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One world, one woman: a transformational leader's approach to primary ovarian insufficiency

Lawrence M. Nelson, MD, CAPT USPHS

Head, Integrative Reproductive Medicine Group, Intramural Research Program on Reproductive and Adult Endocrinology, The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health, CRC, Room 1–3140, 10 Center Drive, MSC-1109, Bethesda, MD 20892-1109, Phone (direct): 301 402 6608, FAX: 301 402 0884

Lawrence M. Nelson: Lawrence_Nelson@nih.gov

Abstract

Lectureship endowment funds are created to honor major contributions that have clearly advanced a field. In some select cases they recognize the contributions of a transformational leader. Such was the case in the creation of the Wulf H. Utian Endowed Lectureship Fund. The express purpose of the fund is to provide travel to the annual meeting by a lecturer selected by the North American Menopause Society Scientific Program Committee. Wulf H. Utian changed the paradigm for menopause by creating an organization whose major purpose was to employ an integrated approach to the condition. Such an approach would benefit many areas of healthcare. This report summarizes my thoughts on how such an integrated approach might advance the field of primary ovarian insufficiency.

Keywords

menopause; premature menopause; premature ovarian failure; primary ovarian insufficiency; integrated care; community-based participatory research; patient registries

I am putting the final touches on this manuscript as our Nation celebrates the legacy of Dr. Martin Luther King. With courage and vision he moved a nation to become better, stronger, and freer. Dr. King once said, “Of all the forms of inequality, injustice in health care is the most shocking and inhumane.”(1) Dr. King had a way of speaking simple truths that could touch people’s hearts and bring them to concerted action. He was a transformational leader. We have quite a way to go transform the world when it comes to reducing health disparities. (2)

Transformational leaders articulate a vision of the ideal that inspires. They provide a focus that engenders trust. They define a purpose that instills commitment. Transformational leaders are driven by ideas, not by the expectations of others. They are driven to beat the system, not give in to it.(3) A few weeks ago my boss Alan DeCherney brought my attention to an interesting article. It was about how the right brain perspective seems to be ignored in our scientific communications. As technology advances, communication of scientific advances in medicine arguably has become standardized, emotionless, and dispassionate. The argument is “...science rarely sings.” The author called for change. In his view health care needs to be based in science, but givers of health care as well as investigators in the

field need to be engaged through their passions and emotions.(4) Passion and emotion are what drive transformational leaders.

When I first came to the National Institutes of Health (NIH) Intramural Research Program in 1988 as a research fellow I was fortunate to have a transformational leader as one of my mentors. His name was Roy Hertz, MD, PhD. Before entering science his undergraduate work focused on comparative literature; I soon learned this man had both cerebral hemispheres in gear. With his left hemisphere he helped me set up a thymectomized mouse model of autoimmune oophoritis for the program. With his right hemisphere he gave me an admonition. “Larry, don’t let this place (NIH) make you so busy that you don’t have time to think!” Roy Hertz admitted the first patient to the NIH Clinical Center in 1953. He initiated the first NIH Clinical Center translational research program in women’s reproductive health. He received the Lasker Medical Research Award for his role in developing a chemotherapeutic cure for choriocarcinoma. Roy Hertz was indeed a transformational leader who could bring forces together that others could not see.

I give this background to make clear why I felt so honored to be invited to deliver the Wulf H. Utian Endowed Lecture at the 2010 annual meeting of the North American Menopause Society in Chicago. Wulf H. Utian is also a transformational leader. In his own words, “I conceived the idea of NAMS to fulfill a need to bring all scientific and intellectual disciplines together into a single organization that could address research, education, consumer and provider and promote all aspects of interest in menopause.”(5) His vision has been realized around menopause.

