previously or have had prolonged interruptions in therapy, and therefore should be encouraged to continue for longer.

HRT is indicated in all women with POI, except where specific contraindications exist. The only absolute contraindication is in the patients surviving an estrogen-dependent cancer in young age. A personal history of breast cancer contraindicates the use of hormone replacement therapy (6, 309, 394). However, it should be noted that the risk of breast cancer with long-term use of estrogen-progestin therapy in POI is not higher than that of the age-matched general population (395–397). The use of HRT for the management of menopausal symptoms in carriers after risk-reducing bilateral salpingo-oophorectomy (rrBSO) is controversial since data from the few available studies are conflicting: guidelines approach this issue differently, with some recommending offering HRT while others suggest considering and discussing individually risks and benefits with the patients (398, 399). Regarding other tumor types, whose treatments may also lead to POI, HRT is indicated in most conditions but potentially harmful in some hormone-dependent malignancies (e.g., uterine sarcomas, ovarian cancer, meningioma or ER+/PR+ gastric carcinoma). Indeed, in some cancers or their subgroups, the risk of HRT may outweigh the potential benefits and careful individualized decision making is needed (e.g., some ovarian cancers) (394, 400). It also is worth mentioning that an increased thromboembolic risk is not an absolute contraindication to HRT but requires more caution. Women with a history of prior thrombosis or thrombophilic disorder should be evaluated by a hematologist before starting HRT. Screening for thrombophilic disorder should be performed only in patients with a personal or family history of thromboembolic events. Transdermal estradiol is the preferred route of administration for women at increased thromboembolic risk (309). Some clinical conditions, where there is a relative contraindication for postmenopausal contraceptive or replacement therapies, such as migraine, hypertension, or obesity, are not contraindications for HRT in POI. Even in these cases, transdermal administration is preferred for its lower hepatic effect (6, 309).

Once HRT has been established, women with POI should be clinically monitored once a year, to check compliance, satisfaction, side effects, and whether the regimen or route of administration needs to be changed. No routine monitoring tests are required but may be prompted by specific symptoms or concerns (309). Monitoring estrogen levels may be useful to assess the appropriateness of therapy, having as a target the average values typical of women of childbearing age (100–150 pg/mL) (328, 373, 401). However, there is currently no consensus on the usefulness of this practice. Likewise, there is no indication for monitoring FSH, although it has been

shown to correlate with bone loss. Still, available data showed that serum FSH levels in women on physiological hormone replacement therapy were still significantly higher than control levels (376). Also, markers of bone turnover (BTMs) could potentially be used to monitor adequacy of the HRT dose, as decreases in BTM are observed in clinical trials of HRT in women with POI; however, this is not established in current guidelines (309, 346).

5.2 Other therapies

If genitourinary symptoms persist despite systemic HRT, low-dose vaginal estrogen or prasterone can be additionally administered (6, 402). In addition, some women with POI may benefit from androgen replacement, as it is recognized that the levels of women with POI have lower androgen levels than age-matched controls (403), possibly adversely affecting sexual desire and function and physical performance. Nonetheless, data showed that the addition of physiological transdermal testosterone replacement did not provide additional benefit in BMD increase (376). Currently, the only indication for testosterone use in women is postmenopausal hypoactive sexual desire disorder (404). However, the lack of licensed treatment options that can easily provide the required physiological dose of 5 mg/day of testosterone makes it challenging to use this therapy.

Non-hormonal pharmacological options are indicated for the alleviation of vasomotor symptoms in cases where HRT is contraindicated (405, 406). Low doses of antidepressants drugs are effective for the relief of hot flashes are lower than those commonly used for the treatment of depression, with onset of relief generally occurring. Paroxetine mesylate (7.5 mg per day) is the only nonhormonal treatment for vasomotor symptoms that has been approved by the FDA. Trials have shown a similar reduction in vasomotor symptoms with low doses of oral estradiol (0.5 mg per day), venlafaxine XR (75 mg per day), and escitalopram (10 to 20 mg per day) (407). Neurokinin 3 receptor (NK3R) antagonists, as Fezolinetant, have recently been developed as novel therapeutic agents for the amelioration of VMS through their action on NK3 receptors within the hypothalamus and consequent regulation of the thermoregulatory center. Fezolinetant has demonstrated significant reductions in VMS frequency and severity, improving transform patients' quality of life (408, 409). In order to alleviate genito-urinary symptoms, vaginal moisturizers and lubricants can be used.

