

Review Article

Premature Ovarian Failure

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Keywords: Premature ovarian failure; Epidemiology; Genetic causes; Chemotherapy; Immunological causes; Ovarian surgery



Abstract

Objective: To provide a rigorous, multidisciplinary synthesis of the epidemiological, genetic, immunological, and environmental factors contributing to Premature Ovarian Failure (POF), with particular attention to regional disparities, occupational exposures, the impact of chemotherapy, the occurrence and recurrence of endometriosis, and emerging fertility preservation strategies.

Design: A structured literature review with an emphasis on recent advances in genetic and immunological understanding.

Setting: Academic research and clinical insights from multidisciplinary contributors.

Patients: Individuals diagnosed with POF as reported in the literature.

Interventions: Review of literature concerning epidemiology, genetic mutations, immunological disorders, and surgical outcomes linked to POF.

Main outcome measures: Identification of both established and emerging risk factors, validation of genetic and immunological markers, and clarification of diagnostic and preventive clinical approaches.

Results: The prevalence of POF varies globally, affecting 1% of women under 40. Genetic factors, particularly mutations in the FMRI and BMP15 genes, play a significant role, alongside autoimmune diseases. Chemotherapy is a leading iatrogenic cause, while endometriosis and ovarian cyst surgeries significantly contribute to diminished ovarian reserve.

Conclusion: POF is a multifactorial condition with rising incidence in specific subgroups. Improved early detection, standardized biomarker use, and expanded access to fertility preservation are essential. Targeted genomic and occupational risk screening may enable personalized interventions. Further genomic studies are needed to elucidate rare mutations and their impact.

Introduction

Premature Ovarian Failure (POF), also known as Primary Ovarian Insufficiency (POI), is characterized by the cessation of ovarian function before the age of 40. This condition, distinct from natural menopause, is marked by amenorrhea, elevated gonadotropins, and low estrogen levels. Affecting approximately 1% of women globally, POF is a significant

contributor to infertility and has profound implications for women's physical and psychological health [1].

The etiology of POF is complex and multifaceted, involving genetic, immunological, and environmental factors. Advances in genomic technology have revealed novel mutations associated with the condition, while immunological research has highlighted autoimmune oophoritis as a key pathological

mechanism. Additionally, environmental exposures, including chemotherapy and cytotoxic drugs, have been implicated in accelerating ovarian decline [2].

This review aims to synthesize current knowledge on the epidemiology and etiological factors of POF, with a particular focus on genetic and immunological causes, as well as iatrogenic and surgical contributors. By integrating findings from recent studies, this paper seeks to provide a comprehensive resource for clinicians and researchers in the field of reproductive medicine. Recent advances in environmental epigenetics, occupational health research, and systems biology have contributed to a broader understanding of how chronic exposures and genetic-environmental interactions influence ovarian longevity. This conceptual expansion underscores the need to reframe POF not only as a reproductive disorder but as a systemic, environmentally sensitive condition with significant public health implications.

Materials and methods

This review was conducted through a systematic search of peer-reviewed literature published in the past two decades. Databases including PubMed, Scopus, and Web of Science were used to identify studies related to POF. INPLASY registration number is INPLASY202510101 β (DOI: 10.37766/inplasy2025.1.0101). Keywords such as “premature ovarian failure,” “genetic causes of POF,” “immunological factors in infertility,” and “cytotoxic drug effects on ovaries” were employed in various combinations. Inclusion criteria comprised studies published in English, addressing epidemiology, genetics, immunology, chemotherapy, and surgical causes of POF. Exclusion criteria were case studies and articles without primary data or systematic review components.

Data were extracted on study design, sample size, primary outcomes, and key findings. The extracted information was synthesized to identify patterns and gaps in the current knowledge base. Graphs and tables were created using Excel and R to summarize epidemiological data and genetic findings.

