Journal of Advanced Zoology

ISSN: 0253-7214

*Volume **44** Issue **S-5 Year 2023** Page **994:1007***

Primary Ovarian Insufficiency: Current Understanding and Diagnostic Approaches

Priya R[1], K. Bhaskaran[2], Suresh A[2], N Muninathan [2], Gopikrishnan V[3], Deepthi S[1], Aswathi RK[1], Surekha V[4], Dinesh Roy D[5*]

[1]Research Scholar Meenakshi Academy of Higher Education and Research (MAHER- Deemed to be University), West K.K Nagar, Chennai, Tamil Nadu, India.
[2]Central Research Laboratory, Meenakshi Medical College Hospital & Research Institute, Kanchipuram, Tamil Nadu.
[3]Scientist, Centre for Drug discovery and Development, Sathyabhama Institute of Science and Technology, Chennai, Tamil Nadu, India.
[4]Deen - Research, Meenakshi Academy of Higher Education and Research (MAHER- Deemed to be University), West K.K Nagar, Chennai, Tamil Nadu, India
[5]Genetika, Centre for Advanced Genetic Studies, Thiruvananthapuram-695024, Kerala, India.
ORCID ID: 0009-0005-7124-148X[5]

**Corresponding author's E-mail: drdineshroyd@gmail.com*

Article History

Received: 06 June 2023
Revised: 05 Sept 2023
Accepted: 17 Oct 2023

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Abstract

Primary ovarian insufficiency (POI) is a medical condition where ovarian function stops prematurely, typically before the age of 40. This condition leads to infertility and produces symptoms similar to those experienced during menopause. Although the origins of POIs are diverse, genetic elements substantially influence their emergence. This assessment delves into the genetic facets of POI, covering genetic triggers, detection, and genetic consultation. We scrutinize the genes linked to POI and their function in ovarian activity, as well as the genetic deviations and mutations that foster POI onset. We also examine the challenges and limitations of genetic testing and counseling for POI and suggest ways to address these challenges. This review offers a thorough examination of the existing understanding of the genetic factors linked to Primary Ovarian Insufficiency (POI) emphasizing the critical need for further investigation in this field.

Keywords: *Primary ovarian insufficiency, chromosome abnormalities, Genetic Factors, Mutations, Infertility, Receptors*

1. Introduction

Primary ovarian insufficiency (POI), also called premature ovarian failure or early menopause, is a condition where ovarian function ceases before age 40. This leads to irregular menstrual cycles, reduced fertility, and decreased estrogen production, resulting in various symptoms and health concerns. Diagnosis involves primary or secondary amenorrhea, elevated gonadotropin levels, and low estradiol levels [1]. It affects about 1% of women under 40, with lower prevalence in younger age groups [2].

The term "primary ovarian insufficiency" encompasses related conditions like hypogonadotropic hypogonadism, premature ovarian failure, and ovarian dysgenesis, all involving disrupted ovarian function, lowered estrogen levels, irregular menstrual cycles, and reduced fertility [3]. POI was first documented by Albright and colleagues in 1942, characterized by absent or irregular menstrual cycles, insufficient sex hormone levels, and a diagnosis before age 40 [2]. Diagnosis requires two evaluations of serum FSH levels exceeding 40 IU/L at least one month apart in a woman under 40, indicating a deviation from the average age of natural menopause onset [2]. POI is significant as it can cause infertility and low sex hormone levels in premenopausal women [3]. The condition presents with

various clinical characteristics and affects women from adolescence to age 40, often leading to secondary amenorrhea [5]. In the United States, a study involving women aged 40-55 revealed that 1.1% experienced POI, with varying prevalence among ethnic groups [5].

A nationwide study in Sweden found a prevalence of 1.9% for POI, with 1.7% being spontaneous and 0.2% iatrogenic cases [6]. Brazil's POI occurrence is uncertain, potentially influenced by environmental toxins, genetics, and lifestyle changes. Diagnosing POI involves measuring elevated gonadotropin levels twice at least one month apart and the presence of amenorrhea for at least three to four months [7]. Cytogenetic analysis and Next-generation sequencing (NGS) are effective methods for detecting genetic causes of POI [8, 9]. POI development involves factors like diminished primordial follicle reserve, increased follicular atresia, or changes in follicle maturation and recruitment [10]. Genetic abnormalities, autoimmune disorders, iatrogenic interventions, viral infections, toxins, or idiopathic factors can lead to POI [11]. Genetic flaws like chromosomal abnormalities and monogenic deficiencies are known causes of POI [12, 13]. This review aims to comprehensively explore the genetic components of POI and their mechanisms for future research and clinical practice.

