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Premature ovarian failure

Deepti Goswami and Gerard S.Conway[1]

Department of Endocrinology, The Middlesex Hospital, London W1T 3AA, UK

[1]To whom correspondence should be addressed. E-mail: g.conway@ucl.ac.uk

Premature ovarian failure (POF) causing hypergonadotrophic hypogonadism occurs in 1% of women. In majority of cases the underlying cause is not identified. The known causes include: (a) Genetic aberrations, which could involve the X chromosome or autosomes. A large number of genes have been screened as candidates for causing POF; however, few clear causal mutations have been identified. (b) Autoimmune ovarian damage, as suggested by the observed association of POF with other autoimmune disorders. Anti-ovarian antibodies are reported in POF by several studies, but their specificity and pathogenic role are questionable. (c) Iatrogenic following surgical, radiotherapeutic or chemotherapeutic interventions as in malignancies. (d) Environmental factors like viral infections and toxins for whom no clear mechanism is known. The diagnosis is based on finding of amenorrhoea before age 40 associated with FSH levels in the menopausal range. Screening for associated autoimmune disorders and karyotyping, particularly in early onset disease, constitute part of the diagnostic work-up. There is no role of ovarian biopsy or ultrasound in making the diagnosis. Management essentially involves hormone replacement and infertility treatment, the only proven means for the latter being assisted conception with donated oocytes. Embryo cryopreservation, ovarian tissue cryopreservation and oocyte cryopreservation hold promise in cases where ovarian failure is foreseeable as in women undergoing cancer treatments.

Key words: autoimmune ovarian damage/environmental factors/genetic aberrations/hormone replacement/premature ovarian failure

Introduction

The average age for menopause in Western populations of women is approximately 51 years. Premature ovarian failure (POF) or premature menopause refers to development of amenorrhoea due to cessation of ovarian function before the age of 40 years. The diagnosis is based on elevated FSH levels in menopausal range (usually above 40 IU/l) detected on at least two occasions a few weeks apart (Conway, 2000).

Women with POF suffer from anovulation and hypoestrogenism and present with primary or secondary amenorrhoea, infertility, sex steroid deficiency and elevated gonadotrophins (Kalantaridou *et al.*, 1998). The condition affects approximately 1% of women, occurring in 10–28% of women with primary amenorrhoea and 4–18% in those with secondary amenorrhoea (Coulam *et al.*, 1986; Anasti, 1998). Early loss of ovarian function has significant psychosocial sequelae and major health implications (Taylor, 2001); nearly 2-fold age-specific increase in mortality rate has been reported (Snowdon *et al.*, 1989).

A wide spectrum of pathogenic mechanisms may lead to the development of POF including chromosomal, genetic, autoimmune, metabolic (galactosaemia), infectious (mumps) and iatrogenic (anticancer treatments) causes. In a large proportion of cases no cause is found and they are classified as idiopathic or karyotypically normal spontaneous ovarian failure (Laml *et al.*, 2000; Pal and Santoro, 2002); whereas up to 30% of cases may have an autoimmune cause (Conway *et al.*, 1996).

In the embryo, germ cells migrate from the urogenital ridge to the primitive ovary where they proliferate to form 3.5×10^6 oocytes in each ovary by about 20 weeks of intrauterine life. Most of these germ cells are destroyed through apoptosis (Hsueh *et al.*, 1994, 1996). The ovary is endowed with a fixed number of primordial follicles at the time of birth, about 1×10^6 in each ovary. This number steadily dwindles throughout life as a result of atresia and recruitment towards ovulation (Gosden and Faddy, 1998). Fewer than 500 of the original 7×10^6 (0.007%) oocytes are released in the entire reproductive life span of a woman.

In idiopathic POF, there may be involvement of as yet unknown mechanisms affecting the rate of oocyte apoptosis (Morita and Tilly, 1999). This may lead to a reduced complement of oocytes in the ovaries at birth or accelerated atresia. Using ultrasound, follicles have been reported in up to 40% of POF patients (Mehta *et al.*, 1992). However, ultrasonography or ovarian biopsies are not helpful in prognostication of future ovulation and fertility.

In a recent thought provoking article, Johnson *et al.* (2004) have challenged the concept that each woman is endowed with an irreplenishable number of gametes in the ovary. Through three different sets of experiments they came to a conclusion that ovarian germ cells are a dynamic population and undergo constant renewal. Such a novel concept that challenges the central dogma in reproductive sciences is likely to stir a flurry of debate and to be followed by further studies exploring the issue.

Genetic causes of POF

Most cases of POF are idiopathic, and the underlying mechanisms are largely unknown; however, observation of familial cases with POF indicates the role of genetic aberrations in its pathogenesis (Conway, 1997). Though genetic defects mostly involve the X chromosome, an increasing number of studies have documented autosomal involvement (Table I).

Several methods have been used to elucidate the cause of POF—transgenic 'knockout' animals, mutation screening of candidate genes in affected women, analysing pedigree data in linkage analysis and lately, population genetics. Various genetic mechanisms implicated in pathogenesis of POF include reduced gene dosage and non-specific chromosome effects that impair meiosis. These can lead to ovarian failure by causing decrease in the pool of primordial follicles, increased atresia of the ovarian follicles due to apoptosis or failure of follicle maturation.

