

# Primary Ovarian Insufficiency: A Case of the Cart before the Horse

Karima Hijane and Lawrence M. Nelson

Mary Elizabeth Conover Foundation, Tysons, VA, USA

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**Abstract:** Overt Primary Ovarian Insufficiency (POI) is a rare disorder characterized by a constellation of other rare conditions, posing significant diagnostic and management challenges. This disorder necessitates a global mechanism for information exchange, streamlined data sharing, dynamic international partnerships, and the integration of artificial intelligence to enhance diagnostic accuracy through next-generation sequencing and specific antibody testing. Empowering women with POI involves providing them with access to the best available evidence at the point of care and facilitating informed decisions throughout their health journey. A key strategy is transcending the traditional biomedical model by adopting a population-based approach that encourages global cross-sectional collaboration. Optimal care for women with POI is achieved through an integrated, multidisciplinary approach that leverages diverse expertise to evaluate evidence and update care practices effectively. Initiatives are also underway to establish a patient advocacy group, emphasizing the importance of early diagnosis in allowing women to adapt family planning or preserve fertility. The overarching vision for POI research and care aims to cultivate proactive international partnerships and data sharing, driven by the needs and experiences of women with Overt POI.

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## 1. Introduction

Overt Primary Ovarian Insufficiency (POI) is a condition where a woman's ovaries cease to function properly before she reaches 40. It is characterized by oligo-amenorrhea and alterations in hormonal levels, such as elevated follicle-stimulating hormone, luteinizing hormone levels, and deficient 17-beta Estradiol levels. POI shares symptoms with other disorders, such as functional amenorrhea, complicating the accuracy of diagnosis [1]. Overt POI itself is a rare disorder that includes multiple other rare conditions, such as Turner Syndrome (45, X), Fragile X Associated POI (FXPOI), Autoimmune Polyendocrine Syndromes, Galactosemia, and Blepharophimosis, Ptosis, Epicanthus Inversus Syndrome (BPES), among others [1,2]. Adding next-generation sequencing and specific antibody testing to research methods increases the diagnostic findings in POI from 11% to 41%, a panoply of diverse mechanisms needing fundamental research and care insights [3]. The challenge of identifying individuals with the same disorder requires a mechanism of global information exchange. This is crucial for pooling knowledge about rare disorders like POI, which affect a small percentage of the global population. By sharing data and research findings across borders, medical professionals and researchers can access a larger dataset, enhancing their understanding of the disorder's nuances. This exchange not only facilitates earlier and more accurate diagnoses but also improves the development of treatment protocols tailored to diverse populations [3]. Considering that approximately 6% of the world's population is affected by

one of the 8,000 identified rare disorders, we face a formidable public health problem [4]. How do we approach such a complex issue?

## 2. Building on Global Collaboration

Streamlining data sharing and fostering dynamic international partnerships are the keys to breakthroughs in diagnosing and managing rare disorders. This streamlined data sharing involves creating systems that allow for easy access to and utilization of data across different research entities and healthcare providers. This approach minimizes duplication of effort, accelerates research processes, and bolsters collaboration. It ensures that the latest research findings and clinical practices are quickly disseminated and integrated into patient care, leading to improved health outcomes [5]. Just as the Human Genome Project changed everything, dynamic international partnerships will enhance the reach and efficacy of research efforts by combining resources, expertise, and insights from varied cultural and scientific backgrounds. These partnerships drive innovation through shared goals, such as the development of new diagnostic tools or therapies. Just as international registries have advanced the field of hemophilia, collaborating, countries and institutions can overcome the limitations imposed by funding, expertise, or population size that might hinder individual efforts to advance Overt POI [6].

## 3. Empowering Women through Advocacy and Education

Empowered patient advocacy groups play a crucial role in fostering innovative research and elevating healthcare standards [3]. Empowering women with POI involves providing them with the knowledge and resources necessary to make informed decisions about their health. This education not only allows them to actively participate in their healthcare and manage their symptoms effectively but also advocate for themselves in medical settings. Such empowerment supports broader goals of gender equality in healthcare by ensuring that women's health issues receive the attention and priority they deserve [7]. Necessity is the mother of invention, and women and girls with POI are uniquely positioned to articulate their needs. These patients bring outstanding research questions to investigators: "What is wrong with me? Why did this happen to me? What do I do about it?" The woman-girl-centered approach puts the research horse before the cart. For over ten years, the US National Institutes of Health Intramural Research Program (NIH-IRP) has forcefully advocated the woman-at-the-center approach to collaborative international research on POI [8–11].

