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Research Progress on the Etiology and Treatment of Premature Ovarian Insufficiency

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Abstract
Background: Menopause in women marks the knot of reproductive life, and menopause is defined as the last menstrual period in a woman, but this is caused by the failure of the ovarian reserve. The average age of natural menopause in the general population of women has remained around 50–52 years. Premature ovarian insufficiency (POI) is a debilitating clinical syndrome that manifests as a decline in ovarian function in women under 40. This condition is a prominent cause of female infertility. ***Summary:*** POI is a debilitating condition that not only wreaks havoc on patients' physical and mental well-being but also imposes substantial mental, psychological, and economic burdens, particularly on women. In addition to diminished fertility, individuals afflicted with POI face an elevated risk of developing debilitating conditions such as osteoporosis and cardiovascular disease. The etiologies of POI are highly heterogeneous, and it can be caused by spontaneous genetic defects or induced by autoimmune diseases, infections, and iatrogenic or environmental factors. Alarmingly, idiopathic POI, a subtype characterized by an unknown etiology, accounts for more than half of all POI cases. Currently, clinical interventions for POI primarily consist of hormone replacement therapy. Fertility preservation methods are cryopreservation of embryos, oocytes, and ovarian tissue. Immunological interventions, gene editing techniques, and stem cell-based therapies are being explored to unravel the diverse etiologies and underlying mechanisms of POI, thereby enabling the identification of optimal therapeutic interventions. These innovative approaches offer unprecedented opportunities to advance the field of reproductive medicine. ***Key Messages:*** The main aim of this paper was to offer a succinct summary of the latest research breakthroughs concerning the elucidation of the mechanisms governing the origin and management of POI.

Introduction

Premature ovarian insufficiency (POI) is characterized by ovarian hypofunction in women younger than 40. Its primary clinical features comprise atypical menstrual patterns, including amenorrhea, scanty or frequent menstruation, along with elevated levels of gonadotropins, particularly follicle-stimulating hormone (FSH), exceeding 25 U/L, and fluctuations in estrogen levels [1].

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Additionally, individuals with POI are more likely to develop osteoporosis and cardiovascular disease, as well as diminished fertility [2–4].

Etiology and Pathogenesis

Genetic Factors

Approximately 10% of POI cases are genetically influenced by various hereditary disorders [5, 6]. Genetic factors can be further subdivided into two categories: chromosomal abnormalities and genetic mutations. Common chromosomal abnormalities associated with POI include the X haplotype (Turner syndrome, 45, X), trisomy (47, XXX), deletion of the long or short arm of the X- chromosome, and inversions and balanced translocations. Turner syndrome is the most common sex chromosome abnormality observed in women. An X chromosome monosomal karyotype, specifically 45X, is associated with approximately 43–49% of cases of POI. Genetic mutations within the Fragile X mental retardation 1 (*FMR*1) gene are common in POI, and amplification of the CGG repeat sequence to its full mutation state causes Fragile X syndrome to manifest. Prevalence is associated with reduced ovarian function and an increased risk of early loss of fertility in POI patients [7, 8]. Recent breakthroughs have shed light on the pathogenic genes involved in the development and function of ovaries. Notably, several genes have been identified as being linked to follicular atresia, including *NR5A*1, *NOBOX*, *FIGLA*, and *FOXL*2, as well as growth factors that are essential for follicular genes, such as *BMP*15 and *GDF*9. Furthermore, *MCM*8 and *MCM*9 are newly discovered genes belonging to the microchromosome maintenance (*MCM*) family (*MCM*2-*MCM*9), which has been found to cause hypogonadotropic hypogonadism in an autosomal recessive manner in rare consanguineous families [9]. A groundbreaking study carried out by Swapna Desai and colleagues has illuminated the pivotal roles of MCM8 and MCM9 in the regulation of the gonadal process from its onset to aging [10]. Yang et al. [11] further elucidated that the collective impact of heterozygous variants in *MCM*8, *MCM*9, *BRCA*1, and *RAD*54*L* contributes to the severity of symptoms in individuals with POI.