Table I. Genes implicated in POF

Categories	Chromosome	Gene	Gene locus
Mutations identified	X chromosome genes	*FMR1*	Xq27.3
		FMR2	Xq28
		BMP15	Xp11.2
	Autosomal genes	*FOXL2*	3q22–q23
		FSHR	2p21–p16
		LH receptor	2p21
		FSH beta variant	11p13
		LH beta	19q13.32
		Inhibin A	2q33–q36
		GALT	9p13
		AIRE	21q22.3
		EIF2B2, *-4*, and *-5*	14q24.3, 2p23.3, 3q27
		NOGGIN	17q22
		POLG	15q25
Candidate genes	X chromosome genes	*DIAPH2*	Xq22
		DFFRX	Xp11.4
		XPNPEP2	Xq25
		ZFX	Xp22.3–p21.3
		FSHPRH1	Xq22
		XIST	Xq13.2
	Autosomal genes	*WT1*	11p13
		ATM	11q22.3
Mutations not identified	X chromosome genes	*AT2*	Xq22–q23
		c-kit	4q12
		SOX3	Xq26–q27
	Autosomal genes	*MIS*	19p13.3–13.2

Familial POF

The overall incidence of familial cases among women with POF seems to be low, around 4%, though there are conflicting data from various studies (Starup and Sele, 1973; Conway *et al.*, 1996). Epidemiological studies suggested a higher incidence of approximately 30% (Cramer *et al.*, 1995; Torgerson *et al.*, 1997). In a large Italian study, Vegetti *et al.* (1998) showed that in one-third of the idiopathic POF patients this condition was inherited. A subsequent study reported the incidence of familial cases to be 12.7% (van Kasteren *et al.*, 1999). The variation between reported incidences might be explained by differences in the definition of POF and the idiopathic form, by differences in population recruitment and by selection and recall bias.

Pedigree studies on affected families show a mode of inheritance suggestive of autosomal dominant sex-limited transmission or X-linked inheritance with incomplete penetrance (Coulam *et al.*, 1983; Mattison *et al.*, 1984; Bondy *et al.*, 1998; Christin-Maitre *et al.*, 1998; Vegetti *et al.*, 1998). Female sex preponderance was found in siblings of 30 families of idiopathic POF suggesting that an X chromosome defect is inherited as a major cause of ovarian failure (Davis *et al.*, 2000).

An adequate family history can distinguish between familial or sporadic POF. The risk of female relatives developing POF may be high in familial POF as compared to sporadic cases. Early diagnosis of familial predisposition permits prediction of impending menopause and susceptible women can be guided to achieve their reproductive goals by timely planning of pregnancy (Davison *et al.*, 1998).

When considering the following list of genetic associations of POF, it is obvious that the strength of evidence linking each anomaly with POF is variable. In some instances there is a statistical association with the anomaly also occurring in normal women [Fragile site mental retardation 1 gene (*FMR1*)] (Cronister *et al.*, 1991); in others only a single case represents the link (Noggin) (Kosaki *et al.*, 2004). Included here are conditions where the genetic link is indirect such as galactose-1-phosphate uridyltransferase (GALT), where biochemical damage of the ovary occurs and autoimmune regulator (AIRE) which triggers autoimmune damage.

X chromosome defects

Familial as well as non-familial X chromosome abnormalities have been described in women with POF. These abnormalities range from a numerical defect like complete deletion of one X (Turner's syndrome) and trisomy X to partial defects in form of deletions, isochromosomes and balanced X autosome translocations (Zinn, 2001).

X monosomy

Complete or near complete absence of one X chromosome, as seen in Turner's syndrome leads to ovarian dysgenesis characterized by primary amenorrhoea, short stature and characteristic phenotypic features.

One X chromosome is inactivated in each cell of female mammals for dosage compensation of X-linked genes between

males and females (Lyon, 1994). However, several X-linked genes escape inactivation and are vital for normal function of X chromosome (Zinn *et al.*, 1993; Zinn and Ross, 1998). Two functioning X chromosomes are therefore necessary for normal ovarian function.

In the presence of only one X chromosome in Turner's syndrome, ovarian follicles degenerate by birth. This may be the result of a lack of diploid dosage of one or more vital genes, both alleles of which are active in oogenesis. Histological data indicate that oogenesis proceeds normally in these individuals until diplotene oocytes begin to be incorporated into nascent follicles. There is a subsequent block to production of complete follicles manifesting as fetal follicular atresia. In 80% of cases, the paternally derived X is lost (Loughlin *et al.*, 1991).

Cytogenetic data indicate that most Turner's syndrome physical features map to the short arms of the X (Xp) and Y (Yp) chromosomes (Kalousek *et al.*, 1979; Fryns *et al.*, 1981; Goldman *et al.*, 1982; Jacobs *et al.*, 1990; Temtamy *et al.*, 1992; Ogata and Matsuo, 1995) and result from reduced dosage of genes on the short arm of the X chromosome. Further investigations narrowed down the search for the affected chromosomal segment to the 2.6 Mb Xp–Yp pseudoautosomal region. Zinn *et al.* (1998) using a statistical method to examine genotype/phenotype relations mapped Turner's syndrome traits, including POF, to a critical region in Xp11.2–p22.1. X and Y copies of the region are identical, and all genes within this region appear to escape X inactivation (Rappold, 1993). Eighteen such candidate genes have been reported (Lahn and Page, 1997) and more are likely to exist.

Trisomy X

It is commonly believed that X trisomy, which affects 1 in 900 women in general population, has no significant effect on fertility; however, association with hypergonadotrophic POF has been reported. Jacobs *et al.* (1959) first described triple X syndrome with POF in 1959. Further documentation of associated ovarian failure in this rare sex chromosome aneuploidy is in form of occasional case reports (Menon *et al.*, 1984; Itu *et al.*, 1990; Holland, 2001). Its relative prevalence among women with POF is not known (Lucas *et al.*, 1971). In one reported series, 2 of 52 (3.8%) patients with POF had the triple X syndrome (Goswami *et al.*, 2003). POF has also been reported in a girl with 48XXXX (Rooman *et al.*, 2002). The underlying mechanism could be analogous to that observed among patients with Klinefelter's syndrome.

Mosaicism

45X/46XX and 45X/47XXX: These individuals carry mixed germ lines and manifest phenotypic abnormalities and POF similar to monosomy X but 12% are reported to menstruate (Simpson, 1975).

Deletions

X chromosome deletions associated with POF are more common than translocations. Deleted X chromosomes necessarily leave a portion of the normal X unpaired and isodicentrics probably interfere with pairing, resulting in atresia of oocytes.