Bisphosphonates should be avoided in this young population because of the potential desire for pregnancy and the possible need for long-term use with associated reduction in bone turnover. However, bisphosphonates may be necessary if HRT is contraindicated or considered if there is high risk of fracture despite optimal hormone therapy (6, 345, 348, 350).

5.3 Fertility preservation and future prospective

Fertility preservation techniques have made great advancement in the last years. While embryo and oocyte cryopreservation are now

considered as established techniques, several positive data are now available on ovarian tissue cryopreservation (OTC), and new innovative technique like *in vitro* maturation of oocytes and *in vitro* activation are beginning to be explored with success. Nevertheless, in women with overt POI, the opportunity for fertility preservation is still missed, due to the loss of most of the reproductive material (410). In this case, recent guidelines still report oocyte donation as the only realistic therapeutic option for a pregnancy (6, 202, 309). Indeed, the possibility of preserving fertility strongly depends on an early diagnosis. However, current guidelines do not recommend specific indication on fertility preservation in patients with genetic risk of POI (202). The ESHRE guideline for female fertility preservation (410) recommend individualized counselling for women with a poor ovarian reserve (AMH <0.5 ng/ml and AFC <5) as the value of fertility preservation is unclear, adding, nevertheless, that OTC should not be offered to most of these patients considering the poor success rate. Still, more studies are needed to guide counseling and decision-making in patients seeking these services despite a poor ovarian reserve (411). For girls diagnosed with TS, karyotype-based management has been proposed: Oktay et al. suggest fertility preservation in patients with monosomal karyotype 45, X (in whom the ovarian reserve may be exhausted within the first few years of life) as soon as the diagnosis is made, even in childhood. For mosaic patients, on the contrary, it is proposed to delay fertility preservation to the post menarche age, if possible, based on ovarian reserve monitoring (328, 412). Same Authors state that ovarian reserve can be exhausted if AMH < 0.1 ng/ml, AFC 0 at ultrasound, and FSH > 30 IU/L, whereas it can be considered severely diminished if AMH < 1.1 ng/ml, AFC < 7, and FSH 12–30 IU/L, although evaluation should always be individualized (413). Cryopreservation of ovarian tissue and subsequent ovarian transplantation is identified by several authors as the most appropriate technique for prepubertal girls at risk of POI. This technique has been recently recognized as an established technique in cancer patients (414). Nonetheless, given the limited evidence existing, it should still be considered experimental in patients with idiopathic POI (412, 415, 416). However, given the frequent familiarity for POI and the improved sensitivity of NGS in identifying heritable predisposing variants in a woman with idiopathic POI, we propose the investigation of the carrier status in the young female relatives of an index case. The OTC could then be proposed only to the young relatives carrying the predisposing variant at the preclinical stage of POI, when FSH and AMH levels are still in the normal range and the ovarian reserve is still intact or not completely exhausted.

It is hopeful that in the future, it will be possible to associate to the OTC technique the *in vitro* maturation (IVM) and activation (IVA) of small antral follicles retrieved *ex vivo* from the taken ovarian tissue (202, 417–422). In this view, knowledge of underlying molecular processes of POI can be particularly useful: in fact, patients who harbor a defect in genes involved in the initial phases of ovarian reserve development will more likely present clinically ovarian dysgenesis or reduced pool of primordial follicles, while for mutations that impair the most advanced stages of follicle development, the presence of a residual follicular pool could be assumed. Moreover, specific clinical and ethical issues concerning possible association with syndromic clinical conditions need to be taken into consideration. However, to date, there are no established

treatments to increase the chance of conception, although many approaches have been investigated. Several approaches involve the use of mesenchymal stem cells (MSC) (423), from a variety of sources including bone marrow, placenta and umbilical cord, that had shown to have efficacy in animal models of POI (424). Another approach involves the use of Platelet-rich Plasma (PRP), an autologous blood derivative with high concentration of growth factors (GFs) that can act in a paracrine manner, mediating tissue regeneration and homeostasis. According to preliminary data in animal models of POI, intraperitoneal or intraovarian administration of PRP is demonstrated to increase ovarian cortex volume, AFC and ovarian function, with recently emerging data from few clinical studies in women with POI support the efficacy of PRP in ovarian rejuvenation (425, 426). As mentioned, activation of primordial follicles (IVA) through physical or chemical manipulation of key regulatory pathways (notably the phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) and Hippo pathways) is also being developed (418–422). The latter two techniques appear to be quite effective in achieving IVF conception, with rates of 4% and 7%–8% respectively (426). However, currently, much of the clinical data are uncontrolled, and mostly in women with a reduced ovarian reserve rather than POI. Further studies are needed to substantiate the preliminary claims of success of these approaches (415, 426, 427).

