Mechanisms of premature ovarian failure

N. Santoro
Division of Reproductive Endocrinology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461.
e-mail: glicktoro@aol.com

INTRODUCTION

The median age at natural menopause in most studies is approximately 51 years [20, 30]. There is little evidence to suggest that this median age has changed greatly over the past 100 years [18]. Menopause is considered premature when hypergonadotropic amenorrhea persists for at least 6 months in a woman who is less than 40 years old. This clinical condition, commonly called premature ovarian failure (POF), has a prevalence of approximately 1% [12]. Early menopause is considered by some to be a separate clinical condition, and is diagnosed when hypergonadotropic amenorrhea presents in a woman between age 40 and 45. This latter condition is much more common, and occurs in up to 4-5% of the population [10, 35, 37]. Since both conditions share similar risk factors and family histories, and may only represent differing degrees of severity of the same underlying defect, they are sometimes considered a single diagnosis. However, the distribution of specific diagnoses, when they can be found, among genetic, immune, environmental and other causes of ovarian failure, differ greatly depending upon the age at which a woman is diagnosed. Chromosomal defects are far more likely to be found in young women under the age of 25 with premature ovarian failure than they are to be found in a woman who is 44 and experiencing early menopause [29]. A third, related condition, the “resistant ovary syndrome” has been coined to refer
Les causes immunitaires et autres causes idiopathiques d’insuffisance ovarienne précoce nécessitent davantage de clarification. Il est clair que cela représente un domaine où le potentiel de recherche est énorme. Une meilleure compréhension du mécanisme par lequel l’insuffisance ovarienne survient pourrait permettre d’aider les femmes souffrant de cette condition, en facilitant le développement de nouvelles options thérapeutiques. Par ailleurs, de telles connaissances pourraient même permettre d’optimiser la fonction ovarienne chez les individus sans insuffisance ovarienne précoce qui cherchent actuellement par d’autres approches à prolonger leur fenêtre reproductrice ainsi que leur potentiel de fertilité.

Mechanisms of premature ovarian failure

The median age at menopause in Western populations of women is approximately 51 years. While very late (i.e., after 54 years) menopause is exceedingly uncommon, a sizeable minority of women experience cessation of ovarian function at or prior to age 45. By convention, menopause that occurs at ages 40-45 is considered “early” and occurs in about 5% of women. Premature ovarian failure (POF) is reserved for the approximately 1% of women who experience hypergonadotropic amenorrhea prior to age 40 years. POF represents the end stage of a variety of disorders that result in the loss of ovarian follicles. Depending upon the age at diagnosis, the probability of a genetic, autoimmune, or idiopathic cause will be more or less likely.

Two functioning X chromosomes appear necessary for normal ovarian function. The most obvious genetic cause of POF is Turner Syndrome, in which a complete or near-complete loss of the second X chromosome occurs. Turner Syndrome typically results in the most severe and irreversible POF, often clinically evident prior to menarche. Typically, in Turner Syndrome, menopause precedes menarche, and there is no evidence of ovarian function. However, cases with multiple tissues diagnosed as 45, X have been reported to result in ovarian function and even pregnancy. It is likely that mitigating factors, perhaps autosomal, can modify this most severe and irreversible cause of ovarian failure. Lesser degrees of ovarian failure have also been attributed to partial X chromosome deletions and milder degrees of X chromosome mosaicism. Fragile X syndrome is another example of mild POF that can be linked to disorders of the X chromosome.

Other genetic defects are believed to cause POF, yet their prevalence has been difficult to determine. The localization of the gene for the blepharophimosis/ptosis/POF Syndrome has been recently reported, yet this finding has not been seen commonly in POF. Other genetic syndromes including POF await elucidation. Many transgenic “knock-out” animals have been created with deficient ovarian function. Most interesting along these lines is the heterozygous FSH receptor knock-out, which exhibits a reduced follicle reserve and early ovarian depletion. Application of this knowledge and translation of these transgenic experiments into elucidation of clinical disease has been difficult, but represents an area of tremendous potential progress in the understanding of the pathogenesis of POF.

Another approach to the genetics of POF has been to examine the genome of affected and unaffected individuals. The genetics appear to differ greatly depending upon the timing of the expression of the POF. For example, women with early menopause are more likely to possess the PVUII polymorphic allele for estrogen receptor alpha. Whether or not this polymorphism is more common in women with earlier menopause, i.e., POF, is unclear. Pedigree data indicate that early menopause and premature menopause sort similarly within families. The only difference between women with true POF and those with early menopause may be in the timing of the expression of the syndrome, and not in the genetics. Population genetic approaches analyzing affected and unaffected individuals are underway in several research centers and represent another area of progress.