Wulf, through NAMS, has transformed the efforts on menopause from a silo approach to an integrative approach. A similar transformation is needed for primary ovarian insufficiency, the subject of my lecture. An October 2008 meeting of relevant stakeholders held at the William F. Bolger Center for Leadership and Development in Potomac, Maryland concluded, “An international collaborative approach that combines the structure of a patient registry with the principles of integrative care and community-based participatory research is needed to advance the field of primary ovarian insufficiency.”(6)

Primary ovarian insufficiency, also known as “premature menopause” and “premature ovarian failure,” is a serious chronic disease with no cure. An integrative team approach is needed to address the associated endocrine, emotional, social, genetic, mental health, and reproductive health issues. Further, as a rare disease consisting of multiple ultra-rare diseases, progress in this field requires international collaboration in order to adequately power studies. An international patient registry for the condition would provide the coordinated infrastructure.

Primary Ovarian Insufficiency is Not an Early Menopause

The focus of my research is 46,XX spontaneous primary ovarian insufficiency. Women with this condition develop oligo/amenorrhea in association with menopausal level serum gonadotropins before the age of 40 years. By definition they have a normal karyotype and have no iatrogenic cause of the disorder, such as chemotherapy, surgery, or radiation therapy.(7) In my view, the terms “premature menopause” and “premature ovarian failure” are not only stigmatizing to young women they are also scientifically inaccurate. The terms imply that the pathophysiology of the impaired ovarian function is an earlier onset of the normal menopausal process, i.e., an age-related decline in ovarian follicle number, ultimately a state of complete depletion of potentially functional primordial follicles. Clearly this perspective is a gross simplification that cannot be justified based on the evidence.

One undisputed mechanism of primary ovarian insufficiency that flies in the face of the concept of 46,XX spontaneous primary ovarian insufficiency being an earlier occurrence of the normal menopausal process is mutation in the FSH receptor. Ovarian biopsies from these women show many primordial ovarian follicles, not a depletion of follicles. The problem is that the follicles are unable to respond to FSH.(8) Another clear example in which the pathophysiology is one of follicle dysfunction rather than an age-related follicle depletion is autoimmune lymphocytic oophoritis. In this condition ovarian function is impaired by a lymphocytic infiltration most notable in the theca of growing follicles. These patients commonly have enlarged multi-follicular ovaries on ultrasound examination and on histologic examination of excised ovaries. This clearly is a different pathophysiology than an early onset of menopause.(9)(10)(7)

Further, recent evidence using state of the art ultrasound technology has demonstrated that 75% of women with idiopathic 46,XX spontaneous primary ovarian insufficiency have detectable ovarian follicles. In fact, the evidence supports a conclusion that these follicles are endocrinologically active.(11) These findings are consistent with multiple reports that some patients with this condition are able to conceive without medical intervention, sometimes many years after the diagnosis.(12) In most women 46,XX spontaneous primary ovarian insufficiency can be best described as “intermittent and unpredictable ovarian function that can persist for decades.” In sum, these findings are not consistent with a diagnosis of “premature menopause” or “premature ovarian failure.”

Fuller Albright, another transformational leader, was an American endocrinologist who made numerous contributions to his field.(13) His work in Turner syndrome clarified the pathophysiology of the hypogonadism in this condition. Before his publication on the subject in 1942 the prevailing thinking was that the hypogonadism was due to a defect in pituitary function. He demonstrated that these patients had elevated urinary gonadotropins, and thus clarified for the first time that the disorder was one of “primary ovarian insufficiency,” the term he used to describe the state of ovarian function.(14) As an endocrinologist he used the term “primary” to mean that the ovary is the primary problem. “Secondary” ovarian insufficiency in this scheme would be due to a failure of ovarian stimulation “secondary” to a defect in pituitary or hypothalamic dysfunction.

Admittedly there is room for confusion around the terms “primary” and “secondary” in this context. Gynecologists use the terms in reference to the menstrual cycle. Endocrinologists use the terms in reference to the ovary. Of course both are correct. Proper education and understanding between the domains will avoid confusion. To gynecologists the term “primary” amenorrhea means that a first spontaneous menses never occurred. “Secondary” means the amenorrhea occurred sometime subsequent to the first menses. Endocrinologists use the terms “primary” and “secondary” in referring to the mechanism of ovarian insufficiency. It is possible to have primary or secondary amenorrhea due to primary ovarian insufficiency.