Women with Primary Ovarian Insufficiency (POI) have voiced their needs in an open letter to the POI community. They call for a durable approach that empowers women with the necessary knowledge and guidance to make informed decisions throughout their POI journey [12]. "To do this effectively, any approach must:

1. Be available and accessible to women regardless of geography or socioeconomic status;
2. Bring together diverse perspectives, such as the NIH protocol, including a wide array of medical fields, therapists, and spiritual care counselors, in an integrated fashion; and
3. Be developed with the individual patient foremost in mind and tend to her at each life stage.

Reflecting on her experience, one woman noted, "My time at the NIH was among the most affirming, productive, and caring experiences of my life. Please help me make this possible for others." [12].

## 4. Implementing a Comprehensive Care Model

This sentiment echoes the potential for adopting a proven model of care, specifically that of the NIH Cancer Center, tailored to meet the unique needs of the POI community [13]. To adopt the NIH Cancer Center's approach to POI, several steps are essential:

1. Establish a Centralized Institute: This hub would be pivotal for integrating research and clinical care, quickly translating new research insights into effective treatments.
2. Develop Partnerships: Collaborating with universities and hospitals will not only enhance research but also ensure that patients receive the best possible care.

3. **Secure Funding and Support:** Adequate funding and supportive policies are critical to sustain and scale the center's operations.
4. **Integrated Care and Research:** Just like the NIH Cancer Center, a dedicated POI center could merge cutting-edge research with top-notch clinical care, significantly improving treatment options for women and girls.
5. **Patient Support Programs:** Tailored programs addressing the specifics of POI, including genetics, pediatrics, psychological support, and fertility counseling, would cater to the comprehensive needs of patients.
6. **Team-Based Approach:** A multidisciplinary team comprising endocrinologists, gynecologists, geneticists, pediatricians, reproductive specialists, and mental health professionals would ensure integrated care.
7. **Outreach and Education:** By raising public awareness and educating healthcare providers about POI, early diagnosis and treatment can be achieved, similar to the initiatives at the NIH Cancer Center.
8. **Advanced Technology and Clinical Trials:** Utilizing the latest in genetic and diagnostic technology, alongside offering access to clinical trials, would provide patients with the most advanced care tailored to their individual needs.

Adopting this model could transform the management of POI, providing women and girls with superior care and outcomes, inspired by the success of the NIH Cancer Center. As we implement these strategies, it is crucial to underscore the importance of underpinning all these efforts with the highest quality evidence available. Only the best evidence will empower women effectively with the knowledge and tailored guidance to quality integrated care and appropriate ongoing management.

This commitment to evidence-based practice is essential not only for ensuring the effectiveness of the treatments but also for securing the trust and engagement of the community we serve. The vision is to go beyond the traditional biomedical model and embrace a population-based approach that incorporates cross-sectional worldwide community collaboration [14,15]. By doing so, we can create a more integrated and inclusive framework that addresses the diverse needs of women and girls with POI, ensuring that advancements in care are accessible to all, regardless of geographic or socioeconomic status. By adopting a model inspired by the NIH Cancer Center, we aim to significantly enhance the management and outcomes for women with POI through a unified approach that leverages the latest research and clinical practices. As we push forward with these initiatives, the emergence of platforms for data sharing will prove to be invaluable [16–18]. These platforms facilitate the dissemination and accessibility of high-quality data across the global research and medical communities, enhancing the collaborative efforts needed to tackle complex conditions like POI.

Women with Overt POI are best served by an integrated approach in a multidisciplinary setting that comprises diverse expertise. Such research teams know how to evaluate the best evidence and publish the best reviews and updates regarding care. While consensus statements and review articles play a crucial role in summarizing available knowledge, accessing original findings that represent the highest quality evidence is paramount in providing individualized care that truly centers on the patient. This approach acknowledges that evidence has both quality and quantity [19]. There is a hierarchy of study designs with systematic reviews of quality studies at the top. Next in line are prospective, randomized, double-masked, controlled studies. Then come observational studies, case series, case reports, expert opinions, and animal studies.

Women's hormonal health is an issue across the lifespan, including initiation of puberty, support of ovulation and pregnancy, and maintenance of bone, heart, brain, skin, and hair health [20]. Women's hormonal health is more than menopause. There is a need for more research aimed at the specifics of hormonal health during puberty and the years as young adult women. One initiative bringing attention to this area of need is the global digital women's hormonal health program called My28Days.org [21,22]. The My28Days.org initiative, organized by the nonprofit Mary Elizabeth Conover Foundation, is establishing a social enterprise approach to Overt POI to permit nonprofit and for-profit entities to collaborate ethically and advance patient care and research on the condition with the needs of patients maintained at the center of the enterprise [22].