While deletions commonly involve the short arm of the X chromosome (Xp), the fraction of deletions that show POF is far higher in the Xq13–25 region (Simpson and Rajkovic, 1999). Deletions at Xp11 result in 50% primary amenorrhoea and 50% secondary amenorrhoea. Deletions at Xq13 usually produce primary amenorrhoea. A phenotypic difference has also been noted between distal deletions, associated with preserved ovarian function, and proximal deletions, associated with ovarian failure. However, the relation is imperfect, since large deletions that remove the whole critical region for POF, in Xq21, were found not to be associated with ovarian failure (Merry *et al.*, 1989).

Translocations

In contrast to generally neutral effects of balanced autosomal translocations, balanced X/autosomal translocations very often lead to POF with more than 100 cases of post-pubertal women with X/autosomal balanced translocations reported (Therman *et al.*, 1990).

The deleterious effect on ovarian function results from X breakpoints that fall on the long arm between Xq13 and Xq26. A 'critical region' for normal ovarian function has therefore been proposed for Xq13–q26 (Sarto *et al.*, 1973; Phelan *et al.*, 1977; Therman *et al.*, 1990). Within this region the most frequent breakpoints involve two specific regions defined as POF loci. POF1 Xq26–qter (Tharapel *et al.*, 1993) and POF2 Xq13.3–Xq21.1 (Powell *et al.*, 1994). These are separated by a short region in Xq22. It has been suggested that chromosome dynamics in the region could be sensitive to structural changes and the resulting unpaired chromosome provokes a pachytene checkpoint during meiosis leading to oocyte apoptosis (Burgoyne and Baker, 1984).

Distal deletions involving the POF1 locus are associated with POF at ages 24–39 years (Krauss *et al.*, 1987; Tharapel *et al.*, 1993). Various molecular techniques and bioinformatics have been used to map the POF1 locus and identify the putative genes for POF (Davison *et al.*, 2000).

The translocations involving the POF2 locus cause POF at an earlier age of 16–21 years (Powell *et al.*, 1994). Sala *et al.* mapped the X autosome translocations in 11 women with POF to POF2 locus involving a 15 Mb YAC contig, with the majority of the breakpoints localized along the whole Xq21 region between loci DXS233 and DXS1171 (Sala *et al.*, 1997). They suggested that a single gene is unlikely to be responsible for ovary development and/or oogenesis rather several genes may be present along the critical region and they may be interrupted by the balanced translocations. However, it must be noted that many breakpoints on the X chromosome are not associated with POF (Therman *et al.*, 1990).

POF *genes on the X chromosomes*

Molecular investigations in women with POF and experiments on transgenic animal models have led to the identification of a number of candidate genes for POF. It is assumed that POF may result from mutations involving these genes. Such mutations have been identified in $<10\%$ of POF cases (Harris *et al.*, 2002) and functions of many of these genes are not known. Therefore, none is accepted as a genetic marker for POF.

FMR1

The *FMR1* gene is situated in Xq27.3, outside the Xq POF critical region. The mutations in this gene can lead to expansion of

a trinucleotide repeat located at its 5′ UTR region. Four types of alleles are identified based on the number of repeats: normal (6–40), grey-zone (41–60), premutated (61–200) and fully mutated (>200). The full mutation is associated with fragile X mental retardation syndrome, the most common form of inherited mental retardation.

The *FMR1* gene is expressed in oocytes and encodes an RNA-binding protein involved in translation. Rife *et al.* conducted immunohistochemical fragile X mental retardation protein (FMRP) studies in a full mutated female fetus. In the ovary samples, FMRP expression was seen in all germ cells surrounded by FMRP-negative paragranulosa and interstitial cells. The Mullerian epithelium of the fetal Fallopian tube was continuously positive in the control case, whereas the full mutation carrier showed a discontinuous patchy pattern (Rife *et al.*, 2004). In a study of murine *FMR1* expression pattern, enhanced levels were seen in the fetal ovary while in the mature ovary no specific *FMR1* expression signal was found. As proliferation of oogonia takes place in fetal ovary, it was suggested that *FMR1* serves a special function during germ cell proliferation (Bachner *et al.*, 1993).

POF was first noted as an unexpected phenotype among heterozygous carriers of the fragile X premutation in the early 1990s. Subsequent studies showed that *FMR1* trinucleotide expansions in the premutation range of 50–200 repeat units, but not full mutations, are associated with POF (Cronister *et al.*, 1991; Schwartz *et al.*, 1994, Partington *et al.*, 1996). The underlying mechanism for this association is not clear.

Presently, there exists firm evidence for a significant association between fragile X premutation carrier status and premature menopause as shown both by the analysis of women carrying the premutated allele (Cronister *et al.*, 1991) and by the screening of women affected by POF (Conway *et al.*, 1995, 1998; Vianna-Morgante *et al.*, 1996; Murray *et al.*, 1998). The results of an international collaborative study examining premature menopause in 760 women from fragile X families showed that 16% of the 395 premutation carriers had experienced menopause prior to the age of 40 compared with none of the 238 full mutation carriers and one (0.4%) of the 237 controls (Allingham-Hawkins *et al.*, 1999).

The incidence of *FRAXA* premutations has been shown to vary among women with POF depending on the proportion of sporadic and familial cases. Thirteen per cent of pedigrees with the familial POF and 3% of women with the sporadic form of POF have been found to carry *FRAXA* premutations compared with an expected prevalence of 1:590 (Conway *et al.*, 1998). Hundscheid *et al.* (2000) reported that carriers who received the premutation from their fathers were at a higher risk of POF (28%) than those who received the premutation from their mothers (4%) suggesting that POF may be limited to premutations that are paternally inherited. However, this finding was not substantiated in subsequent studies (Murray *et al.*, 2000; Vianna-Morgante and Costa, 2000). From the practical point of view, *FRAXA* premutations are certainly worth seeking in those with familial POF in order to enable genetic counselling and hopefully, limiting the transmission of Fragile X syndrome to future generations. Some units might also consider screening for *FRAXA* premutations in sporadic cases.