Primary Ovarian Insufficiency is Not Necessarily Early Ovarian Aging

Our team has published data about women’s recollections regarding their feelings in the hours immediately after getting the diagnosis. The most common words they used to describe how they felt at that time were “devastated,” “shocked,” and “confused.” (15) These are words describing emotional trauma. Our team has also published data, acquired with validated instruments, showing that the more stigmatized women feel by this disorder the more symptoms of depression they report.(16) It seems prudent that we should use scientifically accurate terminology that avoids stigmatizing words.

Based on my interactions with teens and young women who get this diagnosis, this is how I believe they hear these terms: “You have premature MENOPAUSE!” “You have premature ovarian FAILURE!” “You have premature ovarian AGING!” These are stigmatizing and frightening terms to girls and young women. Not only are they stigmatizing, they are scientifically inaccurate for reasons already mentioned.

Some authors have used the term early ovarian “aging” to describe the pathophysiology of 46,XX spontaneous primary ovarian insufficiency in general.(17)(18)(19) In my view this is particularly unfortunate. Our current understanding of the molecular mechanisms underlying the normal aging process is rudimentary at best. Authors who have referred to this condition as “ovarian aging” have to my knowledge presented no molecular evidence that the mechanism of the impaired ovarian function is due to the same pathophysiologic process as the normal aging process. Absent such evidence, in my view, the term should not be used to define the diagnosis to patients or to report on a series of patients with impaired ovarian function.

There are indeed ultra rare diseases such as Hutchinson-Gilford progeria and Werner syndrome that are associated with generalized aging, and it is true primary ovarian insufficiency can be part of the constellation of clinical findings.(7)(20) However, in these syndromes the molecular changes such as genome instability, telomere attrition and defective stem cell homeostasis are associated with premature senescence in general, certainly not isolated ovarian effects. Werner syndrome results from mutations in Werner syndrome ATP-dependent helicase (WRN), which has several enzymatic functions linked to DNA metabolism. Unless such molecular mechanisms can be demonstrated in patients with isolated 46,XX spontaneous primary ovarian insufficiency the term early ovarian “aging” is not strictly accurate scientifically. In my opinion the term should be avoided because it unnecessarily introduces into the clinical situation stigma, scientific confusion as to basic mechanism, and unwelcome broader health concerns to girls and young women about aging in general.

Fragile X Associated Primary Ovarian Insufficiency (FXPOI) Is Leading a Paradigm Shift

Paul and Randi Hagerman are two fragile X syndrome researchers who qualify as transformational leaders in their field. They discovered a new, progressive neurologic disease that affects men and some women over the age of 50. The disorder, known as fragile X associated tremor ataxia syndrome (FXTAS), results in tremors, ataxia, and dementia that becomes increasingly more severe with age.(21)(22)

Fragile X syndrome is the most common heritable cause of developmental delay and intellectual impairment.(23) Fragile X syndrome is a CGG triplet repeat disorder. In the normal *FMRI* gene there are fewer than 45 CGG triplet repeats in the promoter region of the gene. This permits a normal amount of transcription of mRNA and production of a normal amount of FMRP (Familial Mental Retardation Protein), the protein produced by this gene. This of course gives a normal phenotype. However, when these CGG triplet repeats expand during oogenesis or early embryonic development to number more than 200 the gene becomes methylated. This shuts off the gene, prevents production of normal levels of FMRP, and this protein deficiency is the cause of intellectual disability that is part of fragile X syndrome.

For many years, patients who carried CGG triplet repeat numbers in the premutation range (between 55 and 200) were thought to be asymptomatic with no phenotype of their own. Now we know that was not correct. Carriers of the *FMRI* premutation are at risk for

developing fragile X associated tremor ataxia syndrome (FXTAS) and fragile X associated primary ovarian insufficiency (FXPOI).(21)(24) Over expression of the expanded CGG repeat messenger RNA results in direct gain-of-function cellular toxicity that is believed to be the pathogenic basis for the neurodegeneration seen in FXTAS.(25) A similar gain-of-function cellular toxicity may be at work as a mechanism in the development of fragile X associated primary ovarian insufficiency.