Immune and other, idiopathic causes of POF await further clarification. It is clear that this is an area of great research potential. Understanding how ovaries fail may assist women with this disorder by facilitating the development of novel therapies. Additionally, such information will provide important clues about optimizing ovarian function in individuals without POF who are seeking extension of their reproductive life spans or fertility enhancement by other means.

to situations in which ovarian follicles are present, but are unresponsive to hypergonadotropic stimulation. In some of these cases, ovarian follicle reserve can be normal or near-normal [1]. In these conditions there is typically a molecular defect that prevents the normal process of follicular maturation from occurring. This review will be confined to conditions that result in a genuine loss of follicle reserve resulting in the syndrome of POF. Mechanisms that have been described include genetic -both sex chromosome and autosomal- immunologic, environmental and iatrogenic. Despite these insights, many cases of premature menopause still have no identifiable underlying etiology and are considered idiopathic. The desire of women with this diagnosis to understand the root cause is intense, and the author’s experience as an internet consultant to women with premature menopause will also be described.
PREMATURE MENOPAUSE
AND EARLY MENOPAUSE
THE CASE FOR A UNIFIED DIAGNOSIS

The age at which a woman experiences her final menstrual period may be conceptualized as a process that may be modified in a number of different ways. The total ovarian follicle complement is determined by events that occur before birth [5]. This initial supply of follicles may be further influenced by an individual’s genetics. The follicle pool is then subjected to serial waves of atresia over time, supplemented by additional insults. These additional insults may be autoimmune, infectious, surgical, vascular, toxic (environmental or iatrogenic, as in the case of chemotherapy), or, perhaps, even psychological [21]. Host factors will then determine the extent to which each of these potential insults will further compromise the follicle pool. Women with an identical follicle pool size might have very different ultimate ages at menopause. For example, if one woman smokes cigarettes and has underlying vascular disease, her residual follicles may become depleted more readily. Another woman with an identical follicular reserve may, by dint of her lifestyle, her occupation, or even her country of origin, have a much longer reproductive life span. Pedigrees of women with premature ovarian failure (POF) and early menopause (EM) indicate that both entities occur in the same families [37]. It is important to consider that the distinction between “premature” and “early” menopause is probably arbitrary. While it may reflect a difference in the distribution of underlying disorders, it does not necessarily indicate a different pathophysiology.

GENETIC MECHANISMS OF POF

The most clear-cut cause of POF has long been understood to occur in women with Turner Syndrome (TS; 38). The essential nature of a functioning second X chromosome has been demonstrated repeatedly in families with this disorder. In many women with TS, menopause precedes menarche, but in sporadic cases, intermittent menstruation and even ovulation and pregnancy have been documented [4, 34]. Such cases are often believed to reflect at least some X chromosome mosaicism, although cases exist wherein multiple tissues have been biopsied and found negative for a second X chromosome [6]. A re-evaluation of the time course of follicle loss in Turner Syndrome has indicated that ovarian follicles can still be found in a sizeable number of adolescent girls with the disorder [22].

Women with Turner Syndrome are typically diagnosed early in life, due to the characteristic physical features associated with the disorder. When ruling out X chromosomal mosaicism in phenotypically normal women, counting 50 cells, rather than the customary 20, can be helpful. Women with X chromosome mosaicism and/or TS are at high risk for abnormal pregnancies, if they should conceive [16]. Sex chromosome abnormalities and genetic defects associated with chromosomal non-disjunction are relatively common. Lesser degrees of X chromosome loss are also associated with POF [26]. A “critical region” of the X chromosome has been identified and deletions in this area are associated with premature loss of ovarian function. High-resolution banding techniques can be used clinically to identify women with these defects, but unless there is a familial history of POF, the yield is likely to be low.

A second chromosomal cause of POF is associated with Fragile X Syndrome (FRAXA). Women who carry FRAXA are phenotypically normal, but appear more likely to undergo early menopause. They are at risk for delivering affected male offspring. Although it is often reported in association with affected kindreds, FRAXA is overall an uncommon cause of POF and routine screening for FRAXA is not believed to be cost-effective [24].

The genetic revolution may begin to shed light on POF in several different ways. The identification of proteins and families of proteins that may be intimately involved in ovarian development and function has led to the proliferation of potential causes of POF. The FSH receptor polymorphism identified by Aittomaki et al. [1], causes a POF-like syndrome, in which hypergonadotrophic amenorrhea is present but the ovarian follicular pool is normal. This condition is not present in detectable proportions of people other than from Finland [8, 27]. The forkhead transcription factor, FOXL-2, has been identified as being associated with the blepharophimosis/p toesis/epicanthus inversus syndrome and POF [13]. How this family of transcription factors might be responsible for premature ovarian senescence is not clear. Mutation of the gene for growth differentiation factor-9 (GDF-9) has been shown to result in ovarian failure in a transgenic animal model [41]; however, a search for similar mutations in humans has not demonstrated any cases in a screening study of women with a variety of ovarian disorders, including POF [36]. Elucidation of single gene defects responsible for POF is underway at several research centers using a variety of genomic approaches. These techniques may be better applied to large, population studies. Weel et al. [40], using such an approach, were able to identify an association between the Pvu II estrogen receptor alpha polymorph and the earlier onset of menopause, along with a higher risk of hysterectomy.