Medical Factors

POI can also be induced by medical treatments such as radiotherapy, chemotherapy, and pelvic surgery [12–14]. Radiation exposure, such as during total body, craniospinal axis, or total abdominal or pelvic irradiation, can have adverse effects on the ovaries, potentially resulting in ovarian failure. Ionizing radiation has adverse effects on gonadal function at all ages, and the degree and persistence of the damage depend on the dose, irradiation field, and patient age, with older women being at greater risk of damage [15]. Radiation sensitivity can vary depending on the species, meiotic, and follicular development stage. Nonetheless, exposure to radiation may cause cell death, chromosomal aberrations, and dominant lethal mutations in oocytes. Moreover, the total number of irradiated oocytes decreases in a dose-dependent manner, and doses below 2 Gray can result in the destruction of 50% of primordial follicles [16]. Chemotherapeutic drugs affect various cellular components of the ovary. Among these drugs, alkylating agents are the most potent cytotoxic agents that may lead to a rapid depletion of the ovarian follicular reserve and gonadal dysfunction [14, 17]. They do so by triggering a cascade of events, including the death of primordial follicles, acceleration of primordial follicle activation, and atresia of growing follicles. Moreover, they aggravate damage to the blood vessels and interstitial tissue, while simultaneously amplifying inflammation in the ovaries [18]. Consequently, advanced age presents a notably heightened risk of infertility and ovarian failure [19, 20], while the utilization of both abdominal radiotherapy and alkylating agents results in POI, culminating in infertility in virtually all patients [16]. Pelvic surgeries such as uterine artery embolization, hysterectomy, and ovarian tumor removal can inflict harm on the ovarian cortex or blood vessels, ultimately resulting in POI.

Immune Factors

The presence of immune disorders and systemic proinflammatory conditions can disrupt ovarian homeostasis and lead to serological abnormalities that negatively impact follicular dynamics. Such disturbances directly impede the developmental process of oocytes, increasing the risk of POI. Therefore, it is essential to consider the impact of immune factors on follicular development to maintain optimal ovarian health [21]. In the cohort of women diagnosed with autoimmune POI, a noteworthy subset may exhibit the presence of adrenal or 21-hydroxylase autoantibodies. The presence of these autoantibodies can trigger an immune response against ovarian tissue, setting off a complex interplay between cytokines, B cells, and T cells [22]. In a study carried out by Gerard et al. [23], autoimmune screening was conducted on a cohort comprising 135 patients with idiopathic premature ovarian failure, and

the findings indicated that a substantial proportion of patients, namely, 34% (n = 33), exhibited positive results for at least one autoantibody. In a study conducted by Melissa et al., it was discovered that out of 27 patients diagnosed with Addison's disease and adrenal antibodies, 40.7% (11 individuals) also exhibited antibodies targeting the endometrial/granular layer cells of Graafian follicles located within ovarian tissue. Recent research has indicated that the presence of steroid cell autoantibodies (SCAs) is significantly higher among women afflicted with premature ovarian failure and adrenal autoimmune diseases, most notably Addison's disease. This finding highlights the significance of SCA presence in female patients without ovarian failure as it signals a heightened risk of developing premature ovarian failure.

Endocrine Factors

Female reproduction is a highly orchestrated and regulated process controlled by the hypothalamic-pituitary-ovarian axis. Pulsatile gonadotropin-releasing hormone, and therefore gonadotropins (FSH and LH), primarily governs the hypothalamic-pituitary-ovarian axis at puberty and maintains cyclic function in adulthood [24]. Kisspeptins are a family of neuropeptides that are critical for initiating puberty and regulating ovulation in sexually mature females via the central control of the hypothalamic-pituitary-gonadal axis [25]. Studies have shown that kisspeptins can activate a wide variety of signals via their binding to KISS1R [26], Milen Kirilov et al. [27] used complimentary cell-specific knockout and knock-in approaches and demonstrated that gonadotropin-releasing hormone neurons are the key site of kisspeptin-Gpr54 signaling for fertility. Recently gathered experimental data suggest a putative role of kisspeptin signaling in the direct control of ovarian function, including follicular development, oocyte maturation, steroidogenesis, and ovulation. During follicular development, kisspeptin suppresses the initial follicle recruitment through the upregulation of circulating anti-Mullerian hormone, which can inhibit the activation of primordial follicles [28]. A. Kemal Topaloglu, et al. [29] showed that KISS1 mutation inactivation is closely associated with hypogonadotropic hypogonadism. Dysregulation or naturally occurring mutations of the kisspeptin/KISS1R system may negatively affect ovarian function, leading to reproductive pathology or female infertility. A series of animal studies indicate a direct role of kisspeptin signaling in the ovary, and a defect in the kisspeptin/KISS1R system precipitates a state of POF (or primary ovarian insufficiency).