Fragile site, folic acid type, rare (*FRAXE*)*/fragile site mental retardation 2 gene* (*FMR2*)

In patients who have the cytogenetic changes of fragile X syndrome but who are *FMR1*-mutation negative, Sutherland and Baker (1992) identified a second site of fragility, symbolized *FRAXE*. It was found to lie approximately 150–600 kb distal to the *FRAXA* site at Xq28 and to be folate sensitive.

An excess of small alleles with fewer than 11 repeats at the *FRAXE* locus were found in women with POF (Murray *et al.*, 1998). In their subsequent study involving a cohort of 209 women with POF, these were traced to three females with cryptic deletions in *FMR2*, the gene associated with *FRAXE*. They proposed that microdeletions within *FMR2* may be a significant cause of POF, being found in 1.5% of women with the condition, and in only 0.04% of the general female population (Murray *et al.*, 1999).

Bone morphogenetic protein 15 gene, BMP15 *(GDF-9B)*

Bone morphogenetic proteins (BMPs) are extracellular signalling proteins belonging to transforming growth factor-β superfamily, which also includes growth/differentiation factors (GDFs). *BMP15* is an oocyte-specific GDF that stimulates folliculogenesis and granulosa cell growth and is expressed in oocytes during early folliculogenesis. It shares a coincident expression pattern with the closely related mouse *GDF-9* gene, which is essential for normal folliculogenesis in mice (Dong *et al.*, 1996).

BMP15 gene maps to Xp11.2 within the Xp POF critical region (Dube *et al.*, 1998; Aaltonen *et al.*, 1999). It is presumably expressed from both X chromosomes in oocytes, and could potentially show a gene dosage effect.

Di Pasquale *et al.* (2004) reported heterozygous mutation in *BMP15* in two sisters with POF presenting with primary amenorrhoea. The mutation involved A to G transition at base pair 704 of the *BMP15* gene that resulted in a tyr235-to-cys (Y235C) amino acid substitution. The father was a hemizygous carrier, whereas the mother had a wild type BMP15 coding sequence. The mutation was found in a highly conserved part of the *BMP15* gene encoding the propeptide region and was not found in 210 alleles from 120 ethnically matched controls. This condition represents an unusual example of X-linked human disease exclusively affecting heterozygous females who inherited the genetic alteration from the unaffected father.

Autosomal involvement in POF

Autosomal translocations

Autosomal translocations are uncommon in women with POF; most reports of translocations document X/autosome balanced translocations, with no common autosomal breakpoint. Burton *et al.* (2000) reported translocation between two autosomes, chromosomes 2 and 15–46; XX,t(2;15) (q32.3;q13.3) in a woman with POF. They also reviewed three other cases of autosomal translocations in women with POF (Hens *et al.*, 1989; Kawano *et al.*, 1998).

Autosomal genes

POF is seen in several disorders involving autosomal genes.

Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES)

This autosomal dominant genetic condition, first described by Vignes in 1889, is characterized by complex eyelid malformation. Two forms are described—type I with POF in affected females and type II not associated with POF (Zlotogora *et al.*, 1983). POF related infertility is inherited as an autosomal dominant sex-limited trait in these families.

Amati *et al.* (1996) showed that the BPES-I associated with POF maps to 3q22–q23, as does type II. Crisponi *et al.* (2001) cloned putative winged helix/forkhead transcription factor gene, *FOXL2* that is mutated in both BPES types I and II. *FOXL2* appears predominantly in the ovary in adult humans and its corresponding gene is the first human autosomal gene in which dominant mutations have been implicated in ovarian maintenance and differentiation. Recently, a human *FOXL2* mutation database was published that included 135 intragenic mutations and variants of *FOXL2* (Beysen *et al.*, 2004).

Harris *et al.* (2002) found two *FOXL2* variants with a presumed pathogenic effect in 2 of 70 patients with non-syndromic POF. However, other studies involving phenotypically normal women affected by POF did not reveal any mutations indicating that mutations in the *FOXL2* coding region are rarely associated with non-syndromic POF (De Baere *et al.* 2001, 2002; Bodega *et al.*, 2004).

FSH receptor (FSHR)

FSH has an important role in the recruitment and development of ovarian follicles during the folliculogenesis. *FSHR* gene maps to 2p21–p16.

Aittomaki *et al.* (1995) reported a missense mutation of the *FSHR* in six multiplex families in Finnish population. The mutation at position 566 of exon 7 of the *FSHR* gene resulted in a substitution of a valine for alanine at residue 189 and was manifest as hypergonadotrophic ovarian dysgenesis. Transfection experiments showed that the mutation leads to a dramatically reduced binding capacity and cyclic AMP production after FSH stimulation in spite of apparently normal binding affinity in cells expressing the mutated receptor protein. Other novel mutations involving *FSHR* have also been reported (Touraine *et al.*, 1999; Doherty *et al.*, 2002; Meduri *et al.*, 2003).

In the UK and in other populations, mutations of the *FSHR* gene were found to be rare in women with POF or resistant ovary syndrome (Layman *et al.*, 1998; Conway *et al.* 1999; Takakura *et al.*, 2001; Sundblad *et al.*, 2004).

An earlier study of *FSHR* genes in patients with POF revealed the existence of polymorphisms (Whitney *et al.*, 1995), which do not appear to have pathophysiological significance with regard to ovarian function (Liu *et al.*, 1998; Conway *et al.*, 1999).

LH receptor

LH receptor maps to 2p21. Latronico *et al.* (1996) reported a woman with amenorrhoea and ovarian resistance to LH who had a homozygous substitution of thymidine for cytosine at position 1660 of the LH receptor gene that resulted in abnormal truncation of the receptor. The affected male siblings had Leydig cell hypoplasia.