The question of how to best manage fragile X associated primary ovarian insufficiency is indeed leading a paradigm shift on several fronts. It is now the most common single gene mechanism for 46,XX spontaneous primary ovarian insufficiency. Testing for this is clinically indicated. Now, explaining the availability of *FMR1* genetic testing and informing the patient of the ramifications of a positive result for her and family members is part of clinical practice.(26)(27)(28) If the index of suspicion for a positive result is high based on a suggestive family history (other cases of primary ovarian insufficiency, developmental delay, or Parkinsonism), then referral to a genetic counselor before testing may be indicated. This permits the patient to have a more in depth understanding of the results of a positive test, and can start her down the road of developing a plan for informing other family members if indeed the test is positive. Also, fragile X associated primary ovarian insufficiency is leading a paradigm shift in that integrative multidisciplinary care is clearly indicated in this condition. Evidence suggests that women who carry the *FMR1* premutation and have fathers with FXTAS are at increased risk for neurologic symptoms including tremor, balance problems, memory problems, dizziness, and psychiatric involvement including difficulty with sleep and anxiety.(29) As compared to control women, the phenotype of women with the *FMR1* premutation has been reported to include more complaints of chronic muscle pain and persistent paraesthesias in the extremities.(30)

The *FMR1* premutation as a specific cause of primary ovarian insufficiency makes it perfectly clear why an integrative approach is preferred. Based on our team's experience, such an approach is beneficial whether or not an *FMR1* premutation is the mechanism. We have found it helpful to take an integrative wellness-oriented approach with these women rather than a disease-oriented approach. We have team members who bring expertise from medical endocrinology, reproductive endocrinology, reproductive psychiatry, occupational therapy, recreational therapy, spiritual ministry, and nutrition. These women have issues related to their general health as well as to reproductive health. A visual representation of the difference between the traditional model of research and patient care and an integrative model is illustrated in Figure 1.(6) As mentioned above, in his role as a transformational leader Wulf H. Utian saw the need for integrative care for women with menopause. This same type of approach is needed for women with primary ovarian insufficiency.

Wake-up Calls from Patients

My passion when I first came to the NIH was to investigate a mouse model of autoimmune primary ovarian insufficiency and to ultimately translate these findings into clinically useful insights. Along this investigational path our team used sera from mice with autoimmune oophoritis to screen an ovarian cDNA library. In doing so we discovered *MATER*, a maternal effect gene critical to reproduction.(31;32) Subsequent studies from another laboratory have demonstrated that antibodies against *MATER* protein (also known as NALP5) are associated with the autoimmune hypogonadism that develops in autoimmune polyendocrine syndrome type 1.(33) Thus, it appears that our basic science investigation in a mouse model indeed has clinical relevance.

While I have found this basic science discovery quite rewarding, from a scientific perspective, over the years I have found that insights gained from my personal interactions

with specific individual patients even more rewarding. Before coming to the NIH I was in private practice in general obstetrics and gynecology for 8 years in Lynchburg, Virginia. I have experienced the world of patient care and research from opposite sides of the system. I have learned first hand that a physician is indeed a combination of emotion, passion, and science.(4)

While my initial major scientific interest at NIH was in autoimmune primary ovarian insufficiency, over the years it became clear to our team that this approach was too narrow. As investigators and providers of health care we could not ignore other important aspects of the disorder that patients brought to us. Over the years specific patients with specific dramatic clinical findings have given us wake-up calls about new directions that our scientific investigations should take. To me, these wake-up calls have been dramatic. I am thankful to the individual patients who provided them by coming to the NIH Clinical Center to participate in our studies.

A Wake-up Call - Bone Health and Primary Ovarian Insufficiency

Early in our studies two identical twin young sisters together provided our team a dramatic wake-up call about bone health in primary ovarian insufficiency. We first saw the young women when they were age 23. Both had experienced oligo-amenorrhea during their entire teen years. The symptom had never been properly evaluated and managed. At age 19 one of the twins fell and injured her wrist. She went to the local emergency room query fracture. The x-ray of the wrist showed no fracture, but did show that the young woman's epiphyses had not closed yet. Of course, closure of the epiphysis is an estrogen dependent event. The x-ray finding finally led to an endocrinologic evaluation of both young women only to determine that they both had hypergonadotropic hypogonadism, which we later determined was due to 46,XX spontaneous primary ovarian insufficiency. They had both missed out on the major bone-building effects of estradiol during their teen years. When we saw them both of the sisters had severely reduced bone mineral density for their age.