Environmental Factors

Environmental endocrine disruptors are a prevalent group of chemical compounds that pervade our living environment and disrupt the intricate processes of synthesis, release, transport, and metabolism in organisms. These substances are characterized as highly toxic to the ovary and can impact hormone levels, leading to interference with the development of ovarian follicles [30]. Steroid hormones possess the remarkable ability to regulate a multitude of cellular processes through their interaction with nuclear receptors, activation of ion channels, induction of pro-inflammatory cytokines and chemokines, promotion of oxidative stress, and modulation of cellular proliferation and differentiation, via both genomic and non-genomic pathways. They can exert their effects not only through steroid hormone receptors, but also via non-steroidal hormone receptors. Moreover, a growing body of empirical evidence confirms the crucial significance of epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA expression, in the regulation of gene expression, cellular and tissue functionality, and ultimately, the pathogenesis of a broad range of disorders. Various chemical substances, such as pesticides, plasticizers, perfluorinated compounds, metals (including lead, cadmium, and arsenic), and phthalates, have been found to negatively impact the proliferation and differentiation of granulosa cells. These harmful agents can lead to a reduction in ovarian reserve and hasten the depletion of follicles [31]. Epidemiological investigations indicate that certain phthalate exposures may compromise ovarian function and escalate the likelihood of POI among women [32]. Polycyclic aromatic hydrocarbons and nicotine found in tobacco have been shown to decrease serum estrogen levels, induce oocyte apoptosis, and reduce the number of follicles, ultimately resulting in ovarian dysfunction. Suzhou and colleagues have recently shed light on the influence of PM2.5 on gene expression in the context of ovarian function. Their study demonstrated that PM2.5-induced differentially expressed genes were significantly enriched in pathways related to ovarian steroid synthesis, reactive oxygen species, and oxidative phosphorylation. This remarkable finding highlights the potential impact of PM2.5 on the intricate biological processes underlying ovarian function. The underlying mechanism is believed to implicate PM2.5 or air pollution as the trigger for ovarian dysfunction through the activation of both mitochondria-dependent pathways and NF-κB/IL-6-mediated signaling. These

discoveries underscore the significance of accounting for the impacts of environmental factors on reproductive health, and furnish novel insights into the biological mechanisms linking air pollution with female infertility [33].

Psycho-Sociological Factors

In recent years, the rapid development of the social economy, the accelerated pace of life, and the changing lifestyle have contributed to an exponential surge in both work-related and mental pressures on individuals. When confronted with the ongoing pressures of daily life, individuals often find themselves in a state of heightened tension. As a result, it is not uncommon to observe a variety of symptoms, including but not limited to insomnia, anxiety, depression, and overload. Living with persistent negative emotions such as anxiety, depression, and fear can have a profound impact on the regulation of the hypothalamus-pituitary-gonadal axis. Specifically, dysfunction of this system can lead to abnormal hormone secretion, ultimately affecting ovarian function.

Symptoms and Diagnosis

Clinical Manifestations

POI typically presents as secondary amenorrhea, menorrhagia, or a shortened and irregular menstrual cycle. On the other hand, primary POI typically manifests as primary amenorrhea.

POI is characterized by a precipitous decline in fertility, accompanied by a gradual deterioration of ovarian reserve function that eventually culminates in functional failure. However, the ovary is a uniquely dynamic organ that undergoes constant remodeling as follicles grow and die, and sometimes ovulate and form corpora lutea. The organ also changes with age, and this includes diminishing numbers of follicles, alterations in the ovarian stroma, and changes in blood vessels and their distribution.

Joshua Johnson et al. [34] created a mathematical model of human ovarian aging and found that activation of the integrated stress response pathway can slow follicular granulosa cell proliferation by activating cell cycle checkpoints. Strengths of the authors' model included not only growth threshold as a key parameter but also, consideration of population heterogeneity and comparison of follicle loss rates based on the number of primordial follicles in a given woman's birth reserve (i.e., the number of follicles affected by fertility), which represents the number of follicles affected by genetic or environmental exposures. Follicle loss, in addition to a dramatic reduction in the number of follicles at different ages across the lifespan, observed in female cancer patients undergoing gonadotoxic cancer treatments.

Estrogen deficiency can trigger a multitude of systemic effects, ranging from intense hot flashes and sweating to discomforting vaginal dryness and a burning sensation.

