Chapter 2
Etiologies of Primary Ovarian Insufficiency

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Clinical Vignette

> "*I could not stop crying when my doctor told me I was in menopause! I was only 32 years old and married less than year ago! I wondered whether I had done anything wrong. Later I found out that my grandmother, mother and my aunt went through menopause when they were in their 30's, but we had never talked about these things before. I never expected this would happen to me because everyone in my family has had several children. I wish I had known about this problem sooner. I really want to understand why this happened.*"

Primary ovarian insufficiency (POI), formerly known as premature ovarian failure (POF), is defined as the cessation of ovarian function before the age of 40, considering 52.5 years old as an average age of menopause (51–53 years old) in the USA [1, 2]. POI can present with infertility and eventually progress to cessation of ovarian function, which is considered the end point of the disease [3]. There are many contributors to POI, including genetics, environmental exposures, autoimmunity, etc. In this chapter, we review the major known contributors to POI.

A basic understanding of ovarian follicle development and loss provides a foundation for understanding the diversity of processes that can affect ovarian reserve. During embryonic development in humans, germ cells initially appear in the genital

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ridge and migrate to the primitive ovary where they proliferate to more than 3.5 million by about 20 weeks of gestation. The majority of these follicles will be lost during fetal and postnatal life by atresia [4, 5]. Females begin their reproductive life at puberty with only about 300,000 follicles in their ovaries. During each ovulatory cycle about 10 or 20 follicles undergo a maturation process that results in the release of one mature oocyte [6]. In sum, about 400–500 follicles are released during cycles of ovulation that occur during the childbearing years. Eventually, when the number of reserved follicles reaches approximately 1000, cessation of menses, or menopause, occurs [4, 5].

A variety of pathogenic mechanisms lead to the development of POI. These can be divided into four major categories: a follicular migration defect early in embryogenesis; an initial decrease in the primordial follicle pool; accelerated follicular atresia; or altered maturation or recruitment of primordial follicles. The etiologies of POI are highly heterogeneous and include genetic, autoimmune, metabolic or enzyme defects, infectious, and iatrogenic factors. Taken together, these account for only 10 % of the cases and the remaining 90 % are idiopathic, or largely unknown [7].

Genetic Causes

The evidence for genetic causes of POI comes from cases of chromosome abnormalities such as Turner syndrome [8–10], familial cases of POI [11–16], and evidence that the timing of natural menopause between sisters, daughters, and mothers is heritable [14, 17–20]. The most common X chromosomal abnormality is Turner syndrome (TS) with an incidence of 1:2500. Turner syndrome results when only one normal X chromosome is present and the other X chromosome is either missing or structurally altered. In 80 % of the cases, the lost X chromosome is paternal in origin [21]. In some cases the affected woman is mosaic for a normal karyotype and monosomy X. The missing genetic material in classical TS affects ovarian follicular development and function. The ovary begins to develop normally, but ovarian follicles of TS patients degenerate rapidly during prenatal life, often leading to gonadal dysgenesis with streak ovaries [7, 22]. Almost all patients require hormone therapy to undergo puberty [23].

Trisomy X and partial X chromosome defects in the form of deletions, isochromosomes, and balanced X autosome translocations can cause POI [10]. A major goal is to identify the genes that are critical for normal ovarian function that are disrupted in these chromosomal abnormalities. TS patients who lack only a portion of one of the X chromosomes or have an autosomal translocation with an X chromosome are valuable for identifying these critical genes. Cytogenetic analysis of these patients reveals that reduced dosage of genes on both the long (q) and short (p) arms of the X chromosome contributes to POI [23–25]. Deletions of the short arm of the X chromosome usually result in primary amenorrhea, whereas deletions of the long arm of the X chromosome result in either primary or secondary ovarian insufficiency [26, 27]. The critical region for ovarian development and function on

Xq chromosome spans Xq13.3 to q27, but the specific genes in this region that contribute to the phenotype are not yet known [25, 28, 29]. The short stature associated with Turner's syndrome results from reduced dosage of genes on Xp, and *SHOX* is a contributing gene [9, 26, 30–33]. Some chromosomal abnormalities may not delete the critical genes but cause "position effects," or epigenetic changes that affect gene expression [34].

