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Familial Premature Ovarian Failure

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SUMMARY

Premature menopause, ovarian failure younger than 40 years of age, is relatively rare but may preclude childbearing for some women who delay attempts at fertility. We present five kindreds in which a genetic association for premature ovarian failure is strongly suggested. Transmission is either autosomal or (less likely) X-linked dominant in these examples. Chromosomal abnormalities, history of diseases, and toxic chemical or viral exposures previously associated with premature ovarian failure could not be demonstrated in these women. This suggests that these kindreds all represent familial idiopathic premature ovarian failure. These data support the need for menopausal histories on both sides of the family for women seeking to postpone reproduction, as well as for patients with ovarian failure.

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INTRODUCTION

Epidemiologic data have confirmed that the average age of menarche has decreased [1] and have suggested that the average age of menopause may have increased from the middle 1800s to the present time [2, 3]. However, the suggested increase in the age of menopause appears to reflect methodological errors of earlier studies, including the fact that older women tend to understate their age of menopause [4–6]. A broad range of epidemiological studies suggest that the mean age of menopause is invariant in time and by race and approximately 50 years of age [2–6].

In premature ovarian failure (POF), there is the advent of secondary amenorrhea with elevated gonadotropins occurring prior to age 40, although some authors have used an age limit of 35 years [7, 8]. Because most women cease menstruation between the ages of 45 and 55, with less than 2% experiencing menopause younger than 40, the threshold of 40 years of age appears to be an appropriate definition for premature ovarian failure [4]. In fact, menopause before the age of 45 is unusual, and occurs in only 15% of women [4]. Hypergonadotropic-hypogonadal amenorrhea is usually reflective of ovaries that are depleted of ova, although an ovary that is no longer sensitive to gonadotropins (resistant ovary syndrome) may be present and masquerade as true failure [9–14].

Although premature ovarian failure is usually idiopathic, sometimes it may be due to a known genetic disorder associated with rapid atresia of follicles (e.g., Turner variants) [15–17], formation of a small number of follicles (e.g., galactosemia) [18], or destruction of germ cells in pre- or postpubertal life by viral infections [19], drugs [20, 21], or radiation [21, 22]. In addition, certain immune disorders such as the presence of antiovarian antibodies and myasthesia gravis are known to produce premature ovarian failure [23, 24], although attempts to associate certain HLA antigens with POF have so far been unsuccessful [25]. Prior to the onset of POF, women appear to have a normal menstrual history, age of menarche, and fertility. Although approximately 2% of women in the population have menopause before 40, there have been reports of only two kindreds in which heritability of POF is suggested [26, 27]; however, a familial association for POF has been suggested by other authors [8, 28]. This paper reports five additional kindreds in which idiopathic premature ovarian failure appears to be genetic [26, 29].

Although POF has not been previously classified as a Mendelian disorder [30], the pedigrees presented here provide strong evidence for Mendelian inheritance in some cases of POF. Sensitivity to the familial nature of some forms of premature menopause should allow prior counseling of women at risk for premature ovarian failure regarding the possible necessity for early childbearing. Our experience also highlights that POF may be inherited either maternally or paternally; thus, in POF, a menstrual history on relatives from both parental lines should be obtained.

MATERIALS AND METHODS

All studied patients had evaluations that included thorough physical exams, pelvic ultrasound examinations, and cytogenetic, immune, and endocrine studies (table 1). Established radioimmunoassays were used to measure circulating levels of leutinizing hormone,

TABLE 1

EVALUATION OF PATIENTS WITH FAMILIAL POF OVARIAN FAILURE

PATIENT	PHYSICAL EXAMINATION	OVARIAN ULTRASOUND	OVARIAN BIOPSY	GONADOTROPINS		HORMONES		ANTIBODIES			KARYOTYPE BANDING	ASSOCIATED DISEASE	CHEMICAL EXPOSURE
				LH	FSH	E_2	Prog	Ovary	Thyroid	Adrenal			
1. A	NL	NL	...	↑	↑	↓	↓	Neg	Neg	Neg	46,XX,nl	None	None
B	NL	NL	...	↑	↑	↓	↓	Neg	Neg	Neg	46,XX,nl	None	None
2. C	NL	NL	Afollicular	↑	↑	↓	↓	Neg	Neg	Neg	46,XX,nl	None	None
3. D	NL	NL	...	↑	↑	↓	↓	Neg	Neg	Neg	46,XX,nl	None	None
E	NL	...	...										
4. F	NL	NL	...	NL	NL	↑	↑	Neg	Neg	Neg	46,XX,nl	None	None
G	NL	NL	...	↑	↑	↓	↓	Neg	Neg	Neg	46,XX,nl	None	None
5. H	NL	NL	...	↑	↑	↓	↓	Neg	Neg	Neg	46,XX,nl	None	None

follicle-stimulating hormone, estradiol, and progesterone [31]. Cytogenetic analysis of all patients was performed on venous blood lymphocytes using Giemsa-trypsin-banding at the 850-band level and counts of at least 50 metaphase preparations per patient.