Additionally, it can lead to mood disorders, loss of libido, cardiovascular symptoms, and even osteoporosis [35].

Clinical Diagnosis

Diagnostic criteria are as follows: (1) age 40 years old; (2) sporadic menstruation or menopause ≥4 months; and (3) basal serum FSH >25 U/L for at least 2 times (interval >4 weeks) [36]. Ancillary diagnosis is as follows: serum anti-Mullerian hormone ≤7.85 pmol/L (i.e., 1.1 ng/mL) and basal serum inhibin *B* ≤45 ng/L, which suggest POI risk [37].

Genetics and Immunology Diagnostics

Karyotype analysis is the gold standard for assessing chromosomal abnormalities in cases of POI. Thus, chromosomal testing and genetic screening should be conducted to arrive at a definite diagnosis for these patients. POI has been associated with various genetic abnormalities, encompassing deficiencies in gonadal development, DNA replication and meiosis, DNA repair, hormonal signaling, immune function, and metabolism. However, POI is highly heterogeneous in genetic etiology. With the development of sequencing technology, some large-scale medical sequencing has been carried out to reveal the mechanism of POI and assist in diagnosis (ClinicalTrials.gov ID: NCT00001275). Recent approaches using next-generation sequencing, particularly whole-exome sequencing (WES), have identified novel pathogenic factors and proposed relevant candidates in large POI lineages, mainly enriched in DNA damage repair, homologous recombination, and meiosis [38, 39]. Next-generation sequencing or whole-exome sequencing will help better locate pathogenic genes and will facilitate risk prediction of POI.

Patients with autoimmune diseases, including adrenal autoimmune disease, autoimmune thyroiditis, type-1 diabetes, autoimmune hemolytic anemia, myasthenia gravis, and systemic lupus erythematosus, should be considered for associated autoimmune POI. The ovary represents a frequent target of autoimmune assault, and it

Table 1. Hormone replacement therapy in premature ovarian insufficiency (POI)

				Estrogen	Progestogen
Prior to epiphyseal closure	12–13 years old (before)			17β-estradiol 0.25–0.5 mg/day	
	14–16 years	Before the start of menstruation		Gradual increase of 17β-estradiol from the initial phase	
		After the start of menstruation		Gradual increase of 17β-estradiol from the initial phase	Depending on the clinical assessment
After epiphysis closure	16 years – natural age of menopause (50–51 years)	Without uterus		1 Oral estradiol 2 mg/day 2 Combined estrogen 0.625 mg/day 3 Transdermal estradiol 50 μg/day	
		With uterus	No contraceptive requirements	1 Oral estradiol 2 mg/day 2 Oral combined estrogen 0.625–1.25 mg/day 3 Transdermal estradiol 50 μg/day	1 Oral dydrogesterone 10 mg/day per menstrual cycle (days 14–28) 2 Micronized natural progesterone 2.00 mg/d (oral or vaginal placement) (days 14–28)
				Estradiol-estradiol digestrol (1/10) tablets or estradiol-estradiol digestrol (2/10) tablets	
			Contraceptive requirements	Compounded hormonal contraceptives or implanted levonorgestrel IUDs*	

Use one of the estrogen and progestin. *Use of estrogen and progestin doses in combination with hormonal contraceptives is not a replacement dose.

is crucial to consider the autoimmune etiology of POI when anti-oocyte antibodies and lymphocytic ovarian inflammation are evident on biopsy. In 2016, the European Society of Human Reproduction and Embryology (ESHRE) issued a recommendation advocating for the routine screening of thyroid autoantibodies and 21OH-Abs/ACAs in all cases of POI.