Although many POI patients have genetic defects involving the X chromosome, an increasing number of studies have documented autosomal gene involvement in the etiology of POI [27, 35, 36]. Some familial forms of POI have autosomal dominant sex-limited transmission or X-linked inheritance with incomplete penetrance [16, 36–39]. Recently, molecular genetic investigations of women with POI and experiments in genetically engineered mice have led to the identification of several genes that are critical for follicle function and oogenesis, such as BMP15, FOXL2, GDF9, NR5A1, NOBOX, LHR, and FSHR. Only a small fraction of POI cases can be explained by mutations in these genes, and the molecular pathogenesis remains speculative [40–44]. Currently, none of these genes are accepted as clinical genetic markers for POI [45, 46]. Much more regarding the genetics of POI is discussed in other chapters.

FMR (Fragile X Mental Retardation) Gene

The FMR1 gene has a clinically significant association with POI. The FMR1 gene is located on the X chromosome (Xq27.3) and contains an expandable region composed of trinucleotide repeats of CGG in the 5′UTR [47–50]. Three allelic classes can be defined based on the number of CGG repeats. Normal alleles have 6–55 CGG repeats, premutated alleles have 55–200 CGG repeats, and a full mutation contains 200 or more CGG repeats [51–54]. In males, the consequence of the full mutation is fragile X syndrome, the most common inherited cause of mental retardation. However, 2–5 % of women with the premutation allele have a substantially increased risk of POI [55–57]. It has been estimated that the FMR premutation accounts for about 21 % of familial and 6 % of sporadic forms of POI cases. The mutant FMR allele is toxic, possibly because the mutant transcripts sequester CGG binding proteins that are important for RNA processing. The FMR protein (FMRP) is highly expressed in fetal germinal cells of the ovary, and the mutant allele leads to a decrease of the initial pool of oocytes and increased rate of follicular atresia [35, 50, 58, 59]. Nevertheless, in carriers of the premutation who are over the age of 50, the toxic effect of the FMR mRNA can cause a neurodegenerative disorder: fragile X tremor ataxia syndrome [60].

Patients with FMR premutation have an unusual inheritance pattern. Affected individuals always inherit the expanded repeat from their mothers, and premutation-carrying males always pass on premutation alleles to their children [61, 62]. Furthermore, affected full mutation males produce sperm with only premutation alleles [63], and although full mutation germ cells are present in developing male

fetuses, these are gradually replaced with premutation-bearing germ cells [64]. This could be due to a proliferation advantage of FMR) protein producing cells or to a selection against male germ cells with large trinucleotide repeat expansions [65]. However, in females, selection against germ cells with an expanded full mutation allele on the active X chromosome may reduce the germ cell pool, and expansion on the inactive X chromosome may allow passage of full mutation alleles to offspring [61].

The co-segregation of POI and premutations in some families and the lack of POI in other fragile X families suggest that ovarian function is adversely affected by only a subset of premutation alleles. This model could partially account for the discrepant results of the various association studies between POI and fragile X mutations as the various study groups may differ in the proportion of alleles that are associated with POI. Differences between the POI and non-POI premutation alleles could be due to linkage disequilibrium with a nearby POI-causing mutation or due to variations in the structure of the repeat itself, such as AGG interruption pattern or length of pure CGG tracts. Such changes may be responsible for subtle, but critical, changes in FMRP level. Other confounding factors could include modifying genes, perhaps also affecting FMRP levels, as well as the various genetic and environmental factors known to affect age at menopause. Whatever the mechanism of the association between *FMR1* and ovarian function, the challenges raised by the differing results in various populations reflect the complexity at work in this particular genotype–phenotype relationship.

Autoimmune Causes

Autoimmune disease accounts for approximately 4 % of POI cases [66]. The trigger for ovarian autoimmunity is unknown, but it might be due to abnormalities in self-recognition by the immune system, resulting in a loss of tolerance to some component of ovarian tissue, and ultimately ovarian tissue damage [13, 66, 67]. Animal studies suggest involvement of immune-regulatory regions outside the histocompatibility (H-2) locus on mouse chromosome 3 as an associated factor for ovarian damage [67–70]. In humans, HLA-DQB1*0301 and HLADQB1* 0603 are proposed as an associated factor with 3b-HSD autoimmunity (adrenal autoantibody) in POI subjects [71, 72].