It was clear to us that the menstrual cycle irregularity in these patients had been ignored, and the young women paid a price in terms of reduced bone mineral density. This might have long term health implications for them. This wake-up call about bone density inspired us to collect evidence about delay in diagnosis in a sample of our patients. We wanted to determine how common this was. We asked 50 patients previously diagnosed with the condition to participate in an IRB approved structured interview survey consisting of 38 true-or-false, multiple choice, or open-ended questions.(34) Over 50% of the women reported having to see a clinician three or more times with oligo-amenorrhea before laboratory testing was performed to make the diagnosis. In 25% of the women it took longer than 5 years to get the diagnosis. The data showed that women with primary ovarian insufficiency perceived a need for more aggressive evaluation of secondary amenorrhea and oligo-amenorrhea. Loss of menstrual irregularity can be a sign of ovarian insufficiency, and the associated estrogen deficiency is a well-established risk factor for osteoporosis.

Once our team had demonstrated that delay in diagnosis of primary ovarian insufficiency was common, we next undertook a study to determine the effect of this delay on bone health in these women. We took the opportunity to assess many factors that relate to bone health in a cross-sectional study of 442 women with 46,XX spontaneous primary ovarian insufficiency.(35) Compared to control women, women with primary ovarian insufficiency had on average 2–3% lower bone mineral density at the femoral neck, total hip, and lumbar spine. Delay in diagnosis was statistically significantly related to lower bone mineral density. With proper education, of both patients and clinicians, this delay in diagnosis is a modifiable cause of reduced bone density in these women. Importantly, we identified other

easily correctable modifiable risk factors that significantly related to lower bone mineral density in these women. Over 50% had vitamin D insufficiency, and this was a significant risk factor for reduced bone density. Nearly 50% had inadequate daily intake of calcium, and this was significantly related to lower bone mineral density. Nearly 25% had no regular exercise program, and this was also significantly related to lower bone density. Three readily modifiable risk factors in need of better care.

In 2001 an NIH Consensus Developmental Panel on Osteoporosis concluded that 1) osteoporosis is a major health threat, 2) it is largely preventable, and 3) optimization of bone health must occur throughout life.(36) Our cross sectional study demonstrated that many women with 46,XX spontaneous primary ovarian insufficiency are not getting the health care and monitoring they need for “optimization of bone health ... throughout life.” The wake-up call from these twins tells us there is a need for change in this regard. The menstrual cycle needs to be seen as a vital sign of bone health in girls and young women.

A Wake-up Call - Emotional Health and Primary Ovarian Insufficiency

Years ago I was shocked when I learned that one of my patients with 46, XX spontaneous primary ovarian insufficiency caused by steroidogenic cell autoimmunity had committed suicide. When I heard about this it had been several years since I had last seen her. I was deeply saddened. I found it hard to believe. During all of my prior interactions with this woman she had been bright, upbeat, outgoing, friendly -- a beautiful young woman in so many ways. In the ensuing court proceedings after her death her diary became part of the court record. The diary made it crystal clear that the infertility related to her diagnosis was a major factor in her suicide. The memory of this woman haunts me. To me, she is the “One Woman” in the “One World, One Woman” approach to primary ovarian insufficiency. Her death might have been prevented by an integrated approach to primary ovarian insufficiency – an approach that takes seriously the emotional health issues around this condition. This was indeed a powerful wake-up call for me. Our team now screens all of our patients with primary ovarian insufficiency with instruments distributed by the nonprofit organization Screening for Mental Health, Inc. (<http://www.mentalhealthscreening.org/>). This tool screens for depression, generalized anxiety disorder, bipolar disorder, and post traumatic stress disorder.