FSH beta-subunit variant

Gonadotrophins (FSH and LH) and intact hypothalamo–pituitary–ovarian axis are vital for normal ovarian functions. Severe gonadotrophin receptor defects or defects in post-receptor mechanisms may contribute to hyposensitivity or early atresia of follicles leading to POF (Conway, 1996). Matthews *et al.* reported a case with primary amenorrhoea and infertility due to a mutation in the gene (map locus 11p13) encoding β-subunit of FSH (Matthews *et al.*, 1993). However, in another study no mutations were found in the gene for FSH-β in 18 women with POF that would diminish binding of FSH to target cells (Layman *et al.*, 1993).

LH beta-subunit variant

Takahashi *et al.* (1999) have reported an increased prevalence of a variant LH with a mutant beta subunit in women with POF (18.4%) as compared to controls (8.5%). In a subsequent study involving women with ovulatory disorders, they reported five novel silent polymorphisms of LH-β subunit using PCR-amplified gene sequencing (Takahashi *et al.*, 2003).

Inhibins

Inhibin, a glycoprotein, is a gonadal hormone that inhibits synthesis and secretion of pituitary FSH. It has been considered as a strong candidate gene in the aetiology of POF.

An elevated serum FSH level and low inhibin B level in the early follicular phase has been reported to relate with reproductive ageing (Soules *et al.*, 1998) and diminished ovarian reserve (MacNaughton *et al.*, 1992). The presence of low serum inhibin levels in POF further supports its role in the pathophysiology of POF (Petraglia *et al.*, 1998).

One variation of INH alpha gene, G769A, has been associated with POF (Shelling *et al.*, 2000; Marozzi *et al.*, 2002; Dixit *et al.*, 2004), the prevalence of which may vary in different populations from 0–11% (Dixit *et al.*, 2004; Jeong *et al.*, 2004).

GALT *gene*

Impairment in GALT metabolism leads to galactosaemia, a rare autosomal recessive disorder. The *GALT* gene maps to chromosome 9p13. POF is reported in 60–70% of female patients with galactosaemia (Waggoner *et al.*, 1990; Laml *et al.*, 2002). Galactosaemia induced decrease in initial number of oogonia, ovarian follicular damage in fetal life induced by galactose or its metabolites and defective gonadotrophin function and could be involved in pathogenesis of POF.

AIRE *gene*

Mutations in the *AIRE* gene, responsible for autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome, can lead to ovarian insufficiency. The gene maps to chromosome 21q22.3. More than 40 *AIRE* gene mutations are known (Wang *et al.*, 1998; Laml *et al.*, 2002). In a survey of 72 patients with APECED, hypogonadism was present in 60% of patients aged >12 years (Perheentupa, 1996).

Eukaryotic initiation factor 2B

A rare association of ovarian failure with white-matter abnormalities on cerebral magnetic resonance imaging has

been observed (Schiffmann *et al.*, 1997). These cerebral abnormalities are similar to those in childhood ataxia with CNS hypomyelination (CACH)/vanishing white-matter leukodystrophy (Schiffmann *et al.*, 1994; van der Knaap *et al.*, 1997). Fogli *et al.* (2003) tested eight karyotypically normal patients from seven families with association of ovarian failure with white-matter abnormalities for mutations in the five subunits (α–ε) of the eukaryotic translation initiation factor 2B (eIF2B). They found mutations in three of the five *EIF2B* genes (*EIF2B2*, *-4* and *-5*, which map to 14q 24.3, 2p23.3 and 3q27, respectively) that were earlier shown to cause childhood ataxia with central nervous system hypomyelination/vanishing white-matter disease leukodystrophy (Leegwater *et al.*, 2001; van der Knaap *et al.*, 2002). However, in a subsequent study involving 93 patients with POF who did not have leukodystrophy or neurological symptoms none of these mutations were identified. The authors concluded that *EIF2B* mutations are an uncommon cause of pure spontaneous POF (Fogli *et al.*, 2004).

Noggin mutation

Haplo-insufficiency of the *NOG* gene on 17q22 encoding Noggin leads to proximal symphalangism (SYM1), an autosomal-dominant disorder characterized by ankylosis of the proximal interphalangeal joints, fusion of carpal and tarsal bones, brachydactyly and conductive deafness (Gong *et al.*, 1999). *NOG* is expressed in the ovary and acts as an antagonist for BMPs, including BMP4 and BMP7 (Zimmerman *et al.*, 1996; Groppe *et al.*, 2002) which play an important role in ovarian function (Shimasaki *et al.*, 1999, 2003).

Kosaki *et al.* (2004) have recently reported a case of POF and SYM1 with mutation in *NOG*. They proposed that an NOG mutation raises the susceptibility to POF by perturbing the functions of BMPs in a certain fraction of patients who have a high predisposition to POF because of other genetic and/or environmental factors.

Mitochondrial DNA polymerase γ mutations

Luoma *et al.* have reported that women with progressive external ophthalmoplegia have early menopause—before the age 35 years. They analysed the gene sequence of mitochondrial DNA polymerase γ (POLG), the enzyme implicated in pathogenesis of this mitochondrial disease, and documented mutations in members of all the seven families studied. The corresponding gene maps to 15q25. Clinical assessment of these patients showed significant cosegregation of Parkinsonism with POLG mutations (Luoma *et al.*, 2004).

Syndromal associations

Cheng and Stenson (2003) described two siblings with bilateral corneal anaesthesia associated with multiple systemic abnormalities including ovarian failure. The combination of these abnormalities with parental consanguinity was suggestive of an inherited syndrome. Women with POF are also more likely to exhibit ocular surface damage and symptoms of dry eye than age-matched controls suggesting a role of sex hormones in the health and disease of the ocular surface (Smith *et al.*, 2004).

Schupf *et al.* (1997) reported that age-adjusted likelihood of menopause was twice as high in women with Down's syndrome as in women with other intellectual disabilities. Treated thyroid conditions did not influence menstrual status and did not modify the relationship between Down's syndrome and menstrual status. The underlying cause could be related to accelerated ageing.

Candidates genes for POF

While any gene encoding a component of reproductive function can be considered a candidate, here we review a selection of 'candidate' *POF* genes that have been raised in the past.

