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# One World, One Woman: A *Kyosei* Approach to Primary Ovarian Insufficiency

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> Yesterday my boss, Alan DeCherney, gave me a copy of a recent article advocating better insight into what medicine is all about. "Medicine needs to be scientifically based, but physicians need to be engaged through their passions and emotions."<sup>1</sup> I get my energy for a "One World, One Woman" approach to primary ovarian insufficiency because many years ago one of my patients with steroidogenic cell autoimmune primary ovarian insufficiency committed suicide. In the ensuing court process her diary made it clear that her infertility was a major factor in the tragedy. Through a more integrative approach her death might have been prevented. This troubles me, and the experience changed my entire approach. Now integrated care based on science is my top priority for these girls and young women. This is one woman's story. This is the story I think about when trying to take a broader perspective to the disorder: "One World, One Woman."

> A spirit of *kyosei* is needed. Such an approach could harness all activity around primary ovarian insufficiency in a coordinated manner so as to benefit all. Kyosei is a business credo that defines a "spirit of cooperation." Individuals and organizations work together for the common good. In its most advanced form, the concerted effort works toward rectifying global imbalances.<sup>2,3</sup>

Spontaneous primary ovarian insufficiency is a serious chronic disease with no cure. The diagnosis has far reaching implications and is best managed by an integrative team approach. There are issues in need of care around a woman's general health, including special attention to endocrine, emotional, genetic, and reproductive health.<sup>4</sup> The disorder has also been known as "premature ovarian failure," "premature menopause," and a host of other confusing, scientifically inaccurate, and stigmatizing descriptors.<sup>5</sup>

Fuller Albright and colleagues first used the term *primary ovarian insufficiency* when he described the pathophysiology and endocrinology of this disorder in 1942.<sup>6</sup> As an endocrinologist he used the term *primary* to indicate that the ovary is the primary problem, whereas secondary ovarian insufficiency would mean the problem is in the hypothalamus or

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pituitary. He used the term *insufficiency* to describe a continuum of impaired ovarian function, which fits exactly with current scientific findings.<sup>7,8</sup> Indeed, with current ultrasound technology antral follicles can be detected in 75% of women with 46,XX spontaneous primary ovarian insufficiency, and evidence supports a conclusion that many of these structures are endocrinologically active.<sup>8</sup>

Change is in order. A coordinated and integrated approach to primary ovarian insufficiency is sorely needed. As a rare disorder made up of a host of ultra-rare disorders, progress is difficult. There is a need for a dedicated self-sustaining community of practice. In October 2008, representative stakeholders in the field started to develop such a community by convening at the William F. Bolger Center for Leadership and Development in Potomac, Maryland.<sup>5</sup> This was made possible by collaboration between a research-oriented patient advocacy group called Rachel's Well, Inc. (http://RachelsWell.org), a professional organization representing clinicians and investigators who care for these patients known as the American Society for Reproductive Medicine (http://www.ASRM.org), and representatives of the U.S. federal government from the Department of Health and Human Services (http://www.hhs.gov/). The stakeholders concluded this: "An international collaborative approach that combines the structure of a patient registry with the principles of integrative care and community-base participatory research is needed to advance the field of primary ovarian insufficiency."<sup>5</sup>

At the time of this writing, in the past 5 years there have been 368 publications on this condition from 43 countries/territories from around the world (Table 1). This widespread interest is encouraging and forms a working group around which to network and build an international consortium. This approach would advance patient care and research for girls and women living with primary ovarian insufficiency.

This issue of *Seminars in Reproductive Medicine* brings together cutting-edge review and analysis regarding the mechanisms and management of spontaneous primary ovarian insufficiency. Iatrogenic primary ovarian insufficiency is an equally important challenge in its own right but beyond the scope of this review. The areas covered here range from basic ovarian biology, to specific animal models of the disease, to related translational research, and topics on the clinical management of the condition.

Drs. Sullivan and Castrillon provide an elegant review and analysis of insights that have been gleaned through genetically engineered mouse models. Clearly there is a great deal to learn about the molecular mechanisms of primary ovarian insufficiency. Mouse models have been instrumental in advancing our understanding with regard to mechanisms of primordial follicle activation and oocyte death.

Drs. Sullivan, Welt, and Sherman address fragile X–associated primary ovarian insufficiency, what the fragile X community refers to as FXPOI.<sup>9</sup> The term refers to a continuum of impaired ovarian function, and as such FXPOI serves as a leading edge in a paradigm shift in how to approach primary ovarian insufficiency in general. The FMR1 premutation puts women at risk of having children with mental retardation, at risk for a tremor ataxia disorder in later years, and at risk for the sequelae of infertility and the long-

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term risks of sex hormone deficiency. The disorder is not only a model for paradigm shift regarding classification of the disorder but also a model for paradigm shift on how best to integrate the multidisciplinary care they require.