Ministering to the emotional health of young women with primary ovarian insufficiency begins by informing them of the diagnosis in a sensitive manner. In a cross sectional retrospective study we assessed the emotional needs of 100 women previously diagnosed with the condition.(15) A majority was dissatisfied with how they were informed by their clinician. Also, the evidence suggested that the manner in which we inform patients can significantly impact their level of distress around this disorder. Patients with primary ovarian insufficiency perceive a need for clinicians to spend more time with them and to provide more information about the condition.

In another cross sectional study of 100 women we assessed the psychosocial transition associated with the diagnosis of 46,XX spontaneous primary ovarian insufficiency.(16) Using validated instruments we showed that the more illness uncertainty a woman reported the more symptoms of anxiety she was experiencing. The more stigmatized she felt by the condition the more symptoms of depression she was experiencing. The findings suggest that we as clinicians might help these patients recover emotionally by reducing their uncertainty regarding the illness and doing what we can to reduce the associated stigma. Most importantly, however, on multiple regression analysis we found that the single most important measure that remained significant with regard to symptoms of both anxiety and depression was purpose in life.

Our finding that purpose in life is the single factor that survives multiple regression analysis with regard to affect supports a conclusion that loss of a sense of purpose in life is the major emotional impact of the diagnosis for most of these women. Psychiatrist Victor Frankl referred to disruption of life purpose as “identity disruption.”(37) For three years Victor Frankl labored in 4 different Nazi concentration camps while other members of his family perished, including his pregnant wife. In his book about the experience, *Man’s Search for Meaning*, Frankl argues that we as humans cannot avoid suffering, but we can choose how we cope with it, find meaning in it, and move forward with renewed purpose. Frankl’s theory holds that as humans our primary drive in life is not pleasure, as Freud argued, but the discovery and pursuit of what one personally finds meaningful. Another term Frankl uses is “existential frustration.” Here is his description in his own words,

“Existential frustration in itself is neither pathological or pathogenic. A [woman’s] concern, even despair, over the worthiness of [her] life is an existential distress but by no means a mental disease.” (37)

Now, based on our research data and on my four decades of personal interactions with women who have 46,XX spontaneous primary ovarian insufficiency, I have come to see this situation quite differently. I conclude that a clinician’s most direct approach toward helping women with this diagnosis heal emotionally is to assist them in the self-discovery of the meaning and purpose in their life. As clinicians we need to find referral patterns that help patients navigate what Victor Frankl called “meta-clinical” problems (I assume he was using “meta” in the sense of “meta” physical). In his words,

“Some of the people who nowadays call on a psychiatrist would have seen a pastor, priest, or rabbi in former days. Now they often refuse to be handed over to a clergyman and instead confront the doctor with questions such as, ‘What is the meaning of my life.’ ” (37)

How can clinicians help women cope with the diagnosis in the most constructive manner, find meaning in it, and move forward with renewed purpose? If the emotional impact of this diagnosis is indeed mediated through an existential crisis then an existential response is required. The diagnosis raises questions in patients such as, “Where am I?” “What am I?” “Who am I?” and “Why am I here?” These are existential questions that most clinicians are not trained to help patients address. Our experience at the NIH Clinical Center has been that these are domains most appropriately addressed by our spiritual ministry colleagues and also our occupational therapy colleagues. It may seem strange to include occupational therapy here, but I have found them a powerful addition to our team. I was never clear on what these professionals do. Recently it was explained to me by my colleague Susan Robertson, “Occupational therapy helps people build a life around what they find meaningful.”(38) Perfect, this is exactly what is needed.

In collaboration with the Spiritual Ministry Department at the NIH Clinical Center, in another cross sectional study, using validated instruments, our team investigated the relationship between spiritual well-being and functional well-being in these patients. We studied 138 women with 46,XX spontaneous primary ovarian insufficiency.(39) We found the meaning subscale of the spiritual well-being instrument significantly correlated with functional well-being, explaining approximately 62% of the variance. In contrast, the faith subscale of the spiritual well-being instrument explained only 7% of the variance. On regression analysis only the meaning subscale remained significant. The findings support a conclusion that having a clearer sense of meaning and purpose in life are important factors in emotional wellness in this population. We need prospective controlled interventional studies to inform how we can best facilitate a search for renewed meaning and purpose in the lives of those women who, related to the diagnosis, feel lost in this regard.