Approximately 3 % of women with POI have an endocrine dysfunction known as autoimmune polyglandular syndrome (APS), types I and II [73]. The type I syndrome is a rare autosomal recessive disorder characterized by multiple organ-specific autoimmunities secondary to a variety of autoantibodies directed against key intracellular enzymes. Sixty percent of APS type I patients have POI. APS type II is an autosomal dominant disorder, and it is associated with gonadal failure in 4 % of patients [73, 74]. Adrenal insufficiency is a component of both APS types, and 2–10 % of POI cases show evidence of autoimmunity against the adrenal gland [67, 75–77]. In those cases where POI is associated with adrenal autoimmunity,

histological examination almost always confirms the presence of an autoimmune oophoritis in which follicles are infiltrated by lymphocytes, plasma cells, and macrophages that attack mainly steroid-producing cells and eventually result in follicular depletion [78, 79]. Lymphocytic infiltration is more prominent in mature follicles suggesting that production of the self-antigen may be gonadotropin dependent. The zona pellucida (ZP) is an important antigenic determinant of autoimmune POI that affects ZP function, which in turn affects follicular development leading to infertility in women with POI [75, 80]. Lymphocytic infiltration may also be present in the ovarian hilum, with an accumulation of lymphocytes around neural tissue. POI is more common with APS type I than with APS type II. It has been proposed that α-enolase may serve as a candidate target antigen in POI associated with polyglandular syndromes [80–85].

Several other autoimmune disorders have been associated with POI. Hypothyroidism is the most common. In this case, POI subjects will present with antithyroid antibodies and either clinical or subclinical hypothyroidism [74]. The other POI associated autoimmune alterations are parietal cell antibodies, acetylcholine receptor antibodies in myasthenia gravis, chronic candidiasis, idiopathic thrombocytopenic purpura, vitiligo, alopecia, autoimmune hemolytic anemia, systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, Sjögren's syndrome, primary biliary cirrhosis, and insulin-dependent diabetes (2 %) [66, 74, 75, 86–89]. The risk for these diseases in women with POI is higher than in the general population, suggesting that there may be a still unknown autoimmune component involved [90, 91].

Enzyme Deficiency

POI is the most common long-term complication experienced by girls and women with classic galactosemia. Galactosemia is a rare autosomal recessive disorder due to a defect in galactose 1-phosphate uridyltransferase (GALT) enzyme function [92, 93]. The prevalence of POI is 80–90 % in patients with galactosemia despite neonatal diagnosis and careful lifelong dietary restriction of galactose [94]. The cause of POI in classic galactosemia is not yet understood. The most common cause of classical galactosemia is the Q188R mutation, which is followed by the K285N in central European populations [95]. Several other mechanisms also have been proposed, like direct toxicity of metabolites (i.e., galactose-1-phosphate) on follicular structures during fetal life, altered gene expression, or aberrant function of hormones and receptors due to glycosylation abnormalities leading to biological inactivity [81, 94, 96, 97]. Histological findings are consistent with hypoplastic or streak ovaries [98, 99] and fewer follicles than expected for the patient's age to almost complete absence of follicles [100–103]. The few follicles present in the ovaries of classic galactosemia patients are mainly of the primordial type, and maturing follicles are rarely seen [104, 105]. Anecdotal studies in girls at very young prepubertal ages suggest that a normal pool of primordial follicles forms

early in life, but the follicles undergo very rapid atresia, causing a severe decline in the follicular pool and ovarian hypoplasia [101, 104, 106].

Studies in animal models also support a link between galactose metabolism and ovarian toxicity. For example, adult female rats fed a high galactose diet have diminished follicular development [107, 108]. Even prenatal exposure to galactose inhibits germ cell migration and can cause a reduction in oocyte pools [109, 110]. In contrast, the GALT knockout mice have normal fertility, even when challenged with a high galactose diet. The basis for this difference between mice and rat ovaries is unclear [111, 112].

Aberrant FSH function may occur due to abnormal glycosylation of the hormone in women with classic galactosemia. The glycosylation state of follicle-stimulating hormone (FSH) is directly linked to its bioactivity in vivo, as well as to its rate of clearance, potency, and receptor binding and activation; therefore, hypoglycosylated isoform of FSH may even act as an antagonist [113, 114].

Duarte galactosemia is a mild variant of galactose-1-P-uridy-lyltransferase (GALT) deficiency, characterized by the N314D mutation and additional intron and promoter sequence variations [95]. Patients with classic galactosemia have $\leq$1 % normal GALT activity in hemolysates, and patients with Duarte galactosemia have on average 25 % of the normal GALT enzyme activity levels [115–118]. The incidence of Duarte galactosemia in newborns is 10 times higher than classical galactosemia [117, 119, 120]. Whether girls or women with Duarte galactosemia are at increased risk for POI is not completely clear. Small studies of girls with Duarte galactosemia and heterozygous carriers for classic galactosemia, which would be expected to have 50 % the normal level of GALT, did not find any abnormalities in FSH, inhibin B, anti-Müllerian hormone (AMH), or sonographic antral follicle count [121, 122]. The mean age of menopause of classic galactosemia carriers is not different from normal controls. Larger studies are warranted to understand the impact of Duarte galactosemia on risk for POI.