To our knowledge, regarding bone mineral density as the primary outcome, there is only a single prospective, randomized, double-masked, longer-term (3 years) study in young women with Overt POI in which a contemporary control group of age-matched women with normal ovarian function participated. A subset of the NIH omnibus protocol on POI (91-CH-127), the NIH physiologic hormone replacement protocol (P-HRT), restored bone density to normal, induced cyclic menses, and the women tolerated the replacement well. This study provides the highest quality evidence addressing this issue and merits recognition as the treatment of the first choice for women with Overt POI [23].

Earlier diagnosis of decline in ovarian function could permit women to change their family planning or intervene to preserve fertility. Ovarian primordial follicle number declines with age from birth to the midlife transition, and the rate of this decline has been defined histologically along with a decay curve in a mathematical model [24]. FSH has been the traditional marker upon which to make the diagnosis of Overt POI. Yet, careful research by Rosen et al. demonstrates the hormone AMH, a product of small antral follicles, is the leading edge marker in the age-related decline in ovarian endocrine function [25]. Population-based longitudinal research using the AMH marker as the indicator of fertility decline may permit women to adjust their family planning or take other measures to preserve fertility. Most women with Overt POI have potentially functional ovarian follicles present even many years after diagnosis. More research is needed on how these women can optimize fertility [26]. Furthermore, women with Overt POI have significant needs regarding the emotional burdens of the disorder in need of more research and more effective care delivery and guidance on lifestyle factors [27,28].

Efforts by My28Days.org are in progress to empower women with Overt POI and create a patient advocacy group that is essential to innovative research and higher healthcare standards [3,22]. The vision for POI research and care is to streamline data sharing and foster dynamic international research and care partnerships driven by women with Overt POI. Two closed Facebook groups for women with Overt POI are coordinating this effort by collaborating to bridge the patient perspective with the rare disease research perspective. One closed group of 7,000 members (KH) has focused on peer-to-peer support [29]. The other closed group of 4,000 members (LMN) has focused on education and advocacy [30]. There is a need to close the gap between knowledge and care in managing Overt POI by creating a convenient and reliable care distribution process. The exact process will facilitate research. Global internet connectivity makes a global digital women's hormonal health network feasible. One report by My28Days.org has demonstrated proof of principle for this approach [21].

## 5. Utilizing Advanced Technologies

Integrating Artificial Intelligence (AI) into the research and treatment of POI), with proper governance and ethical guidelines, can significantly enhance the precision of diagnostics, personalize treatment plans, and develop potential cures. AI can analyze vast amounts of data rapidly, identifying patterns that may not be apparent to human researchers. This capability can lead to breakthroughs in understanding the genetic, environmental, and personal health factors that influence POI. Furthermore, AI can assist in managing and predicting individual patient responses to various treatments, optimizing patient care [31,32]. By promising breakthroughs in identifying causes and developing new therapies, AI aims to significantly improve the quality of life for those affected. This transformative journey requires the collaboration of AI experts, biologists, clinicians, and patients to fully harness the potential of evolving technologies, underscoring AI's significant impact on advancing POI research and treatment [33].

The Study of Women Across the Nation (SWAN) is a community population-based study about women in the United States and their midlife physiologic hormonal transition to much lower serum levels of 17-beta estradiol [34]. It is a multi-site, prospective, longitudinal, observational, cohort study of biological and psychosocial changes in a racially and ethnically diverse in the United States. Here, My28Days.org calls for a similar global cloud-based study of Overt POI to include a normal control group of women followed longitudinally (Figures 1 and 2).



**Figure 1.** Women worldwide have limited access to education and integrated care for Overt POI [10].



**Figure 2.** A cloud-based network of education, advocacy, integrated care, and research would improve the quality of life for women with Overt POI [10].

These strategies collectively enhance diagnostics and enable early intervention, thereby improving patient outcomes through faster, more accurate diagnoses and effective treatments. International collaborations and advanced data management systems further increase research efficiency, reduce costs, and accelerate scientific discovery. Empowering women with knowledge leads to a more engaged patient community that actively participates in their healthcare and advocacy, driving forward research and improving standards of care. Additionally, these approaches promote global health equity by ensuring that advancements in understanding and treating POI are accessible across diverse geographic and socio-economic groups, thus setting a transformative standard for managing rare diseases worldwide.

## 6. Conclusions

In summary, Overt Primary Ovarian Insufficiency (POI) presents significant challenges as a rare disorder composed of multiple other rare disorders. The vision is to go beyond the traditional biomedical model by emphasizing the significant impacts of global information exchange, streamlined data sharing, dynamic international partnerships, and the empowerment of women through knowledge and artificial intelligence. These strategic essentials not only address the immediate needs in the management and understanding of POI but also set a standard for handling similar rare disorders, potentially transforming the landscape of global health in rare disease management. The needs of women with Overt POI must lead a global community-based participatory research effort. This is the way of My28Days.org.

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