Diaphanous 2 Drosophila *homologue* (*DIAPH2*)

Bione *et al.* (1998) characterized human homologue of the *DIAPH2* and demonstrated that this gene is disrupted by a breakpoint in a family with POF associated with a balanced X; 12 translocation, t(X; 12) (q21; p1.3).

The protein (DIA) is a member of the formin homology FH1/FH2 family of proteins and affects cytokinesis and other actin-mediated morphogenetic processes that are required in early steps of development. Mutated alleles of the gene affect gonadogenesis and lead to sterility (Castrillon and Wasserman, 1994). DIA is proposed to be involved in oogenesis and affects the cell divisions that lead to ovarian follicle formation.

Drosophila *fat facets related X-linked gene* (*DFFRX*)

This gene, also known as *USP9X*, maps to Xp11.4 and encodes an enzyme that removes ubiquitin from protein conjugates, protecting them from proteosomal degradation (Jones *et al.*, 1996). *USP9X* is ubiquitously expressed, has a Y homologue, and escapes X inactivation, consistent with possible gene dosage effects. No mutations have been reported in *USP9X*; however, azoospermic males have been reported to harbour deletions and point mutations of closely related *USP9Y* homologue (Brown *et al.*, 1998; Sun *et al.*, 1999).

X-propyl aminopeptidase 2 (*XPNPEP2*) gene

This gene encodes an X-linked aminopeptidase P enzyme that hydrolyzes N-terminal Xaa–Pro bonds that are found in bradykinins, other cytokines and collagen. It maps to critical region Xq25. Although the physiologic substrates for the enzyme are not known, *XPNPEP2* is believed to be a candidate gene for POF as it was found to be disrupted by a balanced X-autosome translocation associated with secondary amenorrhoea (Prueitt *et al.*, 2000).

X-linked zinc finger gene (*ZFX*)

ZFX lies within the critical region for ovarian failure and maps to Xp22.2–p21.3. It encodes a ubiquitously expressed zinc finger transcription factor of unknown function (Page *et al.*, 1987). *ZFX* was cloned as a homologue of *ZFY*, a former candidate for the testis determining factor on the Y chromosome. It escapes inactivation, and therefore deletions or mutations in one of its copies might cause haploinsufficiency (Schneider-Gadicke *et al.*, 1989). Heterozygous and homozygous *Zfx* mutant female mice have been shown to have a diminished germ cell numbers suggesting a role for this gene in POF (Luoh *et al.*, 1997).

FSH primary response homologue 1 (*FSHPRH1*)

It is the human homologue of rat gene Leucine-Rich Primary Response Gene-1 (*LRPR1*), which is rapidly induced in Sertoli cells in response to FSH (Roberts *et al.*, 1996). It maps to Xq22 and is expressed in the developing ovary, even before the *FSHR*. It is therefore proposed as a candidate gene for disorders of gonadal development and gametogenesis.

X inactivation-specific transcript (*XIST*)

An abnormality in the mechanism of X inactivation may lead to POF. *XIST* is a gene exclusively expressed from the inactive X. It is located within the X inactivation centre at band Xq13.2 and is thought to be intricately involved in X inactivation (Brown *et al.*, 1991). Mutations in human *XIST* might cause skew inactivation patterns resulting in haploinsufficiency of vital ovarian developmental genes and POF.

Wilms tumor 1 gene (*WT1*)

The transcriptional factor *WT1* is expressed in high levels in follicles at early stages of development and because *WT1* overexpression represses the promoter activity of inhibin-alpha gene, this nuclear protein may be important in the maintenance of follicles at early stages of development. The gene is proposed as a candidate gene for POF and maps to 11p13 (Rose *et al.*, 1990).

Ataxia telangectasia

Infertility is a common feature of the inherited human disease ataxia telangectasia (Boder, 1975). *ATM*, the mutated gene maps to chromosome 11q 22.3 and is a member of a family of kinases involved in DNA metabolism and cell-cycle checkpoint control. The *ATM* gene product plays an essential role in a diverse group of cellular processes, including meiosis, the normal growth of somatic tissues, immune development and tumor suppression. *ATM*-deficient mice are completely infertile due to complete absence of mature gametes in adult gonads (Barlow *et al.*, 1996; Elson *et al.*, 1996; Xu *et al.*, 1996). Infertility in the mouse models is attributed to meiotic arrest at the zygotene/pachytene stage of prophase I as a result of abnormal chromosomal synapsis and subsequent chromosome fragmentation.

Negative studies

Here we report those candidate genes that have been subject to mutation screening with a negative result. It is likely that many such studies may not have been published and therefore this cannot be considered a definitive list.

Angiotensin II type 2 (*AT2*) *receptor genes*

AT2 receptor is highly expressed in fetal tissues and rapidly decreases after birth. The receptor is activated in some pathophysiological states and is suggested to be involved in pathogenesis of diseased states like myocardial infarction and cardiac hypertrophy. Granulosa cells of rat atretic follicles express high level of *AT2* receptor and therefore its role in POF has been investigated. However, examination of the entire coding sequence of this receptor (mapped to Xq22–q23) in two different families of sisters with POF failed to reveal any changes in nucleotide sequences (Katsuya *et al.*, 1997).

c-kit gene

Studies in mice have demonstrated that c-kit, a transmembrane tyrosine kinase receptor, plays a critical role in gametogenesis. The human *KIT* gene is located on chromosome 4 at map locus 4q12. Mutations in the human *KIT* gene have been identified as a cause of Piebaldism, a rare autosomal dominant disorder of melanogenesis characterized by patchy absence of pigmentation of the skin and overlying hair (Spritz and Beighton, 1998; Richards *et al.*, 2001). Shibanuma *et al.* (2002) investigated 40 women with, 46; XX spontaneous POF using PCR based single-stranded conformational polymorphism analysis and DNA sequencing and found one silent mutation and two intronic polymorphisms. They concluded that mutations in the coding regions of the *KIT* gene appear not to be a common cause of 46XX spontaneous POF in the studied population of North American women.