Infectious Causes

The autoimmune assault of ovarian tissue can be triggered by various agents like viruses, bacteria, or self-ovarian antigens. The mumps and rubella viruses are well-known triggers of autoantibody production. Mumps oophoritis may cause POI with an incidence of 3–7 % in patients who contracted mumps during epidemic episodes [80, 81, 123]. However, the true incidence of post-oopheritis ovarian failure is unknown. Fortunately, a vast majority of affected women regain their ovarian function following recovery from the disease [124, 125]. There are also anecdotal reports of other viral and microbial infection followed by POI, such as tuberculosis, varicella, cytomegalovirus in immune-compromised patients, malaria, and shigella [7, 124, 126], but a cause and effect relationship has not been established and evidence is inconclusive [123–125].

Latrogenic Causes

Environment and Lifestyle

Environmental factors can significantly affect ovarian function. There are numerous epidemiologic studies confirming the negative impact of cigarette smoking on natural age of menopause. Cigarette smoke is a complex mixture of alkaloids (nicotine), polycyclic aromatic hydrocarbons (PAHs), nitroso compounds, aromatic amines, and protein pyrolysates, which are reactive and carcinogenic [127]. Women who are current smokers have been found to enter menopause, on average, 1–2 years earlier than nonsmokers [128–130]. Current smokers also have decreased follicle density [131] compared to nonsmokers, and therefore, lower age-related AMH [132] and increased FSH levels [133]. It is thought that the negative effect of cigarette smoking is dose dependent. In one retrospective cohort study, 656 naturally postmenopausal women were found to have a declining mean age of menopause with increasing number of cigarettes smoked [134]. In another study of women aged 44– 53 years, there was a trend toward declining of age of menopause when comparing nonsmokers to current >½ to 1 pack/day smokers [135]. The mechanism of these effects is unknown; however, there are multiple animal and in vitro studies that demonstrate the ovotoxicity of PAH [136–138] through inducing accelerated oocyte atresia, follicle depletion, or dysregulation of the hypothalamic–pituitary–ovarian axis [128, 136, 139–141]. PAH was found to bind the aromatic hydrocarbon receptor of oocytes and granulosa cells, activating transcription of the proapoptotic gene *Bax* and consequently exerting its toxicity effect by triggering female germ cell death [142–146]. Taken together, animal studies strongly support the correlation between smoking and early onset of menopause in women.

The effect of nutrition and other endocrine disruptors such as 2,3,7,8-teterachlorodibenzo-para-dioxin (TCDD) or Bisphenol A (BPA) on sex hormone levels and reproductive span has been studied in animal models although large prospective studies in humans are lacking [147–149]. Caloric restriction, particularly during early childhood, decreases the age at natural menopause as evidenced by the famous 1944–1945 Dutch famine [150]. However, studies on dietary factors and age of menopause are conflicting and need further investigation.

The presence of seizures has been reported as a risk factor for developing POI in a small study. Klein et al. [151] reported 14 % incidence of POI in women with epilepsy, irrespective of antiepileptic medication. Nevertheless, due to the small sample size this association needs more investigation.

Radiation

It is estimated that approximately one in 50 women will have a diagnosis of cancer before the age of 40 [152], and with recent advances in success of childhood cancer treatments the prevalence of iatrogenic POI has been increased [153]. Numerous