2. Materials And Methods

For our analysis, we compiled a comprehensive dataset comprising over 30904 articles and reviews focusing on Primary Ovarian Insufficiency (POI), spanning the years 1942 to 2023. These publications were sourced from the Science Core Collection (PubMed & Google Scholar. Approximately 126 articles align closely with our topic's inclusion criteria. The analysis encompassed the examination of various dimensions, including information related to countries and regions, affiliations, authors, journals, keywords, and co-cited references.

3. Results and Discussion

Chromosomal abnormalities and single-gene (monogenic) deficiencies.

Chromosomal abnormalities are a common contributing factor in Primary Ovarian Insufficiency (POI), estimated to occur in about 10 to 13% of cases [14]. Traditional karyotype analysis has identified various chromosomal anomalies in POI, including monosomy X, mosaic X chromosome patterns, deletions, rearrangements involving the X chromosome, translocations between the X chromosome and autosomes, and the presence of isochromosomes [15]. These anomalies encompass a range of abnormalities, such as numerical abnormalities like monosomy X and mosaic X chromosome variations [17]. Additionally, specific abnormalities like X chromosome deletions, X-autosome translocations, X-isochromosomes, and other rearrangements have been observed in individuals with POI [18].

POI can also result from mutations in specific genes, known as monogenic deficiencies, that directly impact the function of a single gene. Various genes related to ovarian development, hormone signaling pathways, and DNA repair mechanisms can be affected. For instance, mutations in the FMR1 gene are associated with Fragile X-associated primary ovarian insufficiency (POI) [19], while mutations in the BMP15 gene can disrupt ovarian follicle development [20]. BMP-15 plays a role in granulosa cell division and regulates the expression of key reproductive genes like the follicle-stimulating hormone (FSH) receptor and the kit ligand [21].

Receptors

The Androgen receptor (AR) belongs to the nuclear transcription factor family and is located on the X chromosome at Xq11-12. Polymorphisms in this gene consist of varying numbers of CAG tandem repeats, determining the length of the polyglutamine chain [22]. These repeats impact the receptor's functionality, with longer repeats associated with reduced receptor function [23]. The first exon of the AR gene contains two types of tandem repeat polymorphisms: CAG repeats, denoted as (CAG)n, and GGN repeats, represented as (GGN)n, as mentioned by Bretherick et al. in 2008 [24]. Some limited research suggests a potential connection between the length of CAG repeats in the AR gene and Primary Ovarian Insufficiency (POI) [25].

Estrogen receptors (ER) are transcription factors found in granulosa cells and other tissues, involved in regulating genes related to cell growth and development [26]. Two types of estrogen receptors, ERα and ERβ, exist. ERα (ESR1) is involved in regulating gonadotropin release in the hypothalamic-hypophyseal axis [27]. Estrogen, through ERβ, positively influences folliculogenesis. A polymorphic

CA tandem repeat sequence was recently identified in the non-coding 3'-region of the ER gene. There is speculation about its potential relationship with bone mineral density in women [28].

The progesterone receptor (PGR) gene is on chromosome 11q22, with multiple polymorphic regions within. One notable genetic variation involves the insertion or deletion of a 306-base pair ALu sequence, known as the PROGINS allele. This allele, whether homozygous or heterozygous, is believed to play a protective role in the female reproductive system [29].

Diagnosis of genetic causes and management of POI

When diagnosing POI, it is essential to consider a patient's family history, particularly if there is a history of spontaneous POI. Genetic counseling should be offered to women with family members who have experienced spontaneous POI. In familial cases, approximately 14% of women were found to have a premutation in the FMR1 gene, whereas in sporadic cases, this figure was around 2% [30, 31].

Although numerous genes are associated with Primary Ovarian Insufficiency (POI), most cases of isolated POI typically involve karyotype and Fragile X (FMR1) testing, as emphasized by Foresta et al., (2002) [32]. Primary diagnostic methods for identifying potential causes of POI include screening for adrenal antibodies, karyotyping, and assessing the presence of the FMR1 gene premutation. It is also advisable to include karyotyping and Fragile X testing, especially when patients present at a young age or have a family history of POI or learning difficulties [33].