Treatment Progress

Hormone Replacement Therapy

Hormone replacement therapy (HRT) is an essential treatment for patients with POI (Table 1). POI patients suffer from chronic estrogen deficiency, which can lead to various health risks, including vasodilatory symptoms, genitourinary atrophy, osteoporosis and fractures, and a significantly increased risk of cardiovascular disease. Therefore, administering HRT can help mitigate these risks and improve the overall health of POI patients. If no contraindications exist, individuals diagnosed with POI ought to initiate personalized systemic hormone therapy (HT) promptly. This treatment approach aims to alleviate symptoms and normalize hormone levels to a physiologically healthy range until the average age of natural menopause (50–51 years) is reached [40, 41]. Presently, two primary approaches are available, namely, oral contraceptive pills and HT. Recent evidence suggests that physiological HRT (which utilizes transdermal estradiol and cyclic progestin) may be a more effective approach for preserving bone health in young women with POI, than continuous combination therapy with oral contraceptive pills. Pierre-Yves Scarabin and his colleagues have effectively showcased the potential of utilizing transdermal and transvaginal routes for hormone administration. Through this approach, hormones can be directly delivered into circulation, thereby mitigating the likelihood of hepatic first-pass effects and venous thromboembolism. In comparison to oral administration of hormones, this alternative method offers a safer and more effective means of hormone delivery [42–44]. Christel Renoux et al. [45] recently conducted research that sheds

light on the increased stroke risk among postmenopausal women with POI who opt for oral estrogen treatment versus transdermal estrogen. Their findings highlight the importance of carefully weighing the potential risks and benefits of different treatment options for this patient population.

Primary POI

In pre- and pubertal patients, such as those with Turner syndrome, children or adolescents undergoing chemotherapy, pelvic radiotherapy, hematopoietic stem cell transplantation, etc., the absence of endogenous estrogen production leads to the onset of POI. In a study by Theintz et al. [40], it was demonstrated that attainment of 90% peak bone mass occurs at the age of 18 years. These findings underscore the importance of addressing POI and its effects on bone health during adolescence, which is a crucial period of bone development and growth. As such, it is imperative to sustain HT without interruption, from the onset of puberty through adulthood, to effectively promote the development of secondary sexual characteristics and enhance overall bone mineral density. The optimal time to initiate puberty induction is between the ages of 12 and 13, with a gradual escalation of the dosage throughout 2–4 years. However, in the case of Turner syndrome, treatment should commence at an earlier stage, specifically between the ages of 11 and 12 [46, 47]. Clinicians should evaluate the timing and route of pubertal induction administration on a case-by-case basis, taking into account the patient's clinical profile and baseline characteristics [48]. Various types of estrogen can be utilized to initiate puberty, including oral estradiol, micronized estradiol, and transdermal 17β-estradiol. Of these options, transdermal 17β-estradiol treatment is the preferred choice, as it results in a concentration profile that closely mimics the physiological levels of estradiol in the bloodstream [49]. The optimal dosage for puberty induction typically falls within the range of 1/8 to 1/4 of the adult dose, mirroring the natural progression of pubertal development. In certain cases where deemed necessary, growth HT may be employed in conjunction with the aforementioned regimen. It is worth noting that after a period of roughly two to 3 years, breakthrough bleeding may manifest, indicating the need to augment estrogen therapy with progestin to protect the endometrium. During the course of treatment, it is imperative to closely monitor a variety of key indicators to guide the necessary dosage adjustments. Specifically, height, bone age, uterine volume, and breast and pubic hair development should all be dynamically assessed in a timely and rigorous fashion.

Secondary POI

Women diagnosed with secondary POI may benefit from hormonal therapy until they reach natural menopausal age. Currently, polycystic ovary syndrome (PCOS) is commonly treated with either menopausal hormone therapy (MHT) or combined oral contraceptives (COCs). In the case of young women seeking contraception, COC represents a more suitable option. By effectively inhibiting ovulation, COC can significantly reduce the likelihood of unintended pregnancy resulting from unexpected spontaneous ovulation [50]. MHT is a highly recommended therapeutic option for perimenopausal or postmenopausal women aged 45 or above. It is specifically designed to alleviate the distressing symptoms commonly experienced during menopause, such as hot flashes, night sweats, and vaginal dryness. Additionally, MHT can alleviate the discomfort caused by vulvovaginal atrophy, and help reduce the risk of postmenopausal osteoporosis. Overall, MHT is a safe and effective treatment option that can greatly improve the quality of life for women during this transitional period. Estrogen therapy typically involves the administration of standard doses of estrogen, without any particular emphasis on lower doses, which are then adjusted as needed to achieve optimal outcomes. The addition of progestin to estrogen therapy is recommended to safeguard the endometrium in women with a uterus. Conversely, estrogen monotherapy may be employed in those without a uterus or who have undergone hysterectomy.