Results

Epidemiology: POF affects 1 in 100 women under the age of 40, with a higher prevalence in individuals with a familial history of the condition. Incidence rates vary globally, with the highest reported rates in South Asia and Sub-Saharan Africa due to limited access to healthcare and higher prevalence of untreated infections [3].

The prevalence of POF affects approximately 1% of women under 40 and about 0.1% of women under 30. While these figures seem small, the impact on fertility and overall health is significant [4]. Precise prevalence varies by region due to genetic, environmental, and healthcare access differences. Higher prevalence in some populations may correlate with genetic predisposition (e.g., Fragile X premutation carriers) or environmental risks. Limited data from low- and middle-income countries may underestimate the true burden.

Geographic factors influence the occurrence of POF through environmental exposures, infectious diseases, and healthcare disparities [5].

Industrialized Regions with high levels of pollutants, such as dioxins, PCBs, and heavy metals, are linked to ovarian dysfunction. Women living in industrial areas of northern Italy have been studied for higher rates of ovarian dysfunction, potentially due to environmental toxins.

Agricultural areas: Exposure to pesticides and herbicides can damage ovarian reserves, particularly in areas with intensive farming practices (e.g., parts of Southeast Asia, Africa, and Latin America).

Infectious diseases: In regions with high rates of Pelvic Inflammatory Diseases (PID) due to untreated STIs or tuberculosis (e.g., South Asia and Sub-Saharan Africa), ovarian damage leading to POF is more common [6,7].

Healthcare access: In developed countries with advanced reproductive medicine, POF is diagnosed earlier, and fertility preservation options (e.g., oocyte cryopreservation) are available. In low-resource settings, delayed diagnosis and limited ART services exacerbate the impact of POF on infertility.

Epidemiology of infertility: Infertility affects an estimated 8% - 12% of reproductive-age couples worldwide, but the prevalence varies by region due to cultural, environmental, and socioeconomic factors. In Europe, North America, and parts of Asia, infertility rates range between 9% - 15%. Lifestyle factors like delayed childbearing, obesity, and stress are key contributors. Higher prevalence is noted in regions like Sub-Saharan Africa and South Asia (10% - 30%), often due to untreated infections (e.g., STIs, tuberculosis) and lack of healthcare access. Pollution, pesticide exposure, and industrial toxins are associated with decreased sperm quality and ovulatory disorders. Industrialized areas in Europe (e.g., northern Italy's "Po Valley") report declining sperm quality linked to air and water pollution.

Certain agricultural regions with high pesticide use show higher infertility rates among residents.

Regions with well-established public healthcare systems (e.g., Nordic countries) often see better ART access and outcomes compared to regions with fragmented or privatized healthcare systems [6,7].

Geographic role in ART access: Italy is an interesting case due to public ART limitations, regional disparities, and long waiting lists in public clinics. Northern regions tend to have more ART resources than southern regions.

Patients from countries with restrictive ART policies or limited availability (e.g., Italy, Poland, Ireland) frequently seek treatment abroad in countries like Spain or the Czech Republic, where private ART clinics are prominent [6,7].



Genetic and genomic causes: Mutations in genes such as FMR1, BMP15, and FOXL2 are closely associated with POF. The FMR1 premutation, linked to fragile X syndrome, is a prominent genetic marker. Recent studies highlight the role of BMP15 in ovarian folliculogenesis, with mutations leading to impaired follicular development [8,9].

Immunological causes: Autoimmune oophoritis accounts for up to 20% of POF cases. Autoantibodies against ovarian antigens disrupt follicular maturation and hormone production. Conditions such as Addison’s disease and systemic lupus erythematosus are commonly associated with autoimmune POF [9,10].

Cytotoxic Drugs and Chemotherapy Chemotherapeutic agents, particularly alkylating agents, are a leading cause of iatrogenic POF. These drugs damage ovarian stromal cells and primordial follicles, accelerating ovarian aging [11].