European recommendations for genetic testing in infertile women suggest that genetic explanations for POI, other than those mentioned, are infrequent and of minimal clinical significance in the field of reproductive medicine professionals [32]. In the search for POI genes, whole exome sequencing (WES) has been relied upon for many years. WES has been instrumental in identifying most of the human POI genes discovered in recent years, such as MCM8 [34], HSD17B4 [35], and SOHLH1 [36]. This method has the potential to be a valuable diagnostic tool, especially as its cost decreases, and processing pipelines improve, given the involvement of multiple genes in POI, many of which are yet to be identified.

Chromosome analysis conducted at institutions like the Gustave Roussy Institute in France has used standard protocols to investigate POI genes involved in DNA repair, not exclusively expressed in germ cells. This analysis involves culturing peripheral lymphocytes from patients with suspected genetic disorders, their mothers (if available), and healthy women as controls. Cellular hypersensitivity to DNA crosslinking agents, a reliable marker of homologous recombination (HR) efficiency, was evaluated by treating lymphocytes with mitomycin C (MMC) to induce DNA damage. Experiments were performed with three different treatment conditions, and chromosome breaks were scored by experienced cytogeneticists using at least 20 metaphases. This approach helps improve the understanding of the underlying mechanisms of POI and potentially leads to new treatment options. However, it only detects homologous DNA repair deficiencies, and other DNA repair pathways cannot be assessed [42]. Therefore, a two-step strategy combining next-generation sequencing (NGS) followed by a chromosomal breakage investigation is more efficient for POI patients, especially when mutations in genes involved in homologous recombination are suspected [43]. This combined approach enhances variant categorization.

Ideally, the management of women with POI should involve a multidisciplinary team of experts from various specialties who can provide comprehensive care to address their diverse needs. This team typically includes clinicians, specialized nurses, counselors (focused on early menopause and psychosexual issues), and dietitians [44]. While newer methods are available, karyotyping remains the gold standard for evaluating chromosomal abnormalities. Turner syndrome (XO) is a common chromosomal abnormality associated with POI [45]. Counseling is crucial for women diagnosed with Turner syndrome, emphasizing the potential risk of gonadal tumors. If Y chromosomal material is detected, gonadectomy is recommended as a preventive measure. Early identification and effective management of gonadal tumors in Turner syndrome patients significantly improve overall clinical outcomes [46]. Upon diagnosing POI, genetic analysis should be considered, particularly with the increasing availability of Next-Generation Sequencing (NGS). Candidate gene sequencing may be suitable for suspected monogenic conditions, while NGS is more appropriate for other scenarios.

Following a genetic diagnosis, patients should receive tailored comprehensive care from a multidisciplinary team of healthcare professionals, addressing the specific underlying cause and individual needs [47].

Genetic causes of POI

The causes of POI can be diverse, including iatrogenic factors, environmental influences, viral infections, metabolic and autoimmune diseases, and genetic abnormalities. However, the majority of cases are idiopathic and likely have a genetic basis. In some instances, POI occurs sporadically, but in 10-15% of cases, there is a familial history [48]. Family planning counseling is recommended for women with affected relatives because pedigree studies suggest autosomal dominant sex-limited transmission or X-linked inheritance with incomplete penetrance [49].

Idiopathic POI has a significant genetic component (Cramer et al., 1995) [50]. Chromosomal abnormalities, a well-established etiological factor with an estimated incidence of 10-13%, have been identified in connection with POI, including monosomy X, mosaicism, X chromosome deletions, rearrangements, X-autosome translocations, and isochromosomes, using classical karyotype techniques. Advanced techniques such as cytogenetic (array CGH) and exome sequencing have indicated a genetic cause in 20-25% of POI cases (Qin et al., 2015) [51].

An elongation of the CGG repeat sequence within the 5' regulatory region of the FMR1 gene, responsible for Fragile-X syndrome, has been linked to the development of syndromic primary ovarian insufficiency (POI). When the FMR1 gene contains more than 200 CGG repeats in affected women, it results in a full mutation due to methylation-induced gene silencing. This genetic alteration is implicated in both Fragile-X syndrome and syndromic POI, contributing to the complex etiology of the condition [52].

The etiology of POI has also been associated with genes disrupted by breakpoints in balanced X-autosome translocations or carrying point mutations on the X chromosome [53, 54, 55]. Genetic alterations related to syndromic and nonsyndromic POI, including sex chromosomal abnormalities and mutations in genes on both the X chromosome and autosomes, will be discussed below.