Certain contraindications to HRT exist that require careful consideration. While benign diseases, such as simple cysts and fibroids of the breast, vulva, vagina, and cervix, may not necessarily prohibit HRT, a thorough assessment of the histological type and biological characteristics of any tumors is still recommended. However, it is important to note that endometrial cancer, ovarian cancer, and malignant breast tumors are definite contraindications to HRT. Such conditions demand the utmost caution and should not be overlooked in any HRT evaluation [51]. Patients with a history of cardiovascular disease, endometriosis, migraine, obesity, and venous thromboembolism who are considering HRT should be strongly advised to consult with a specialist to assess their individual risk factors. In cases where there are no absolute contraindications, transdermal estrogen may be considered a safer option. By taking these precautionary measures, patients can minimize their risk and receive the best possible treatment outcome.

Immunotherapy

Approximately 4–30% of patients diagnosed with POI also present with concomitant autoimmune disorders [21]. Among these disorders, hypothyroidism,

Table 2. Types and mechanisms of treating premature ovarian insufficiency (POI) with mesenchymal stem cells (MSCs)

Type of MSCs	Secretion of various growth factors	Mechanisms of MSCs in the treatment of POI
Bone marrow stem cells	Hepatocyte growth factor	"Homing" effect
Adipose-derived stem cells	Insulin-like growth factor-1	Promoting the growth and development of follicles
Amniotic mesenchymal stem cells	Vascular endothelial growth factor	Differentiation into primordial germ cells
Placenta-derived mesenchymal stem cells	Epidermal growth factor	Inhibiting the apoptosis of granulosa cells
Umbilical cord mesenchymal stem cells	Fibroblast growth factor 2	Formation of ovarian blood vessels
Amniotic fluid mesenchymal stem cells		Immunomodulatory and anti-inflammatory effects
		Reducing oxidative stress response

Hashimoto's thyroiditis, and Graves' disease are the most relevant conditions associated with POI. The immunomodulatory potential of human amniotic epithelial cells (HAECs) has been extensively investigated across diverse disease models in scientific research. Zhang et al. [52] successfully transplanted HAECs into mice with autoimmune ovarian 3 polypeptide (*PZP*3) and demonstrated their restorative effects on the ovaries. The authors reported that HAECs exerted their therapeutic effects through upregulating intrasplenic Treg cells, as well as regulating macrophage activation in a paracrine manner to reduce the inflammatory response and improve mouse ovarian cell apoptosis and fibrosis. These findings highlight the potential of HAECs as a promising therapeutic strategy for the treatment of autoimmune ovarian disorders.

Traditional Chinese Medicine

Traditional Chinese Medicine has shown promising results as an alternative treatment option for early-onset ovarian insufficiency (EOI). While Western medicine remains the primary approach, Wang et al. [53] conducted a study demonstrating the efficacy of acupuncture in reducing granulosa cell apoptosis in rats with EOI. The study revealed that acupuncture restored the *PI3K/Akt* signaling pathway, highlighting its potential as a complementary therapy for EOI in conjunction with Western medicine.

Stem Cell Therapy

Transplantation of MSCs has been shown to promote the restoration of ovarian function and enhance reproductive capacity [54, 55] (Table 2). MSCs have been successfully isolated and cultured from a range of tissues, including bone marrow, adipose tissue, amniotic fluid, amniotic membrane, placenta, menstrual blood, endometrium, and umbilical cord. Extensive research has demonstrated the remarkable ability of MSCs from different tissue sources to differentiate into cells of all three germ layer lineages: endoderm, ectoderm, and mesoderm. Moreover, MSCs have emerged as key regulators of the immune system, exerting their influence on a diverse range of immune cell subsets, including T cells, B cells, natural killer cells, dendritic cells, and macrophages. The broad range of potential applications for MSCs in regenerative medicine and immunotherapy underscores the importance of continued investigation into these fascinating cells. Several animal experiments and clinical trials have provided compelling evidence that mesenchymal stem cell (MSC) homing can enhance ovarian function by inhibiting the apoptosis of ovarian granulosa cells and promoting ovarian angiogenesis [54, 56–60]. The ability of stem cells to secrete these and other growth factors is thought to be an important mechanism by which they can exert their therapeutic effects in a variety of disease and injury settings. This remarkable attribute underscores the immense therapeutic potential of these cells, providing a promising avenue for the field of regenerative medicine. SC therapies derived from various sources have been extensively investigated and validated as effective treatments for POI [61–69]. Nevertheless, the molecular and cellular mechanisms underlying the therapeutic effects of MSCs remain a subject of intense debate and require further elucidation. In addition to stem cells from other tissue sources, a clinical trial identified stem cells in the ovaries of adult women (ClinicalTrials.gov ID: NCT01702935), while there are several studies supporting this idea [70, 71]. In addition, it has been reported that ovarian germ stem cells (oogonium stem cells) have been isolated from human ovaries [72]. However,

Wagner M did not identify oogonium stem cells by analyzing the human ovarian cortex using the single-cell technique [73]. Therefore, whether oogonial stem cells exist in the ovary remains questionable. If so, it is not clear whether oogonial stem cell problems are related to diseases such as premature ovarian failure or decreased ovarian reserve function, thus indicating a need for further research and exploration.