Dr. Cheng and I review my scientific passion, ovarian autoimmunity and the relevant pathogenic mechanisms in translational animal models of the disease. Evidence is accumulating that ovarian autoimmunity likely arises from a limited number of ovarian antigens that are specific to that organ. It is hoped that work in this area will lead to more accurate diagnostic methods and ultimately improved patient care for those women proven to have ovarian autoimmunity as the mechanism.

Hypogonadism is a known risk factor for reduced bone mineral density. Drs. Marino and Misra give us their perspective on bone health in girls and young women with primary ovarian insufficiency. Heart disease is the number-one killer of women, and the relationship between cardiovascular risk and primary ovarian insufficiency is complex. Dr. Wellons reviews this issue and makes recommendations for cardiovascular disease prevention for women with primary ovarian insufficiency. Dr. Reindollar gives us his perspective on Turner syndrome, the most common cause of delayed spontaneous puberty in girls. His review places particular emphasis on analysis of the pregnancy-associated risks to women with primary ovarian insufficiency due to Turner syndrome.

The most common words women use to describe their feelings after first being informed of the diagnosis of primary ovarian insufficiency are "devastated," "shocked," and "confused." Nearly three fourths are unsatisfied with how they are informed of the diagnosis.<sup>10</sup> Dr. Sterling and I suggest that we help these patients transition from a "disease-centered approach" to a "health-centered" approach that puts them in partnership with their health-care providers. The journey helps each girl or young woman move from victim, to survivor, to one who is thriving. Infertility is an important component of this disorder. Dr. Baker reviews the life plans and family-building options for women with primary ovarian insufficiency. She makes the important point that not everyone wants to be a parent. For these patients a life plan at odds with society's expectations can induce stress, and they made need preparation to deal with this. For those who decide parenthood is their choice, she elegantly outlines the paths forward.

It has been a joy to work with such a talented group of authors. I especially thank Mary Ryan, MLS, for her tireless work on preparing this volume. The work was supported in part by the Intramural Research Program on Reproductive and Adult Endocrinology, National Institute of Child Health and Human Development, National Institutes of Health. I am a commissioned officer in the U.S. Public Health Service, and I am proud, grateful, and humbled to have the opportunity to serve in this capacity and as guest editor for this volume.

## Biography



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### Table 1

Publications on Primary Ovarian Insufficiency in the Past 5 Years

| Country/Territory          | No. of Publications | Percentage |
|----------------------------|---------------------|------------|
| United States              | 104                 | 28.26      |
| France                     | 35                  | 9.51       |
| Italy                      | 34                  | 9.24       |
| People's Republic of China | 23                  | 6.25       |
| England                    | 19                  | 5.16       |
| Netherlands                | 19                  | 5.16       |
| India                      | 15                  | 4.08       |
| South Korea                | 14                  | 3.80       |
| Japan                      | 13                  | 3.53       |
| New Zealand                | 13                  | 3.53       |
| Australia                  | 12                  | 3.26       |
| Germany                    | 10                  | 2.72       |
| Tunisia                    | 9                   | 2.45       |
| Brazil                     | 8                   | 2.17       |
| Canada                     | 8                   | 2.17       |
| Spain                      | 8                   | 2.17       |
| Turkey                     | 8                   | 2.17       |
| Belgium                    | 7                   | 1.90       |
| Scotland                   | 7                   | 1.90       |
| Greece                     | 6                   | 1.63       |
| Sweden                     | 6                   | 1.63       |
| Slovenia                   | 5                   | 1.36       |
| Argentina                  | 4                   | 1.09       |
| Serbia                     | 4                   | 1.09       |
| Norway                     | 3                   | 0.82       |
| Poland                     | 3                   | 0.82       |
| Switzerland                | 3                   | 0.82       |
| Austria                    | 2                   | 0.54       |
| Denmark                    | 2                   | 0.54       |
| Egypt                      | 2                   | 0.54       |
| Iran                       | 2                   | 0.54       |
| Israel                     | 2                   | 0.54       |
| Mexico                     | 2                   | 0.54       |
| Colombia                   | 1                   | 0.27       |
| Ethiopia                   | 1                   | 0.27       |
| Finland                    | 1                   | 0.27       |
| Hungary                    | 1                   | 0.27       |
| Ireland                    | 1                   | 0.27       |
| Jamaica                    | 1                   | 0.27       |

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| Country/Territory | No. of Publications | Percentage |
|-------------------|---------------------|------------|
| Lebanon           | 1                   | 0.27       |
| Macedonia         | 1                   | 0.27       |
| Portugal          | 1                   | 0.27       |
| Romania           | 1                   | 0.27       |

\* Search of the Web of Science database at the time of this writing revealed 368 publications from 43 countries/territories. The search strategy was "premature ovarian failure" OR "primary ovarian insufficiency" OR "premature menopause" OR "early menopause" in title; current 5 years. Web of Science analytics were used to sort and rank results by country/territory. Please note 21 (of 368) records did not provide data in the field being analyzed.