SRY *related HMG-box* (*SOX*) *3 gene*

The genes encoding DNA-binding motif of the HMG-box class and showing homology to *SRY* (sex determining region Y), the putative testis determining gene have been named *SOX*, for *SRY* related HMG-box. The close homology between *SRY* and *SOX3* might suggest that each is responsible for its respective gonadal development: *SRY* for the testis and *SOX3* for the ovary.

The *SOX3* gene has been mapped to Xq26–q27 (Stevanovic *et al.*, 1993). A deletion of this gene was detected in a male patient with a contiguous gene syndrome of severe mental retardation, small testes, lower limb skeletal defects and contractures (Wolff *et al.*, 1997). However, screening of 164 women with POF did not reveal any mutations in this gene (Conway, unpublished observations).

Müllerian-inhibiting substance (*MIS*) *gene*

MIS is a testicular hormone responsible for Müllerian duct regression in male sexual development and acts as an oocyte meiosis inhibitor in the rat ovary (Takahashi *et al.*, 1986; Ueno *et al.*, 1989). In mice, *MIS* null females though fertile have been shown to undergo earlier reproductive senescence possibly because of an early depletion of their stock of primordial follicles (Durlinger *et al.*, 1999). The *MIS* gene (map locus 19p13.3–p13.2) and the *MIS* receptor type II gene (map locus 12q13) were evaluated as candidate genes for POF and polycystic ovary syndrome; however, direct sequencing revealed no causative mutations in the coding regions of these genes (Wang *et al.*, 2002).

Autoimmune causes of POF

Some cases of POF may be due to an abnormal self-recognition by the immune system. Irwine *et al.* reported on autoimmunity in patients with POF using indirect immunofluorescence (IFL) in 1968. Subsequently, in the past three decades much evidence has accumulated to suggest that autoimmune mechanisms are involved in pathogenesis of up to 30% of cases of POF (Conway *et al.*, 1996). This evidence takes the form of clinical association of POF with other autoimmune diseases, demonstration of ovarian autoantibodies, studies involving mouse models or histological studies on ovarian tissue from affected patients.

Table II. Autoimmune polyglandular syndromes and POF

APS type	Inheritance	Autoimmune involvement	Age group	Incidence of POF
APS I	Autosomal recessive caused by a mutation in the autoimmune regulator (*AIRE*) gene on chromosome 21	Chronic mucocutaneous candidiasis, adrenal and parathyroid failure	Children age 3–5 years or in early adolescence	17–50% (Ahonen *et al.*, 1990)
APS II (more common)	Polygenic, characterized by dominant inheritance and association with HLA DR3	Primary adrenal failure (Addison's disease) with autoimmune thyroid disease (Schmidt's syndrome) and/or type 1 diabetes (Carpenter's syndrome)	Adults in the third or fourth decade	3.6–10% (Betterle *et al.*, 2004)
APS III	Apart from the absence of adrenal failure, no clinical differences between types II and III have been described	Thyroid failure and other immunological syndromes with exclusion of Addison's disease	Adults	

Clinical associations

The most convincing evidence comes from the commonly observed association of POF with other autoimmune disorders. In general, it is considered that about 20% may have a history of other autoimmune disorders, most commonly autoimmune thyroid disease. Occasional studies have reported this association in as many as 39% of women with chromosomally competent POF (Alper and Garner, 1985; LaBarbera *et al.*, 1988). Both endocrine (thyroid, hypoparathyroid, diabetes mellitus, hypophysitis) and non-endocrine (chronic candidiasis, idiopathic thrombocytopenic purpura, vitiligo, alopecia, autoimmune haemolytic anaemia, pernicious anaemia, systemic lupus erythematosis (SLE), rheumatoid arthritis, Crohn's disease, Sjogren syndrome, primary biliary cirrhosis and chronic active hepatitis) autoimmune associations are described (Rebar and Cedars, 1992; Hoek *et al.*, 1997; Betterle *et al.*, 2002).

Clinically, autoimmune ovarian failure is broadly discussed in two scenarios: (a) in association with autoimmune Addison's disease and (b) isolated or associated with other autoimmune diseases.

Histological evidence for autoimmune damage in POF

Histological examination of ovarian biopsies in POF with associated adrenal autoimmunity reveals lymphocytic and plasma cell infiltration of the ovary particularly around steroid-producing cells of the developing follicles, and sparing of primordial follicles. Perivascular and perineural inflammatory infiltrates are also seen (Sedmak *et al.*, 1987; Bannatyne *et al.*, 1990). Histological evidence of oophoritis is reported to be rare ($<3\%$) in POF in absence of adrenal involvement (Hoek *et al.*, 1997).

POF and Addison's disease

About 2–10% of POF cases are known to be associated with adrenal autoimmunity (Bakalov *et al.*, 2002). This may be clinical or subclinical (presence of adrenal antibodies in absence of hypocortisolism) and may precede Addison's disease by 8–14 years. In the general population, the prevalence of adrenal insufficiency is approximately one in 10 000 (Kong and Jeffcoate, 1994). In a study involving 123 women with POF, four (3.2%) tested positive for adrenal antibodies by IFL assay (Bakalov *et al.*, 2002). The authors suggested that measuring adrenal antibodies would be an effective screening method to detect autoimmune adrenal insufficiency in young women with spontaneous POF and that a standard adrenocorticotropic hormone stimulation test should be performed when positive.

POF may be part of the autoimmune polyglandular syndromes (APS) when accompanied by other autoimmune endocrinopathies (Table II). POF is more common with APS types I and III than with APS type II (Kauffman and Castracane, 2003). Sharing of autoantigens between ovary and adrenal glands, particularly the side-chain cleavage enzyme may explain the association of ovarian failure and Addison's disease. An autoimmune response to these steroidogenic enzymes and ovarian steroid cells appears to mediate destruction of ovarian function in these cases.