Lastly, another thrilling area of current research which may change the course of fertility preservation treatments is human *in vitro* gametogenesis (IVG). IVG is the process of generating gametes in a dish, starting from pluripotent stem cells. Induced pluripotent stem cells (iPSCs) can be used to reproduce *in vitro* the process of gamete formation. iPSCs can be derived from any differentiated somatic cell, such as skin fibroblasts or peripheral blood mononuclear cells, and can be reprogrammed to acquire the ability to differentiate into various cell types, including germ cells. In the last decade, researchers have successfully reproduced *in vitro* the entire process of oogenesis, and also spermatogenesis, starting from pluripotent stem cells of mice (mPSCs). Briefly, mPSCs were first induced to obtain mouse primordial germ cell-like cells (mPGCLCs). The mPGCLCs were further differentiated into oogonia, which were then induced to enter meiosis and produce functional oocytes, either through *in vivo* transplantation or through *in vitro* culture. In particular, the second method takes advantage of the generation of cell aggregates, defined reconstituted ovaries (rOvaries), obtained by mixing the culture of mPGCLCs with somatic cells from mouse embryonic ovaries, which provide structural and hormonal support for the development of mature and functional oocytes. Moreover, efforts have been made to promote the growth and differentiation of mPGCLCs independently of ovarian somatic cells. The resultant oocytes were fully competent and after *in vitro* fertilization, produced live and fertile offspring (428, 429). The translation of the approach used in mouse IVG has been attempted to induce human PGCLCs (hPGCLCs) from hPSCs, pursuing various methods. The process of hPGCLC specification has been elucidated, revealing the involvement of essential transcription factors, driving specific hierarchical actions, and unique regulatory networks, different from those governing mPGCLC specification. Through culturing hPGCLC with mouse embryonic ovarian somatic cells, defined xenogeneic rOvaries (xrOvaries), hPGCLCs went through

epigenetic reprogramming and differentiated through still unknown mechanisms into early oocytes, thus establishing the framework for human IVG (430). IGV provides a new tool for studying mammalian reproduction and prefigures applications in the field of reproductive medicine, enhancing diagnosis and modeling infertility (431). The application of human IVG for reproductive purposes is a possibility, it could be used to produce healthy gametes from patient- or donor-derived iPSCs and used for *in vitro* fertilization or assisted reproduction. This could be beneficial for couples unable to conceive due to fertility issues, genetic diseases, or other conditions. However, the actual low efficiency of the technique, the need of a source of cells equivalent to embryonic gonadal somatic cells in humans and other species, the genetic and epigenetic quality of iPSCs and the resultant gametes, and the risks of genetic abnormalities or diseases in offspring are challenges that researchers are required to solve in coming years (432). Nevertheless, IVG retains great potential for future applications, but inevitably implicates ethical and social considerations.

6 Conclusion

POI is a heterogeneous disorder, which can be acquired or congenital, although most of the cases remain idiopathic. It is a common cause of infertility in women in which X chromosome and autoimmune abnormalities play a prevalent pathogenic role. POI has a multisystem impact with profound physical and emotional implications; as such, its optimal management should be handled by a multidisciplinary team. Once it occurs, POI is relatively easily diagnosed since it is characterized clinically by persistent amenorrhea with typical symptoms and hormonally by a hypergonadotropic hypogonadism. Nonetheless, the real challenges are the certification of the underlying ethiological cause and the identification of markers that can allow an early diagnosis or, even more important, its prediction. Patients with POI need HRT to restore physiological estrogen levels of the different tissues and organs, in line with patients' age, and thus avoid the consequences of an early and prolonged hypoestrogenism. While therapeutic approaches in this respect are quite well consolidated, fertility preservation is still a matter of frontier and although recent advancement, hopefully in the future years we will assist novel and important perspectives and options. Moreover, it is critical to improve the educational health resources to raise women's awareness, health related behaviors and informed decision making, bridging the gap between scientific knowledge and health care provided. The use of the internet and

social media, correctly managed by the competent professionals, could be instrumental for this purpose (433).