In another study, in collaboration with the Section on Behavioral Endocrinology, Intramural Research Program of the National Institute of Mental Health, we examined the lifetime risk of depression in 174 women with 46,XX spontaneous primary ovarian insufficiency.⁽⁴⁰⁾ Patients were evaluated using the Structured Clinical Interview for DMS-IV disorders (SCID), a diagnostic exam used to determine DMS-IV Axis I disorders (major mental disorders) and Axis II disorders (personality disorders). The study characterized the prevalence of psychiatric disorders and the timing of onset of clinically significant depression relative to both the diagnosis of primary ovarian insufficiency and the onset of menstrual irregularity. We found that young women with 46,XX spontaneous primary ovarian insufficiency are much more likely than other women to experience depression sometime in their lives. We found that 67% of these women were either currently depressed or had been depressed at least one time in their lives. This lifetime risk significantly exceeds the rates of depression reported in women with Turner syndrome and community based samples of women. The findings suggest that all women with 46,XX spontaneous primary ovarian insufficiency should be evaluated for depression.

Interestingly, we found that the onset of depression in these women frequently occurs after the onset of menstrual irregularity but before the diagnosis of primary ovarian insufficiency. I got a wake-up call from my patient who committed suicide. The subsequent research findings around this suggest that the menstrual cycle needs to be seen as a vital sign of emotional health in girls and young women.

A Wake-up Call - Family Planning and Primary Ovarian Insufficiency

As readers of this journal well know, for many years this condition was referred to as “premature menopause,” interpreted to mean permanent cessation of menstrual periods and the irreversible loss of fertility. One time, early in these research efforts at the NIH, a clinical associate in training called me to see a woman with “premature menopause.” He had found on her physical exam what he concluded to be an abdominal tumor. Some patients come to see us from great distances, so we always review their existing medical records to confirm menopausal levels of gonadotropins on two occasions before we ask them to make the trip to see us. Such was the case in this woman; there was no doubt she met diagnostic criteria before she came to see us. So, based on thinking at the time, the clinical associate was correct in concluding she should never get pregnant. The patient had been counseled this way by her hometown physician as well. As it turned out the “tumor” was a four month pregnancy. We found fetal heart tones. She was astounded and elated. She subsequently delivered a healthy child.

This was the first of many surprising experiences we have had involving remission, return of ovarian function, return of regular menstrual periods, and even pregnancy in women with confirmed 46,XX primary ovarian insufficiency. Based on our subsequent research we now know that this condition is best described as “intermittent and unpredictable ovarian function that can go on for decades.”

The Need for an International Primary Ovarian Insufficiency Consortium

Primary ovarian insufficiency is a rare disease. The incidence is approximately 1 in 10,000 by age 20, 1 in 1,000 by age 30, and 1 in 100 by age 40.⁽⁴¹⁾ It is diagnosed in girls beginning at the age of expected menarche and in women up until age 40 years.⁽⁷⁾ According to government statistics in 2007, the total population of US girls and women was 152,981,937. Broken down by age categories: 15–19 yrs – 10,708,736, 20–24 yrs – 10,096,808, 25–29 yrs – 10,096,808, 30–34 yrs – 9,637,862, 35–39 yrs – 10,555,754.⁽⁴²⁾ Using mathematical modeling we calculate that the total number of women with primary ovarian insufficiency in the United States is approximately 100,000. The United States

Congress passed the Orphan Drug Act in 1983 and defined a rare disease as one that affects fewer than 200,000 people in the country.