Endometriosis and ovarian cysts: Endometriosis contributes to ovarian tissue damage, reducing follicular reserve. Surgical excision of endometriomas further exacerbates follicular loss. Similarly, recurrent ovarian cysts and their surgical management can lead to significant depletion of ovarian reserve [12].

Clinical management

The diagnosis and risk assessment for Premature Ovarian Failure (POF) involve a combination of clinical evaluations, hormonal assays, imaging, and sometimes genetic or autoimmune testing. Below is a detailed explanation (Table 1) [1-3]:

POF is typically diagnosed (Table 2) when a woman under the age of 40 presents with:

- **Amenorrhea** (absence of menstrual periods for at least 4-6 months).
- **Elevated gonadotropins:** Follicle-stimulating

Table 2: Diagnostic Approach Summary.

Step	Diagnostic Tools / Biomarkers	Clinical Implication
1. Confirm Symptoms	Amenorrhea, menopausal symptoms	Initial identification of suspected premature ovarian failure (POF)
2. Perform Hormonal Tests	FSH > 40 mIU/mL, AMH < 1 ng/mL, Estradiol < 40–50 pg/mL, LH elevated	Indicates diminished ovarian reserve and confirms ovarian dysfunction
3. Conduct Genetic and Autoimmune Testing	FMR1 premutation, karyotyping, ovarian autoantibodies	Suggests genetic predisposition or autoimmune pathogenesis
4. Evaluate Ovarian Reserve with Imaging	Antral Follicle Count (AFC), ovarian volume (TV ultrasound)	Provides a quantitative estimate of ovarian reserve
5. Rule Out Other Endocrine or Structural Causes	TSH, prolactin, cortisol; rule out thyroid dysfunction, pituitary disorders	Excludes differential diagnoses with overlapping symptoms

Table 3: Key Distinctions Between High and Normal Risk.

Criterion	High Risk	Normal Risk
Family History	First-degree relative with POF or early menopause.	No family history of early ovarian insufficiency.
Genetics	FMR1 premutation, Turner syndrome, BMP15/FOXL2 mutations.	No genetic abnormalities detected.
Autoimmune Markers	Positive ovarian autoantibodies or coexisting autoimmune diseases.	No autoimmune activity.
AMH Levels	Low (< 1 ng/mL).	Normal for age (> 1-2 ng/mL).
FSH Levels	Elevated (> 10 IU/L).	Normal for age (< 10 IU/L).
AFC	Low (< 5 follicles per ovary).	Normal (> 8-10 follicles per ovary).
Gonadotoxic Exposure	Chemotherapy, radiation, or recurrent ovarian surgeries.	No exposure to gonadotoxic treatments.
Menstrual History	Irregular or absent cycles (amenorrhea/ oligomenorrhea).	Regular menstrual cycles.
Age	Younger women (< 35) with declining biomarkers or significant risk factors.	Normal ovarian reserve appropriate for age without risk factors.

Hormone (FSH) levels persistently above 40 mIU/mL, measured on at least two occasions.

- **Low estradiol levels:** Indicative of diminished ovarian function.

To assess the risk and confirm a diagnosis, the following tests and evaluations are typically performed:

Hormonal testing: A consistently elevated FSH (> 40 mIU/mL) is a key marker of POF. Anti-Müllerian Hormone (AMH) levels reflect ovarian reserve and are significantly reduced in women at risk of or diagnosed with POF. This test is particularly useful for early detection and monitoring ovarian health.

Luteinizing Hormone (LH): Often elevated alongside FSH, helping confirm ovarian dysfunction. Low levels of estradiol (< 40-50 pg/mL) indicate reduced ovarian estrogen production. Screening for thyroid dysfunction, which can mimic or exacerbate POF symptoms. To rule out hyperprolactinemia as a cause of amenorrhea.

Genetic testing: FMR1 Gene Analysis detects premutations associated with fragile X syndrome, a significant genetic cause of POF. Karyotyping is recommended for younger women (< 30

Table 1: Risk factors for POF.