Assessment for autoimmune antibodies were performed as follows: All sera were obtained by drawing fresh blood in a nonheparinized tube and separating the clot from serum by centrifugation. Positive serum controls were obtained from patients with endocrinopathies due to antibodies to the ovary, adrenal, or thyroid (B. Jenson, unpublished results, 1984), and negative serum controls were taken from hospital nurses and technicians without prior history of endocrine disease. All sera were diluted 1:4, 1:8, and 1:16 for screening. If positive, further dilutions were carried out for titering.

Commercially prepared fluorescein isothiocyanate (FITC) monospecific antisera against human IgG, IgA, IgM, and polyvalent antisera (IgG, IgA, and IgM) were used as the conjugate. These reagents were titrated on murine kidney frozen tissue sections (6–8 microns in thickness) against known antinuclear antibody positive sera obtained from the Center for Disease Control, Atlanta, Georgia.

All slides were washed with phosphate-buffered saline (PBS) for 5 min, and a drop of each serum dilution placed over the appropriate tissue and incubated in a moist chamber at room temperature for 30 min. Slides were then rinsed in a gentle stream of PBS followed by two washes (7 min each) of PBS. A drop of fluoresceinated conjugate at optimal dilutions was then placed on the appropriate tissue, incubated at room temperature for 30 min, washed twice in PBS, and followed by a gentle rinse in distilled water and air-dried. Mounting media (glycerol at pH 7.6) was then applied and the slide coverslipped. Each slide was then read with a fluorescent microscope as positive or negative by two independent observers [32].

CASE REPORTS

Kindred 1

In an Ashkenazi Jewish family, two first cousins developed POF at ages 33 and 34, respectively (fig. 1). Their paternal aunt, grandmother, and great aunt all developed ovarian failure at age 32. Both fathers would have to be considered obligate carriers. The two probands (A, B) had normal physical and pelvic ultrasound examinations. Endocrine studies documented hypergonadotropic-hypogonadism. No antiovarian antibodies were demonstrated. Careful karyotypic examinations by Giemsa-banding failed to reveal any subtle X-chromosome abnormalities, and all karyotypes were 46,XX.

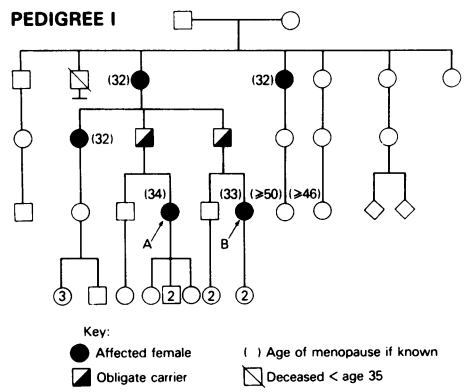

FIG. 1.—Ashkenazi Jewish family. Two first cousins (*A* and *B*) developed premature ovarian failure at ages 33 and 34, respectively. Their paternal aunt, grandmother, and great aunt all had menopause at age 32. By our reasoning, the two fathers would have to be considered obligate carriers of the trait.

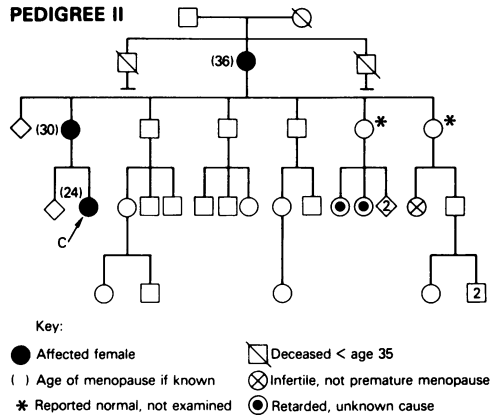

FIG. 2.—Hispanic family. The proband (*C*) developed ovarian failure at age 24. Her mother had menopause at age 30, and her grandmother, at age 36.

Kindred 2

In a Hispanic kindred, in 3 generations of women, ovarian failure occurred at ages 36, 30, and 24 (fig. 2). The proband, who failed at age 24, had a normal physical exam and ultrasound. Studies showed elevated gonadotropins, normal karyotype, and no antiovarian antibodies. This patient underwent laparoscopic ovarian biopsy in which no follicles were seen.