Author contributions

SF: Conceptualization, Validation, Writing – original draft. RR: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. SM: Data curation, Investigation, Writing – original draft, Writing – review & editing. EM: Validation, Writing – original draft. MF: Data curation, Writing – original draft. MB: Data curation, Methodology, Resources, Writing – original draft, Writing – review & editing. LP: Funding acquisition, Resources, Supervision, Writing – original draft, Writing – review & editing.

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Glossary

AARS2	ALANYL-tRNA SYNTHETASE 2;	DAZL	DELETED IN AZOOSPERMIA-LIKE
LIN28A	LIN28 HOMOLOG A	PGRMC1	Progesterone receptor membrane component 1
ACBD5	ACYL-CoA-BINDING DOMAIN-CONTAINING PROTEIN 5	DCAF17	DDB1- AND CUL4-ASSOCIATED FACTOR 17
LMNA	LAMIN A	PMM2	PHOSPHOMANNOMUTASE 2
AMH	ANTI-MÜLLERIAN HORMONE	DMC1	DNA MEIOTIC RECOMBINASE 1
MCM8/MCM9	MINICHROMOSOME MAINTENANCE COMPLEX COMPONENT 8/9	POLG	DNA POLYMERASE GAMMA
AMHR2	ANTI-MULLERIAN HORMONE TYPE II RECEPTOR	EIF2B2; EIF2B4; EIF2B5	EUKARYOTIC TRANSLATION INITIATION FACTOR 2B, SUBUNIT 2, 4 or 5
MEI4	MEIOTIC DOUBLE-STRANDED BREAK FORMATION PROTEIN 4	POLR3H	RNA POLYMERASE III, SUBUNIT H
ANKRD31	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 31	ERAL1	ERA G-PROTEIN-LIKE 1
MEIOB	MEIOSIS-SPECIFIC PROTEIN WITH OB DOMAINS	PRDM9	PR DOMAIN-CONTAINING PROTEIN 9
ANTXR1	ANTHRAX TOXIN RECEPTOR 1	ERCC6	ERCC EXCISION REPAIR 6
MEIOSIN	MEIOSIS INITIATOR	PREPL	PROLYL ENDOPEPTIDASE-LIKE
AR	STEROID HORMONE RECEPTOR FOR ANDROGENS	ESR1/NR3A1	STEROID HORMONE RECEPTOR FOR ESTROGENS
MGME1	MITOCHONDRIAL GENOME MAINTENANCE EXONUCLEASE 1	PRORP	PROTEIN ONLY RNASE P CATALYTIC SUBUNIT
ATG7	AUTOPHAGY-RELATED 7	EXO1	EXONUCLEASE 1
MND1	MEIOTIC NUCLEAR DIVISIONS 1	RAD21L	RAD21 COHESIN COMPLEX COMPONENT-LIKE 1
ATM	ATAXIA-TELANGIECTASIA MUTATED GENE, ATM SERINE/THREONINE KINASE	FANCA; FANCC; FANCM; FANCD1; FANCU; XRCC9/FANCG	FANCONI ANEMIA, COMPLEMENTATION GROUP A; C; M; D; U; G
MRE11	MRE11 HOMOLOG, DOUBLE-STRAND BREAK REPAIR NUCLEASE	RAD50/RAD51	RAD50 DOUBLE-STRAND BREAK REPAIR PROTEIN/RAD51 RECOMBINASE
BLM	BLOOM SYNDROME	FIGLA	FOLLICULOGENESIS-SPECIFIC bHLH TRANSCRIPTION FACTOR
MRPL50	MITOCHONDRIAL RIBOSOMAL PROTEIN L50	RCBTB1	RCC1 DOMAIN- AND BTB DOMAIN-CONTAINING PROTEIN 1
BMP15	BONE MORPHOGENETIC PROTEIN 15	FMRI	FRAGILE X MENTAL RETARDATION 1
MRPS22	MITOCHONDRIAL RIBOSOMAL PROTEIN S22;	REC114	REC114 MEIOTIC RECOMBINATION PROTEIN
BMPRIA/ALK3	BONE MORPHOGENETIC PROTEIN RECEPTOR, TYPE IA	FOXL2	FORKHEAD TRANSCRIPTION FACTOR L2
MRPS7	MITOCHONDRIAL RIBOSOMAL PROTEIN S7	REC8	REC8 MEIOTIC RECOMBINATION PROTEIN
BMPRI1B/ALK6	BONE MORPHOGENETIC PROTEIN RECEPTOR, TYPE IB	FOXO3	FORKHEAD BOX O3
MSH4/MSH5	MutS HOMOLOG 4/5	RECQL4	DNA HELICASE, RECQ-LIKE, TYPE 4
BMPR2	BONE MORPHOGENETIC PROTEIN RECEPTOR, TYPE II	FSHR	FOLLICLE-STIMULATING HORMONE RECEPTOR
NANOS3	NANOS C2HC-TYPE ZINC FINGER 3	RMND1	REQUIRED FOR MEIOTIC NUCLEAR DIVISION 1 HOMOLOG
BRCA1/2	BREAST CANCER DNA REPAIR-ASSOCIATED PROTEIN	GALT	GALACTOSE-1-PHOSPHATE URIDYLTRANSFERASE
NBS1/NBN	NIMBRIN	SMC1B	STRUCTURAL MAINTENANCE OF CHROMOSOMES 1B
CLPP	CASEINOLYTIC MITOCHONDRIAL MATRIX PEPTIDASE PROTEOLYTIC SUBUNIT	GATA4	GATA-BINDING PROTEIN 4
NOBOX	NEWBORN OVARY HOMEBOX	SMC3	STRUCTURAL MAINTENANCE OF CHROMOSOMES 3
CXXC1	CXXC FINGER PROTEIN 1	GDF9	GROWTH/DIFFERENTIATION FACTOR 9
NOG	NOGGIN	SOHLH1; SOHLH2	OOGENESIS SPECIFIC BASIC HELIX-LOOP-HELIX 1 AND 2
CYP17A1	CYTOCHROME P450, FAMILY 17, SUBFAMILY A, POLYPEPTIDE 1	GGPS1	GERANYLGERANYL DIPHOSPHATE SYNTHASE 1
NOTCH2	NOTCH RECEPTOR 2	SOX9	SRY-BOX 9
CYP19A1	CYTOCHROME P450, FAMILY 19, SUBFAMILY A, POLYPEPTIDE 1	GJA4 connexin37	GAP JUNCTION PROTEIN, ALPHA-4
NR5A1	NUCLEAR RECEPTOR SUBFAMILY 5, GROUP A, MEMBER 1	SPATA22	SPERMATOGENESIS-ASSOCIATED PROTEIN 22
		GNAS	GUANINE NUCLEOTIDE-BINDING PROTEIN
		SPO11	SPO11 INITIATOR OF MEIOTIC DOUBLE-STRANDED BREAKS