Rare diseases present challenges not only in patient care but also in research. To better define the condition and to develop improved therapies we need an international approach. The situation with primary ovarian insufficiency is compounded by the fact that it is a rare disease made up of a host of ultra-rare diseases. For example, steroidogenic cell autoimmunity accounts for only approximately 4% of cases of primary ovarian insufficiency.(10) At NIH we have had a randomized placebo controlled trial of alternate day prednisone in place for this condition for more than 10 years. We have only been able to randomize 5 women. For an ultra-rare disorder, the only hope for making real progress is by developing an international consortium.

There is a need to create a dedicated and self-sustaining community of practice around primary ovarian insufficiency. To this end, in October 2008 Rachel's Well, Inc. (<http://RachelsWell.org>), a research oriented patient advocacy group, the American Society for Reproductive Medicine (<http://www.ASRM.org>), a professional organization representing clinicians and investigators, and representatives of the Department of Health and Human Services of the United States Government (<http://www.hhs.gov>) convened a meeting of stakeholders. The meeting took place at the William F. Bolger Center for Leadership and Development in Potomac, Maryland.(6) The summary statement called for an international collaborative approach, combining the structure of a patient registry with the principles of integrative care and community-based participatory research. Figure 2 graphically represents a structure by which this could be accomplished. An umbrella organization such as the nonprofit Rachel's Well would create a community in which to bring together industry, academia, patient advocacy groups, and government into a community of practice around the condition.

One World, One Woman - Joan of Arc and the Path of Kyosei

Transformational leaders have a way of seeing through gloomy skies. In a long range sense there are no gloomy skies when the world is seen through their eyes. Recently I had the pleasure of reading Mark Twain's masterpiece on the life of Joan of Arc.(43) I see similarities here to Martin Luther King's approach. She could speak simple truths to power in a way that touches the heart. This had a transformational effect. As Hungarian revolutionary Louis Kossuth puts it, "Since the writing of human history began, Joan of Arc is the only person, of either sex, who has ever held supreme command of the military forces of a nation *at the age of seventeen*."(43) The amazing thing is that she did this as a farm girl who had no budget and no formal education. Her passion and her ability to communicate simple truths permitted her to bring forces and resources to her cause in ways that others could not. In these stringent economic times we all need to think creatively on how to accomplish more with less. Speaking simple touching truths to power and working together in the spirit of kyosei can help.

Kyosei is a business credo that defines a "spirit of cooperation." (44)(45) The ideals have their origins in practical percepts of Confucianism. These played a key role in the development of Japanese business codes of ethics during the early part of the seventeenth century. Kyosei can be translated literally into English from two Japanese characters which mean "working together" (kyo) and "life" (sei). Taken together, the meaning is cooperative living or symbiosis. In full bloom a kyosei approach leads corporations and nations to global activism and toward rectifying global imbalances. Such an approach is what is required to make real progress in the field of primary ovarian insufficiency.

Conclusions

It was a real joy for me to speak on this topic at the invitation of Wulf H. Utian. His visionary efforts at creating an integrative approach to menopause are much appreciated. They surely ease the path toward using this same approach for other conditions, such as primary ovarian insufficiency. I always enjoy attending the NAMS annual meeting because I appreciate the diverse talents that are brought together to synthesize cogent perspectives and approaches. I also enjoy meeting many enthusiastic members who are clearly charged up by their ability to give integrated care to women. My sincere hope is that my talk and this paper will stimulate a concerted effort towards helping women with primary ovarian insufficiency in the same manner.

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Figure 1.

Visual representation of integrative and traditional systems of research and health care, viewed from the patient perspective. Each black circle represents the patient. Each line represents a specialized area of research or health care. In the traditional model depicted on the left, the patient experiences research and care in one domain at a time. In the integrative model depicted on the right, the different domains come to meet the patient. This results in patient care and research coming together in one system and one database.(6)

Figure 2.

The report of a conference convened by stakeholders in primary ovarian insufficiency suggested the need for a consortium to be organized by an umbrella organization such as Rachel's Well, Inc., a 501c3 nonprofit entity. The role of the federal liaison is to represent the interests of the government with outside organizations. A federal liaison does not participate in the internal business affairs or fundraising activities of the outside organization. As a 501c3 umbrella organization Rachel's Well can facilitate collaboration among academia, industry, philanthropy, and government.(6)