Sex chromosome abnormalities

Aneuploidies

Sex chromosome abnormalities, including aneuploidies and rearrangements, account for approximately 13% of POI cases [56, 57]. Turner syndrome (TS), characterized by monosomy X (45, X), leads to gonadal dysgenesis, primary amenorrhea, and diminished ovarian reserve before puberty. About 10% of individuals with TS experience menarche, a lower percentage than those with 45, X/46, XX mosaicism, where approximately 40% may have menstrual cycles for several years before developing complete primary ovarian insufficiency (POI) [58]. USP9X (Ubiquitin-Specific Protease 9), located on chromosome Xp11.4, is a candidate gene for Turner syndrome in patients as it escapes X inactivation and plays a crucial role in ovarian development [59]. ZFX (Zinc Finger Protein, X-linked) and BMP15 (Bone Morphogenetic Protein 15) are also candidate genes for Turner syndrome [60].

Females with triple X syndrome or trisomy X (47, XXX) can experience primary infertility and clinical manifestations of POI [61, 62]. While POI is not a consistent feature of X chromosome tetrasomy (48, XXXX), it has been linked to it in some cases [63]. Additionally, a 16-year-old girl with pentasomy X mosaicism (47, XXX (1) 48, XXXX (12)/ 49, X) reported primary amenorrhea [64].

Structural abnormalities

Deletions and translocations are more common on the X chromosome, particularly its long arm, in women with POI compared to autosomes. These genetic abnormalities are mainly concentrated within the critical region spanning Xq13.2 to Xq27. Within this region, two key areas with the highest occurrence of breakpoints are POF1 (Xq26-Xqter), which has a higher prevalence of deletions, and POF2 (Xq13.3-Xq21.1), where translocations are more frequently observed. The most prevalent mutations among women with POI involve balanced X-autosome translocations at Xq13 and Xq27 [65]. Rearrangements on the X chromosome's short arm are also significant, particularly in the critical region

between Xp11.1 and Xp21 [59]. Genes causing non-syndromic POI due to X chromosome rearrangements include CHM, DIAPH2, DACH2, POF1B, and XPNPEP2 (Persani et al., 2010) [66]. Mutations in the NR5A1 gene have been found to induce ovarian failure in women and are linked to POI [67].

Other abnormalities

Swyer syndrome (46, XY) and pure gonadal dysgenesis (46, XY) result in nonfunctioning ovaries (bilateral streak gonads) and primary amenorrhea [68]. The initiation of male sex determination is attributed to the SRY (Sex-Determining Region Y) gene. Other relevant gene candidates for gonadal dysgenesis in this syndrome include NR5A1, NR0B1, and DHH [67, 69].

Mutations in genes on the X chromosome

Genetic factors, including genes on both the long and short arms of the X chromosome, play a significant role in primary ovarian insufficiency (POI) [63]. The FMR1 gene on the X chromosomes long arm, responsible for the fragile X mental retardation protein, has been linked to POI, with a premutation found in 15% of affected women, underscoring the genetic contribution [70]. Cryptic deletions in the FMR2 gene, associated with Fragile X-associated tremor ataxia syndrome (FRAXE), induce POI, with microdeletions found in 1.5% of women with POI but only 0.04% of the general female population [71].

A mutation in the XIST gene, located on chromosome Xq13, responsible for X-inactivation, can also cause POI [59]. FSHPRH1, corresponding to Xq22, is a candidate gene for gonadal development, gametogenesis, and POI, as it is quickly activated by FSH in Sertoli cells [72]. Higher CAG repeats lengths in the AR gene have been observed in women with POI compared to controls [72]. FOXL2 mutations are associated with non-syndromic POI [73]. Mutations in the FOXO4 gene have been observed in women with ovarian dysfunction [12]. Additionally, POI has been linked to mutations in the AGTR2 and BHLHB9 genes [74].