Treatment for Fertility Issues

Assisted Reproductive Technology Treatment

Assisted reproductive technology (ART) treatment is a crucial intervention for patients diagnosed with POI. This diagnosis presents a formidable challenge, often accompanied by a substantial decline in ovarian reserve function, follicular failure, compromised oocyte quality, and a noteworthy reduction in fertility potential. ART represents a promising avenue to overcome the challenges posed by POI and improve the chances of successful conception. Women diagnosed with POI who desire pregnancy can receive treatment through various ARTs, such as controlled ovarian stimulation protocols, microstimulation protocols, and natural cycles. These methods can effectively address the infertility issues associated with POI and provide a viable option for women seeking to conceive. Moreover, this cutting-edge reproductive technology boasts impressive success rates of 40–50% in achieving successful pregnancy outcomes.

Fertility Preservation

The imperative for women to preserve their fertility has seen a remarkable surge in recent times. This is attributable to a multitude of factors, ranging from oncological and nononcological reasons to a host of other ailments. Preserving fertility poses a considerable challenge, particularly for those grappling with hematologic malignancies such as Hodgkin's lymphoma, non-Hodgkin's leukemia, and leukemia, as well as breast cancer, which rank among the most common reasons for seeking fertility preservation. Numerous autoimmune diseases and hematologic disorders may necessitate chemotherapy, radiation therapy, or both, and in severe cases, bone marrow transplantation may be necessary [13].

Fertility Preservation Methods

Embryo Cryopreservation

Embryo cryopreservation is a well-established and highly effective method for fertility preservation, offering significant advantages in terms of both efficacy and safety. Moreover, the success rate of embryo cryopreservation is notably high, making it an attractive option for those seeking to preserve their reproductive potential [74, 75].

Oocyte Cryopreservation

The cryopreservation of unfertilized oocytes holds great promise as a viable alternative for women who may not have a male partner, hold ethical or religious concerns about freezing embryos, or have reservations about using donor sperm. The primary cryobiological techniques comprise slow freezing and vitrification freezing, with the latter proving to be highly effective in mitigating crystallization and minimizing cell damage resulting from ice crystal formation and cold-induced injury during the freezing process.

Ovarian Tissue Cryopreservation and Transplantation

In recent decades, impressive advancements have been made in the field of ovarian tissue cryopreservation and transplantation. A recent meta-analysis yielded remarkable findings, revealing live birth and sustained pregnancy rates of 37.7% [76]. Ovarian tissue cryopreservation represents a dependable strategy for safeguarding the fertility of adolescent and young adult females who have been diagnosed with cancer. By preserving ovarian tissue prior to treatment, young women have a better chance of maintaining their fertility and achieving their reproductive goals in the future [13, 14, 77, 78].

Conclusion

POI is a complex pathological condition that cannot be simplistically equated to the hastened onset of natural menopause. Currently, available treatments for various conditions include hormone supplementation therapy, stem cell therapy, and immunotherapy, among others. Simultaneously, there remains a pressing need to undertake additional investigations into the underlying mechanisms driving the production of superior research outcomes. Moreover, it is imperative to conduct prospective clinical trials to confirm whether tailoring treatments to specific pathogenic mechanisms can enhance the prognosis of patients in this cohort, among other factors warranting investigation. In the future, our efforts must remain relentless in the pursuit of discovering dependable biomarkers for predicting and diagnosing POI, precisely evaluating ovarian function, pinpointing the etiology of POI patients,

identifying novel drugs, and selecting the optimal treatment regimen to enhance fertility potential for POI patients.

Conflict of Interest Statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author Contributions

Jian Xu conceived the review. Yuxian Wang and Jianqiu Jiang wrote the paper. Peiyin Fan and Jiali Zhang assisted in the revision of this article.

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