Risk Factor Category	Examples	Strength of Evidence	Representative Studies
Genetic Disorders	FMR1 premutation, Turner syndrome, BMP15/FOXL2 mutations	+++	Chapman, et al. 2015 [2]; Rossetti, et al. 2009 [8]
Family History	First-degree relatives with early menopause or POF	++	Progetto Menopausa Italia, 2003 [4]
Autoimmune Diseases	Thyroiditis, Addison's disease, SLE	++	Bakalov, et al. 2005 [10]; Nash, et al., 2024 [9]
Environmental Exposures	Pesticides, heavy metals, phthalates, radiation	++	Zhu, et al. 2024 [5]; WHO 2024 [6]
Iatrogenic Causes	Chemotherapy, radiation, ovarian surgery	+++	Meirow 2000 [11]; Somigliana, et al. 2003 [12]
Lifestyle Factors	Smoking, high stress, irregular sleep, and sedentary work	+	Walker, et al. 2022 [16]; Goldman et al. 2017 [19]
Recurrent Ovarian Surgeries	Endometriomas, ovarian cyst removal	++	Somigliana, et al. 2003 [12]

years) to identify chromosomal abnormalities such as Turner syndrome (45, X) or mosaicism. Next-Generation Sequencing (NGS) helps to identify rare mutations in genes like BMP15, FOXL2, and GDF9 associated with ovarian dysfunction.

Autoimmune testing: Ovarian Autoantibodies to identify autoimmune oophoritis, a condition where the body attacks its ovarian tissue. Screening for Associated Autoimmune Disorders as tests for Addison's disease, Systemic Lupus Erythematosus (SLE), or other autoimmune conditions.

Imaging studies: Transvaginal Ultrasound to evaluate Antral Follicle Count (AFC) and ovarian volume. Reduced AFC and shrunken ovaries suggest diminished ovarian reserve. Pelvic MRI is used in cases with suspected structural abnormalities, tumors, or developmental anomalies affecting ovarian function.

Biochemical and metabolic testing: Bone Density testing because women with POF are at an increased risk of osteoporosis due to prolonged hypoestrogenism. A Bone Mineral Density (BMD) test via Dual-energy X-ray Absorptiometry (DEXA) is recommended.

Lifestyle and environmental risk factors: Cytotoxic Exposure History, because women who have undergone chemotherapy or radiation should be assessed for ovarian damage. Surgical History suggesting prior ovarian surgeries, such as cyst removal or oophorectomy, contributes to risk.

Menstrual history and symptoms review: Detailed assessment of menstrual irregularities, hot flashes, mood changes, and other menopausal symptoms.

Emerging Biomarkers Advancements in research are uncovering new biomarkers and diagnostic tools, such as Inhibin B, as another marker of ovarian reserve, though less commonly used. MicroRNAs are also emerging as potential non-invasive biomarkers for early ovarian aging.

Occupational Risk Factors for POF Occupational exposure to certain physical, chemical, and psychological factors can increase the risk of ovarian failure [5].

Chemical risks:

- ✓ **Pesticides and toxins:** Agricultural workers exposed to organophosphate pesticides may experience accelerated ovarian aging.
- ✓ **Industrial toxins:** Jobs involving solvents, heavy metals (e.g., cadmium, lead), and phthalates in plastics and manufacturing are linked to ovarian dysfunction.
- ✓ **Healthcare workers:** Exposure to chemotherapy drugs, anesthetic gases, and radiation (e.g., in oncology or radiology professions) increases the risk of POF.