clinical studies, reviews, and meta-analyses have examined the effects of anticancer treatments (i.e., radiation and chemotherapy) on female reproductive function. In general, these treatments frequently result in irreversible loss of ovarian function depending on the type and dose of radiation [154, 155]. Women who are exposed to total body irradiation or irradiation of the abdomen or pelvic area are more likely to suffer irreversible ovarian damage and amenorrhea than those exposed in other places [156–158]. Additionally, radiotherapy that has given in a fractionated protocol is safer than a single protocol with a higher exposure [159]. Although the median lethal dose (LD50) of primordial follicles has been reported to be between 2 and 6–18 Gray (Gy) [160, 161], it is estimated that as little as 2 Gy is able to cause loss of the half of human follicles [162]. At birth, the effective dose of fractionated radiotherapy at which POI ensures is 20.3 Gy; however, at 10 years the dose decreases to 18.4, at 20 years 16.5, and at 30 years 14.3 Gy [162, 163]. One study concluded that 26 % of women with total abdominal radiation for approximately 3.5 years developed POI by the age of 23 [164]. Patients who receive a stem cell transplant with total body irradiation are at the greatest risk of developing POI. Virtually 100 % of patients who undergo a marrow transplant with total body irradiation after age 10 will develop acute ovarian failure, whereas 50 % of girls who received total body irradiation before the age of 10 will suffer from acute loss of ovarian function [158]. Therefore, risk of ovarian failure is dependent on the age at exposure (younger girls or women are more resistant), the dose, whether or not the pelvic area is being exposed, and the fractionation of doses [162, 165, 166].

Chemotherapy

POI is an unfortunate sequel of cytotoxic chemotherapy [167]. The gonadotoxic effect of chemotherapy on ovarian function can be transient, with the most important predictive factors of ovarian damage being age, dose, type of chemotherapeutic agent, and the number of cycles/exposure [158, 168]. Higher doses and older age at treatment are both associated with greater damage [169, 170].

Of the various chemotherapeutic drug classes, alkylating agents are thought to be the most cytotoxic [156, 171]. Examples of commonly cited alkylating agents associated with POI include cyclophosphamide, melphalan, busulfan, chlorambucil, and nitrogen mustard [155, 158, 172–174]. After chemotherapy, patients have significantly decreased primordial follicle counts, and this effect is greater for those who were treated with alkylating agents [175]. In rodent models, cyclophosphamide causes a dose-dependent loss in primordial follicles even at doses as low as 20 mg/kg [176]. However, in a mouse model, a single dose of 200 mg/kg of cyclophosphamide results in an 87 % reduction in primordial follicle count 72 h after intraperitoneal administration [177, 178]. This effect is consistent with observations in humans [175]. The presence of amenorrhea soon after treatments also suggests a direct impact of chemotherapy on growing and antral follicles [158]. Byrne et al. have assessed the risk of early menopause in a cohort of 1067 childhood cancer patients

between 1945 and 1976 and found a 9.2-fold increased relative risk for those treated with alkylating agents and 27-fold for women who received a combination of abdomino-pelvic radiation and alkylating agents [179]. Additionally, adolescent cancer survivors who were diagnosed between the ages of 13–19 have four times greater risk of menopause than controls [179]. In addition to the effect of chemotherapy agents on primordial follicles, most regimens, regardless of whether they include an alkylating agent, may have detrimental effects on ovarian stromal function [175]. Therefore, considering static follicle counts as the sole measure of gonadotoxicity may lead to an underestimation of ovarian damage, as these stromal alterations may culminate in POI.

Surgery

Almost any pelvic surgery has the potential to damage the ovary by affecting its blood supply or causing inflammation in the area. Hysterectomy without bilateral oophorectomy, whether laparoscopic or abdominal, decreases ovarian reserve and causes a nearly twofold increased risk of POI [180–183]. While FSH levels in women with hysterectomies and controls provide compelling evidence to support the increased incidence of POI following hysterectomy, the mechanistic pathway is still unknown [183, 184].

Uterine artery embolization (UAE), an interventional technique used to manage various gynecological disorders, has the potential to cause POI by compromising the vascular supply to the ovary [185, 186]. In a randomized controlled trial of women undergoing either hysterectomy or UAE, both groups were found to have a significant increase in FSH compared to baseline and a significant reduction in AMH levels compared to the age expected levels at the end of the 24-month follow-up [186]. The effect of UAE on ovarian reserve has been found to be equal to that of hysterectomy and myomectomy [186–189]. POI can occur following surgery for bilateral endometriomas [190–192]. The frequency of this complication is estimated to be 2.4 %, but further confirmation is warranted. It is not known whether postsurgical ovarian dysfunction is attributable to the underlying clinical problem that prompted the cystectomy or endometrioma or whether surgery itself is a contributing factor. More studies are necessary to resolve this.

Conclusion

The etiology of POI is clearly heterogeneous and often largely unknown. The advances in genomic, environmental, and biomarker research will give us a better mechanistic understanding of the basic regulation of ovarian development and function as well as pathologic decline in the ovarian reserve. The future holds great promise for having a deeper understanding of the origins of POI.

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