Kindred 3

In a white Anglo-Saxon-Protestant kindred, the proband failed at age 30—close to the age of POF of her monozygotic twin sister (fig. 3). Their mother failed at age 32. Information was not available about the grandmother who died in an accident at age 33. The proband was aware of the family trait and sought advice for her premenarchal daughters.

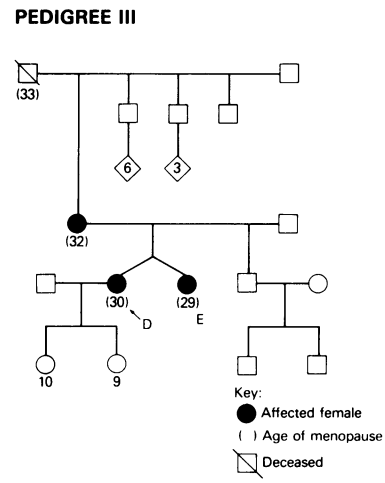

FIG. 3.—White Anglo-Saxon-Protestant family. The proband (*D*) and her monozygotic twin sister (*E*) failed at ages 30 and 29, respectively. Their mother had menopause at age 32. The grandmother died in an accident at age 33, and no information is available about her menstrual status at that time.

Kindred 4

In an Italian kindred, the proband, a 27-year-old primipara, who herself had been exposed to diethylstilbesterol in utero, sought counseling about future pregnancies. Her mother had ovarian failure at age 39, and her maternal grandmother, at age 31. As with the previous kindreds, evaluation of the mother and daughter revealed normal physical examinations, pelvic ultrasounds, and 46,XX karyotypes. There were no antiovarian or other antibodies. Endocrine studies revealed hypergonadotropic-hypogonadism in the mother.

Kindred 5

In another Hispanic pedigree, the proband had normal periods until age 36 when they became irregular, menses ceased at age 37, and she had menopausal symptoms. Two sisters became menopausal at ages 25 and 33, and their mother had menopause at age 28. Physical exams, ultrasound, karyotypic analysis, and antiovarian antibodies were all negative.

DISCUSSION

The five families presented here suggest that familial idiopathic premature ovarian failure may not be very rare. Clearly, premature ovarian failure must be recognized as a heritable entity. Our pedigrees were from several different ethnic backgrounds, and transmission can be through either maternal or paternal relatives. Transmission is probably autosomal dominant, although until a female-male-male-female pedigree is ascertained, dominant X linkage cannot be excluded. No underlying pathogenesis is evident, but prospective counseling of individuals at risk including asymptomatic males who could be carriers seems necessary.

A growing body of data demonstrates that several human diseases are associated with premature or early ovarian failure. Women with galactosemia have premature ovarian failure [18]. Indeed, in animal models, prenatal treatment with galactose can impair ovarian development and produce a smaller number of oocytes in the ovary [33].

Early ovarian failure is also associated with the presence of antiovarian antibodies both in women and experimental animals [14, 23, 24]. In mice, a model for immune modulation of ovarian lifespan has been explored in athymic nude mice and in mice treated with neonatal thymectomy [12, 14]. Cigarette smoking has also been associated with an early cigarette-dose-dependent ovarian failure [34]. Extensive experiments have demonstrated that benzo(a)pyrene, one component of cigarette smoke, and some benzo(a)pyrene metabolites are potent ovotoxins in rodents [35]. Many antitumor drugs are also ovotoxins, producing premature ovarian failure by increasing the rate of atresia as well as by direct oocyte destruction [20, 21]. In all of these families, however, there was no evidence that any pre-existing disease state or xenobiotic exposure was associated with the observed premature ovarian failure.

There are several interesting experiments using rodents that have described strain differences in oocyte number and rate of atresia [36]. The genetics of this effect has also been explored, although not in great detail. A mathematical model has been developed to explore the relationship between oocyte number at birth and rate of atresia on the age of menopause. That model suggests that the rate

of atresia, rather than oocyte number at birth, is more important in determining the age of menopause [37]. In these families, therefore, genetic alterations in the rate of atresia may be the factor producing the idiopathic premature ovarian failure.

Information from these pedigrees emphasizes the importance of obtaining menopausal histories on both sides of the family for all women who seek to postpone pregnancy beyond the age of 25. In our series, most women failed at approximately the same age as their closest relatives, but there were notable exceptions. Because of apparently high penetrance and lack of a specific marker, we recommend that pregnancy in women at risk for premature ovarian failure not be delayed beyond the age of menopause in near relatives, and almost surely not beyond age 30.

In the absence of a specific cytogenetic or other marker for heritable form(s) of POF, one can only speculate about the risk to any individual in the instance when only one other female in her family has undergone POF. There is insufficient data available to help in counseling such women who may be at risk for premature ovarian failure. For these women, it is not known if the likelihood of premature failure might be higher than in the general population at any given age.

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