Mechanistic elucidation of POF may be forthcoming from the examination of animal models. Transgenic

technology has led to many advances in the understanding of pathophysiology. Many “knock-out” (KO) animals have abnormal reproductive phenotypes. Mutations that seem to display POF-like syndromes include GDF-9, FSH receptor, and the MutS homolog [15, 17, 41]. The identification of these abnormal animal genotypes often initiates a search for an analogous human phenotype. Unfortunately, the follow-up human studies are often disappointing as was the case for GDF-9 [36].

**AUTOIMMUNITY AND POF**

POF has long been associated with multiple endocrine autoantibodies. The original association was made by Irvine et al. [23], who detected an unusually high prevalence of women with POF among a clinic sample of women with primary adrenal failure due to autoimmunity (Addison’s Disease; [23]). Since then, linkages between POF and thyroid autoimmunity have been proposed by some [3], but refuted by others [39]. POF has been reported in association with virtually every autoimmune disorder known to occur. Screening of patients with POF to rule out some of the more common autoimmune associations should be considered [25].

It is somewhat frustrating, given the long and likely association between autoimmunity and POF, that so little understanding of the mechanisms responsible for autoimmunity is available. Antibodies against the ovary have been determined by a number of methods [11, 14, 28]. Most indicate that some increase in autoantibodies is detectable in women with POF, but these tests lack the diagnostic precision of other, similar types of tests directed at endocrine organs. The typical endocrine autoantibody is a specific, circulating molecule that can be readily identified using indirect immunofluorescence. When one applies these types of techniques to the ovary, and appropriate control groups are used, it is readily apparent that many normal women have evidence of ovarian autoimmunity. It may be that the monthly process of ovulation, breaking the basement membrane between the avascular ovarian follicle and the bloodstream, results in some degree of low-level autoimmunity in many women. Why some go on to develop POF on this basis while others tolerate this monthly immunologic breach is unknown and suggests that the pathway for ovarian autoimmunity is more complex than for other endocrine organs. The titer of ovarian autoantibodies may also wax and wane with the stage of the disease. By the time many women present for a medical evaluation, the process may be near-complete, and the evidence of the destructive autoanti-bodies or cell-mediated tissue destruction may no longer be present. Recent data suggest that women with POF have a selective defect in cell surface markers on peripheral blood lymphocytes that may predispose them to the development of ovarian autoimmunity [42].

**THE ROLE OF THE ENVIRONMENT IN POF**

There are a number of potential environmental toxicants that have been proposed to play a role in advancing ovarian senescence. It is interesting that most of these agents are associated with early menopause and not POF per se. Cigarette smoking is a major adverse environmental influence, and advances the age at final menses by up to 2 years [30]. Excessive galactose consumption may also be responsible for early menopause [9]. Ovarian disease and repeated ovarian surgeries are associated with diminished ovarian reserve [43]. Iatrogenic causes for POF include chemotherapy, particularly alkylating agents [14].

In addition to these extracorporeal factors, there are several within-woman factors that are believed to be related to POF. Endogenous depression has been linked to a greater prevalence of POF [21]. The underlying mechanism for this finding is not known. It appears that the diagnosis of depression precedes the diagnosis of POF, often by many years. It is tempting to speculate how the physiological stress of depression, which includes disruption of many circadian systems (including the 24-hour circadian glucocorticoid biorhythm) might impact adversely on a woman’s follicular reserve.

The link between extreme physiological stress and hypergonadotrophic amenorrhea was first made in 1958 by Netter et al. [32]. Dubbed “ovarioplegic amenorrhea”, the author related several case reports of women who had experienced life-threatening stress and had developed POF. The cases reported did not appear to demonstrate any “recovery” over the variable follow-up interval.

**EXPERIENCE AS AN “INTERNET CONSULTANT” TO WOMEN WITH POF**

An international support group for women with POF has formed, originally based in Virginia (www.pofsupport.com). The relative rarity of POF makes it difficult for women to come to terms with the diagnosis, and to be able to develop coping skills by learning from others’ example. This internet-based support service provides a
CONCLUSIONS

POF is a relatively rare clinical condition that has a devastating impact on a woman’s desire to bear children. Both premature and early menopause may, however, be linked entities, and the elucidation of the mechanisms of one syndrome may well inform the search for pathophysiology in the other. Genetic causes, including X chromosome disorders, fragile X syndrome, and autosomal defects of varying types, have great potential in elucidating how the ovary fails. Most of this potential is as yet unrealized, since many animal models have not “translated” into human disease. Population genetic approaches may lend themselves to greater use in detecting determinants of early ovarian senescence. Similarly, it remains unclear to what extent autoimmunity plays a role in premature ovarian failure and how autoimmune processes result in follicular destruction. It is likely that we currently lack an appropriate paradigm with which to understand the types of autoimmune processes that attack the ovary. While environmental toxicants have been known to affect the ovary adversely, many of the identifiable agents seem to be linked more to early menopause and not to POF. Whether there are rare, sporadic exposures to key agents that cause a more severe loss of ovarian function in women with POF is currently speculative. Clearly, much further work is needed to illuminate our understanding of this clinically frustrating disease.

REFERENCES