Physical stressors:

- ✓ **Radiation and chemotherapy:** Women undergoing occupational radiation exposure (e.g., in nuclear power plants or radiology) may face higher risks of ovarian failure due to DNA damage.
- ✓ **Chronic heat exposure:** Continuous exposure to high temperatures, as seen in certain industrial jobs, can affect ovarian function indirectly by causing systemic oxidative stress.
- ✓ **Psychological and lifestyle factors:** High-stress jobs, shift work, and irregular sleep patterns can contribute to hormonal dysregulation, potentially hastening ovarian aging.
- ✓ **Sedentary Work Office jobs or long hours sitting** (e.g., IT professionals, drivers) can lead to metabolic changes, weight gain, and increased oxidative stress, affecting both male and female fertility.

Novel investigations suggest a cumulative effect of low-dose Endocrine-disrupting Chemical (EDC) exposure over time, even in non-industrial settings. These findings advocate for expanded surveillance in both high- and medium-risk occupations, regardless of perceived exposure severity.

Public health and epidemiological implications: Early Detection and Screening. Screening programs for women in high-risk professions (e.g., agriculture, healthcare) or with a family history of POF. Use of biomarkers like AMH (anti-Müllerian hormone) for ovarian reserve estimation.

Occupational protection: Implementing protective measures in workplaces, such as limiting exposure to chemicals, radiation, and extreme heat.

Offering fertility preservation options (e.g., egg freezing) for women in high-risk occupations.

Geographical health interventions: Focused public health campaigns in regions with high environmental toxin exposure or limited access to healthcare. Policy changes to regulate industrial pollutants and pesticide use.

Certain regions are more prone to occupational or environmental risk factors:

Europe: Workers in northern Italian industries are often exposed to heavy metals and air pollutants.

South Asia and Africa: High STI prevalence and untreated infections are major infertility factors, compounded by limited ART access.

Urban areas worldwide: Urban residents face increased exposure to air pollution, stressful lifestyles, and delays in childbearing due to career priorities

How to preserve fertility: Identifying high-risk women for Premature Ovarian Failure (POF) and selecting candidates for oocyte cryopreservation involves evaluating clinical, genetic, hormonal, and environmental factors. The following are the best criteria for distinguishing women at high risk versus those at normal risk, which can guide decisions about fertility preservation.

Prioritization for oocyte cryopreservation

High-risk women:

These women should be prioritized for oocyte cryopreservation:

- Young women (<35 years) with low AMH or AFC, even if they are asymptomatic.
- Women with genetic predispositions (e.g., FMR1 premutation, Turner syndrome).
- Women undergoing gonadotoxic therapies, such as chemotherapy or radiation.
- Women with autoimmune diseases and evidence of ovarian-specific autoantibodies.

Women planning surgical interventions (e.g., bilateral oophorectomy, ovarian cyst removal) that could compromise ovarian reserve.

Normal risk women:

For women at normal risk, oocyte cryopreservation may still be considered for elective reasons, such as delaying childbearing, but it is not urgently recommended unless ovarian reserve begins to decline based on age or biomarkers.

Fertility preservation and ART: Increase access to affordable fertility preservation (e.g., cryopreservation) and ART in underserved areas. Advocate for equitable healthcare policies, especially in countries like Italy, where access to ART is regionally variable [13,14].

Preserving fertility through oocyte cryopreservation is a critical strategy for women at elevated risk of Premature Ovarian Failure (POF). The likelihood of success depends on several variables, including the woman's age at the time of retrieval, the number and maturity of oocytes collected, and baseline ovarian reserve.

Success Rates of Oocyte Cryopreservation in High-Risk Women. For women facing medical conditions that threaten ovarian function, such as those undergoing gonadotoxic therapies, oocyte cryopreservation offers a viable fertility preservation option. Studies indicate that the outcomes of oocyte cryopreservation in these medical contexts are promising. However, data are currently insufficient to predict exact live birth rates or determine the precise number of oocytes needed to achieve a live birth in this specific group. Notably, oocyte yield and live birth rates tend to be more

favorable in patients younger than 37.5 years or with Anti-Müllerian Hormone (AMH) levels exceeding 1.995 ng/dL at the time of oocyte retrieval [16].