<i>HARS2</i>	HISTIDYL-tRNA SYNTHETASE 2	<i>IHO1</i>	INTERACTOR OF HORMAD1 1
<i>SRY</i>	SEX REVERSAL 1	<i>TOPOVIB-Like</i>	TOPOISOMERASE VI-B LIKE
<i>HELLS</i>	HELICASE, LYMPHOID-SPECIFIC	<i>INHA</i>	INHIBIN ALPHA
<i>STAG3</i>	STROMAL ANTIGEN 3	<i>TP63</i>	TUMOR PROTEIN p63
<i>HFM1</i>	HELICASE FOR MEIOSIS 1	<i>INSL3</i>	INSULIN-LIKE 3
<i>STAR</i>	STEROIDOGENIC ACUTE REGULATORY PROTEIN	<i>TWINK</i>	TWINKLE mtDNA HELICASE
<i>HOP2/PSMC3IP</i>	PSMC3 Interacting Protein	<i>LARS2</i>	LEUCYL-tRNA SYNTHETASE 2
<i>STRA8</i>	STIMULATED BY RETINOIC ACID 8	<i>WRN</i>	WERNER SYNDROME
<i>HORMAD1</i>	HORMA DOMAIN-CONTAINING PROTEIN 1	<i>LHCGR</i>	LUTEINIZING HORMONE/CHORIOGONADOTROPIN RECEPTOR
<i>SYCE1</i>	SYNAPTONEMAL COMPLEX CENTRAL ELEMENT PROTEIN 1	<i>WT1</i>	WILMS TUMOR TRANSCRIPTION FACTOR 1
<i>HSD17B4</i>	17-BETA-HYDROXYSTEROID DEHYDROGENASE IV	<i>LHX8</i>	LIM homeobox 8
<i>SYCP1/SYCP2/SYCP3</i>	SYNAPTONEMAL COMPLEX PROTEIN 1/2/3	<i>XRCC4</i>	X-RAY REPAIR CROSS COMPLEMENTING 4