Table 1: Candidate genes for POI on the long arm of X chromosome

Sl. No.	Genes	Locus	Reference
1	FMR1	Xq27.3	[70]
2	FMR2	Xq28	[71]
3	XIST	Xq13.2	[59]
4	FSHPRH1	Xq22	[65]
5	AR	Xq12	[72]
6	FOXO4	Xq13.1	[12]
7	AGTR2	Xq22-23	[75]
8	BHLHB9	Xq22.1	[74]

Candidate genes on the short arm of the X chromosome associated with Primary Ovarian Insufficiency (POI) include BMP15 (Bone Morphogenetic Protein 15), ZFX, and SHOX. Variations in the BMP15 gene have been found in approximately 3-12% of individuals with POI [10]. A mutation in the DNA-binding gene ZFX (Zinc Finger X), homologous to ZFY (Zinc Finger Y), has been linked to POI (Simpson et al., 2008) [59]. The SHOX (Short Stature Homeobox) gene, present in the pseudo autosomal region, is associated with the short stature seen in Turner syndrome patients. A POI patient was found to have a cryptic duplication including this gene (Tachdjian et al., 2008) [76].

Table 2: Candidate genes for POI on the short arm of X chromosome

Sl. No.	Genes	Locus	Reference
1	BMP15	Xp11.2	[77]
2	ZFX	Xp22.1-21.3	[59]
3	SHOX	Xp22.33	[76]

Mutations in autosomal genes

Autosomal genes, including FSHR, GNAS, GALT, AIRE, StAR, CYP17A1, CYP19A1, EIF2B, NOG, POLG, PMM1, BMPR1B, GJA4, and others, have been extensively investigated for their associations with syndromic primary ovarian insufficiency (POI) [63]. Mutations in FSHR, such as the p.R59X mutation, have been linked to POI by halting folliculogenesis [78]. In individuals with Pseudohypoparathyroidism Type 1a (PHP1A), a mutated maternal allele of the GNAS gene is associated with both gonadotropin resistance and POI due to its role in the GPCR-Gs-cAMP pathway [79]. Mutations in the GALT gene, leading to a rare metabolic disorder, often result in POI [80, 63]. A defective AIRE gene can cause fast follicle depletion and, consequently, POI [81]. The StAR gene, responsible for regulating steroid hormone production, can lead to lipoid congenital adrenal hyperplasia and subsequent ovarian cell damage, resulting in POI [63].

Mutations in CYP17A1 and CYP19A1 genes can also be associated with POI [83]. The eIF4ENIF1 gene mutations are linked to POI [84]. NOG gene mutations, which cause proximal symphalangism, are also associated with POI [85, 86]. POLG gene mutations are connected to POI but are more commonly associated with neurological diseases [87]. Additionally, a single-nucleotide polymorphism (rs1054875) near POLG may contribute to the more prevalent polygenic variants of POI [88]. The PMM1 gene is linked to the metabolic disorder carbohydrate-deficient glycoprotein deficit, which is associated with POI [89].

Table 3: Autosomal genes associated with syndromic POI

Sl. No.	Genes	Locus	Reference
1	FSHR	2p21-p16	[90]
2	GNAS	20q13.3	[10]
3	GALT	9p13	[91]
4	AIRE	21q22.3	[92]
5	StAR	8p11.2	[93]
6	CYP17A1	10q24.3	[94]
7	CYP19A1	15q21.1	[95]
8	EIF2B	14q24.3	[96]
9	NOG	17q22	[85]
10	POLG	15q25	[97]
11	PMM1	22q13.2	[89]
12	BMPR1B	4q22-q24	[98]
13	GJA4	1p34.3	[99]

Various genes have been proposed in cases of primary ovarian insufficiency (POI), including INHA, GDF9, TGFBR3, NOBOX, NANOS3, FIGL, ESR1, WT1, PTEN, CDKN1B, CITED2, SF1, WNT4, DMC1, and MSH5 [63]. An INHA gene mutation (INHA G769A) strongly linked to POI was identified in 7% of New Zealand patients, 10.5% of Indian patients, and 4.5% of Italian patients [100]. Chinese POI patients showed GDF9 gene coding region variations associated with POI [101, 102]. In Sweden, a tandem duplication in the GDF9 promoter region, likely causing POI, was found [103]. TGFBR3 gene variations (p.E459G and p.P825L) were identified in Chinese POI patients, along with a p.P775S variation in an Indian case (Venturella et al., 2019) [104]. NOBOX gene mutations, including p.R355H, were discovered in Caucasian POI patients and [105, 106].