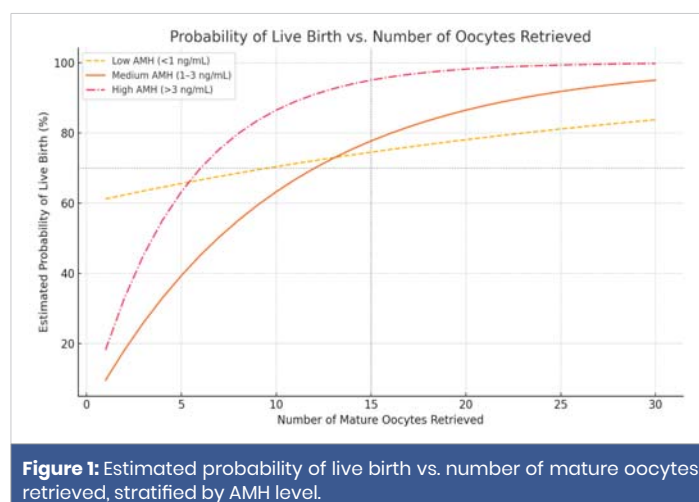
Optimal number of oocytes to collect: The number of oocytes required to achieve a successful live birth varies based on age and ovarian reserve. Research suggests the following estimates for a 70% chance of one live birth:

- **Ages 30–34:** Approximately 14 mature oocytes
- **Ages 35–37:** Approximately 15 mature oocytes
- **Ages 38–40:** Approximately 26 mature oocytes [17,18].

These curves (Figure 1) serve as general guidelines; individual circumstances, such as underlying medical conditions and ovarian reserve, can influence the optimal number of oocytes to collect [19].

This graph (Figure 1) shows the relationship between the number of oocytes collected and the success rate of achieving a live birth, categorized by basal ovarian reserve (low, medium, and high AMH levels). Low AMH Group: Success rates improve modestly as more oocytes are collected, but plateau around 25% - 30%. Collecting more oocytes (beyond 10–15) may not significantly improve outcomes for this group. Medium AMH Group: Success rates increase more significantly, reaching about 70% with 15–20 oocytes collected. This group benefits most from optimal stimulation and retrieval. High AMH Group: Success rates increase rapidly, reaching over 70% with 10–15 oocytes collected. These women are more likely to achieve success with fewer oocytes collected.

Oocyte cryopreservation is a promising fertility preservation strategy for women at high risk of POF [20] (Figures 2,3). While precise success rates and the optimal number of oocytes for this specific group require further research, current evidence underscores the importance of early intervention and individualized assessment [14]. Consultation with a fertility specialist is essential to tailor the approach based on personal health factors and reproductive goals [19].



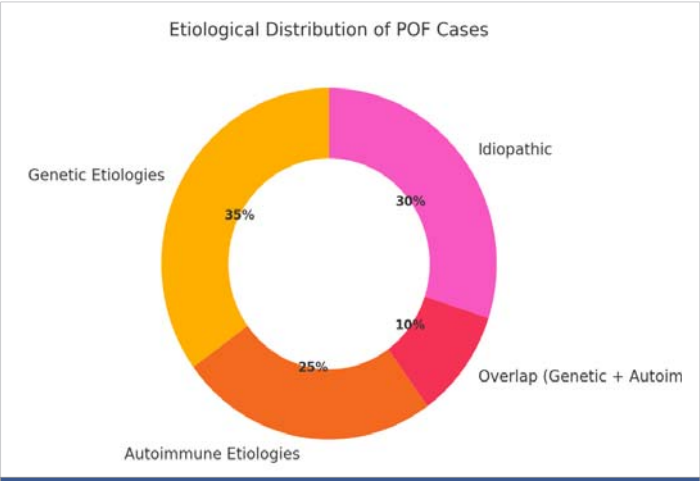


Figure 2: Etiological distribution of Premature Ovarian Failure (POF) based on literature synthesis.