A NANOS3 mutation affecting apoptosis prevention was found in sisters with primary amenorrhea [109]. FIGLα gene mutations were detected in two POI-afflicted women [110]. Significant SNPs were found in HK3, ESR1, and BRSK1 genes in Han Chinese with POI [111]. ESR1 gene polymorphisms (PvuII and XbaI) were linked to idiopathic POI [112]. The Wt1 gene was associated with reduced ovarian size and follicles, resembling POI [113]. A PTEN gene mutation in exon 7 was identified in a patient with POI [114]. CDKN1B gene nonsynonymous variations were potentially linked to POI [115]. Other genes linked to POI include CITED2, SF1, WNT4, DMC1, MSH5, and more [63].

Table 4: Autosomal genes associated with non-syndromic POI

Sl. No.	Genes	Locus	Reference
1	INHA	2q33-q36	[100]
2	GDF9	5q23.2	[59]
3	TGFBR3	1p33-p32,1	[116]
4	NOBOX	7q35	[107]
5	NANOS3	19p13.13	[59]
6	FIGL	2p13.3	[110]
7	ESR1	6p35	[111, 112]
8	WT1	11p13	[113]
9	PTEN	10q23.31	[114]
10	CDKN1B	12p13.1	[115]
11	CITED2	6q24.1	[117]
12	SF1	11q13.1	[118]
13	WNT4	1p36.12	[119]
14	DMC1	22q13.1	[120]
15	MSH5	6p21.3	[120]

Discovery of Novel Candidate Genes for Primary Ovarian Insufficiency Through Genome-Wide Analysis

Novel candidate gene approach, genome-wide analysis, which includes GWAS and linkage analysis, offers an alternative strategy for discovering new genes associated with primary ovarian insufficiency (POI). GWAS examines genetic variations in affected individuals compared to controls to identify candidate genes, while linkage analysis tracks genetic markers in related individuals. Limited patient availability makes linkage analysis challenging for POI. Some genes relevant to POI have been identified through GWAS, as listed in Table 5.

Table 5: Novel candidate genes identified by GWAS

Sl. No.	Genes	Locus	Reference
1	PTHB1	7p14	[121]
2	BCKDHB	6q14.1	[121]
3	ACSL6	5q31	[122]
4	HK3	5q35.2	[123]
5	AKT1	14q32.32	[124]
6	CARD11	7p22.2	[125]
7	CPEB1	15q25.2	[126]
8	CCBE1	18q21.32	[126]
9	PMAIP1	18q21.32	[126]
10	CTNNA3	10q21.3	[126]
11	ANKRD22	10q23.31	[126]
12	STAMBPL1	10q23.31	[126]
13	HSD3B2	1p12	[126]
14	HAO2	1p12	[126]

Future directions and research perspectives in the field of POI

Ongoing research is continuously enhancing our ability to diagnose and treat primary ovarian insufficiency (POI) by illuminating its genetic mechanisms. Future directions in this area may encompass further exploration of genetic variations that contribute to POI, along with an investigation into how epigenetic modifications play a role in its development. The utilization of advanced technologies such as Next-Generation Sequencing (NGS) and genome-wide association studies (GWAS) empowers researchers to achieve a more comprehensive understanding of the complex genetic foundations of POI. Additionally, it remains essential to develop effective treatments for POI,

potentially involving personalized medicine strategies tailored to the specific genetic and epigenetic factors involved in each case. The synergy between genetic research and innovative treatment approaches has the potential to transform how we diagnose and manage this debilitating condition. Future research endeavors in the field of POI hold the promise of significantly advancing our comprehension of this ailment and elevating our capabilities in both diagnosis and therapy.

4. Conclusion

Primary ovarian insufficiency (POI) is a multifaceted and complex condition that can significantly impact a woman's reproductive health. In recent years, there has been a substantial increase in research focused on understanding the genetic aspects of POI. This research has led to a better grasp of the numerous genes and genetic mutations associated with the development of this condition. While there is still much to uncover about the genetic foundations of POI, advancements in technology and research methods have greatly improved our ability to identify and analyze these genetic factors. These discoveries have profound implications for the development of more targeted and personalized treatments for women dealing with POI. Additionally, they contribute to an enhanced overall understanding of the biological processes underlying this condition. The correlation between genetic research and treatment development is crucial, as it allows for more effective interventions for individuals with POI. To further advance our knowledge of the genetic mechanisms governing ovarian function and improve the lives of affected women, it is imperative to continue research in this field.

Conflict Of Interest

The authors affirm that they have no conflicts of interest to disclose.

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