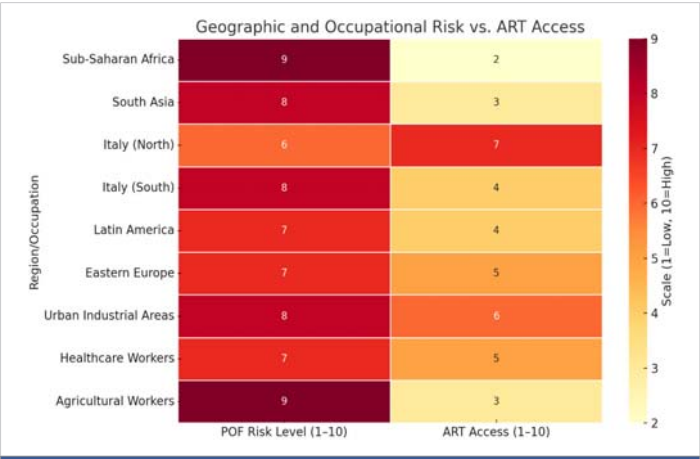


Figure 3: Geographic and occupational risk levels for POF, and corresponding access to ART (assisted reproductive technologies).

Preserving fertility through oocyte cryopreservation is a crucial consideration for women at high risk of Premature Ovarian Failure (POF). The success of this procedure depends on several factors, including the woman's age at the time of oocyte retrieval, the number of mature oocytes collected, and her basal ovarian reserve.

Success rates of oocyte cryopreservation in high-risk women: For women facing medical conditions that threaten ovarian function, such as those undergoing gonadotoxic therapies (Figure 4), oocyte cryopreservation offers a viable fertility preservation option. Studies indicate that the outcomes of oocyte cryopreservation in these medical contexts are promising. However, data are currently insufficient to predict exact live birth rates or determine the precise number of oocytes needed to achieve a live birth in this specific group. Notably, oocyte yield and live birth rates tend to be more favorable in patients younger than 37.5 years or with anti-Müllerian hormone (AMH) levels exceeding 1.995 ng/dL at the time of oocyte retrieval [16].

Optimal number of oocytes to collect: The number of oocytes needed to achieve a live birth varies based on age and

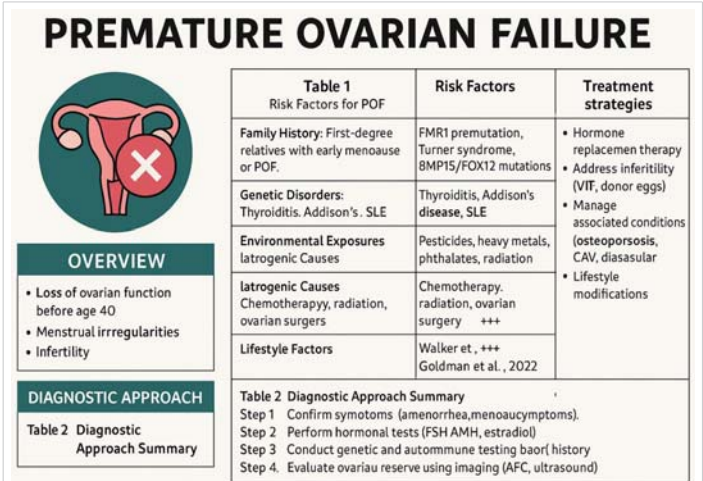


Figure 4: Premature Ovarian Failure: risk factors, diagnostic approach, and intervention strategy.

ovarian reserve. A meta-analysis found that the live birth rate per thawed oocyte is approximately 2.75% [21].

This suggests that to achieve a reasonable chance of live birth, a substantial number of oocytes may be required, especially as age increases.

Clinical implications: By identifying women at high risk, clinicians can offer early oocyte cryopreservation to preserve fertility before ovarian reserve significantly declines. Or tailor counseling and monitoring plans based on individual risk profiles and develop preventive strategies for women exposed to gonadotoxic treatments or surgical interventions.

Limitations of the study: While this review is based on existing published data, it is important to acknowledge that many of the referenced studies present findings from small cohorts or non-replicated datasets. The reproducibility of genomic and immunological markers in POF, particularly across ethnically diverse populations, remains limited. Future multicenter studies with standardized protocols are essential to validate the predictive value of these biomarkers and interventions.

A key limitation in synthesizing evidence across studies lies in the diversity of statistical approaches used. Some studies fail to adjust for confounding variables (e.g., age, comorbidities), while others apply differing thresholds for AMH, FSH, and AFC interpretations. This heterogeneity restricts direct comparisons and meta-analysis validity. Future studies should adopt harmonized statistical models and multivariable adjustments to enhance comparability and robustness.

The relatively small sample sizes in many POF-related studies limit the generalizability of findings. Large-scale registries and biobank-driven research could help overcome this barrier by enabling deeper genomic and environmental profiling across populations. Such expansion is critical for stratifying risk and refining clinical recommendations.

Discussion

POF is increasingly recognized as a complex syndrome at the intersection of genetics, autoimmunity, environmental toxicology, and clinical interventions. While the role of mutations in FMR1, BMP15, and FOXL2 is well established, the phenotypic variability among carriers indicates that polygenic risk scores and epigenetic modifications may play a larger role than previously understood. Similarly, autoimmune contributions to POF may involve not only organ-specific but also systemic inflammatory processes, suggesting a need for broader immunological profiling in at-risk women. The role of environmental factors, including chemotherapy, highlights the importance of fertility preservation strategies for at-risk individuals.

Surgical management of ovarian pathologies must balance the need for symptom relief with the preservation of ovarian function. Advanced laparoscopic techniques and improved surgical protocols have reduced the impact of these interventions on ovarian reserve. In geographical areas where sterility, understood as a disease and not as a pleasant desire (WHO, ASRM, IFFS), public health care must extend to cover these problems. The possibility of identifying and therefore supporting women at risk of premature ovarian failure requires, on an ethical and deontological level, attention, assistance, and prevention of the conditions of psycho-physical suffering to which they would otherwise be destined. In areas where there is no public intervention to support health problems, insurance companies must make efforts to include this possibility in their coverage portfolios. Aligning clinical management with evolving evidence requires integrating population-specific data into decision-making algorithms. As shown, AMH levels and oocyte yields differ significantly by age and baseline ovarian reserve, necessitating individualized protocols. Furthermore, the promising role of oocyte cryopreservation in high-risk women should be contextualized with socioeconomic access disparities and long-term outcome uncertainties, especially in publicly funded healthcare systems.

Conclusion

Premature ovarian failure is a clinically and socially significant condition that requires precision diagnostics, personalized fertility preservation strategies, and policy-level interventions to reduce disparities. While advances in genetic and immunological screening offer hope for early detection, implementation across diverse health systems remains limited. Stronger alignment of clinical decisions with biomarker-based risk assessment, combined with equitable ART access, will be critical in mitigating POF's impact. Preventive strategies, including fertility preservation and minimizing surgical and environmental risks, are critical to mitigating the impact of POF on women's reproductive health.

Author contributions

Francesco Maria Bulletti conceptualized and supervised the study. Maurizio Guido and Evaldo Giacomucci contributed to the epidemiological analysis. Antonio Palagiano and Maria Elisabetta Coccia contributed to data collection and the analysis of immunological causes. Romualdo Sciorio and Carlo Bulletti provided insights on surgical and genomic aspects and coordinated the final manuscript preparation.

Capsule

A comprehensive review on premature ovarian failure, exploring its epidemiology, genetic and genomic contributions, and the role of environmental, immunological, and surgical factors. With solution proposals.

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