POF in absence of Addison's disease

Thyroid autoimmunity is the most common association followed by parietal cell antibodies (Hoek *et al.*, 1997). More than normal association with insulin-dependent diabetes mellitus (IDDM) and myasthenia gravis has also been reported (Ryan and Jones, 2004). In one study of women with SLE, anti-ovarian antibodies were detected in 84% (Moncayo-Naveda *et al.*, 1989). In many cases non-ovarian autoimmune involvement may exist only at subclinical level.

Non-ovarian autoantibodies

Several studies have reported increased prevalence of positive thyroid peroxidase and parietal cell autoantibodies in POF (de Moraes *et al.*, 1972; Mignot *et al.* 1989a). Belvisi *et al.* (1993) reported that 40% of 45 women with POF were positive for at least one organ-specific autoantibody most common being antithyroid antibodies (20%). In the control group, only one woman (3.6%) showed autoimmunity. A more recent study by Novosad *et al.* (2003) reported similar findings; they did not find higher prevalence of antinuclear antibodies as reported earlier (Ishizuka *et al.*, 1999).

Ovarian autoantibodies

The presence of organ specific autoantibodies supports the role of autoimmune mechanism in several endocrine diseases. Anti-ovarian antibodies are reported in POF by several studies but their specificity and pathogenic role are questionable.

In an initial study, Coulam and Ryan (1979) demonstrated presence of ovarian antibodies in serum of patients with POF by immunoprecipitation of radiolabelled human ovarian protein. Different methods have since been tried to identify anti-ovarian antibodies the most common being enzyme-linked immunosorbent assay (ELISA) and IFL. However, search for organ specific ovarian antibodies in POF has yielded conflicting results so far.

Luborsky *et al.* (1990) used ELISA to study sera from 45 patients POF. A combined total of 69% of the sera were positive for either ovary or oocytes. In a subsequent study, ovarian antibodies were found in 53% of women with premature menopause (Luborsky *et al.*, 1999). Using whole tissue homogenate from human ovaries at different ages as antigen, Fenichel *et al.* (1997) found positive circulating ovarian antibodies with ELISA in 59% of patients with idiopathic POF. Wheatcroft *et al.* (1997) found that ovarian antibodies were detected in 27% of idiopathic POF patients by ELISA but only 7% were positive by IFL. Such variable results were attributed to the different stages of the disease when tested, methodological differences and by the multiplicity of potential immune targets that comprise various steroidogenic enzymes, gonadotrophins and their receptors, the corpus luteum, zona pellucida and oocyte.

Presently none of these tests is well standardized, nor do they relate with ovarian histology. Use of commercial ovarian antibody tests therefore needs caution as immunomodulatory treatment based on these results may cause more harm than good; osteonecrosis secondary to glucocorticoid therapy in POF has been reported (Kalantaridou *et al.*, 1999).

Possible antigenic targets for antibody mediated autoimmune damage in POF

Study of anti-ovarian autoantibodies has led to the identification of putative ovarian epitopes, which may enable better understanding of the pathologic mechanisms involved in POF.

Steroid producing cells

Autoantibodies to steroid-producing cells—steroid cell autoantibodies (SCA)—have been detected in POF by IFL (Elder *et al.*, 1981; Sotsiou *et al.*, 1980; Betterle *et al.*, 1993). SCA react with cells active in steroid synthesis, such as adrenal cortex, ovarian theca interna and corpus luteum, testicular Leydig cells, and placental trophoblasts (Elder *et al.*, 1981). These antibodies are widely present in POF associated with Addison's disease (87%) but are rare in POF with non-adrenal associations or in isolated POF (Falorni *et al.*, 2002). These findings support the idea of a shared autoimmune response in ovarian and adrenal autoimmunity. The molecular nature of autoantigen(s) in POF unassociated with Addison's disease (idiopathic POF) remains unclear.

3β-hydroxysteroid dehydrogenase (3β-HSD) autoantibodies

The steroid cell enzyme, 3β-HSD has been identified as a target of SCA in POF. It is involved in the steroid metabolic pathway and is expressed in tissues recognized by SCA. 3β-HSD autoantibodies were found in 21% women with isolated idiopathic POF using immunoblotting techniques and adrenal cDNA library screening (Arif *et al.*, 1996). However, a later study reported 3β-HSD antibodies to be rare (2%) in women with POF (Reimand *et al.*, 2000).

Gonadotrophin receptors blocking antibodies

Antibodies against FSH and LH receptors have been postulated as having a role in the mechanism of ovarian failure (Anonymous, Case records of the Massachusetts General Hospital, 1986) akin to the antireceptor antibodies in other autoimmune disorders, such as myasthenia gravis (Lindstrom *et al.*, 1976) (blocking antibodies to the acetylcholine receptor), some forms of insulin-resistant diabetes (blocking antibodies to the insulin receptor), and primary hypothyroidism (blocking antibodies to the TSH receptor) (Drexhage *et al.*, 1981). Studies by Austin *et al.* (1979), Tang and Faiman (1983) and Anasti *et al.* (1995) were unable to demonstrate blocking antibodies to LH or FSHRs in patients with POF. However, Tang and Faiman did observe greatest interference with FSHR interaction in a patient who had POF with other autoimmune associations. In a recent study using cell lines expressing human gonadotrophin receptors, gonadotrophin receptor blocking antibodies were not detectable in 69 patients with POF (Tonacchera *et al.*, 2004).

Other ovarian antigens

Several other targets within the ovary for autoantibody induced damage have been identified (Forges *et al.*, 2004). McNatty *et al.* (1975) detected cytotoxic effect of serum from patients with Addison's disease and autoimmune ovarian failure on human granulosa cells in culture. In another study, sera from 21 of 26 patients with POF were able to block the growth of rat granulosa cells *in vitro* (van Weissenbruch *et al.*, 1991). The oocyte and zona pellucida are other possible antigenic sites (Shivers and Dunbar, 1977; Rhim *et al.*, 1992; Smith and Hosid, 1994). Autoantibody to a zona pellucida 3 epitope has been shown to induce autoimmune ovarian disease and POF in neonatal mice (Setiady *et al.*, 2003). The underlying mechanism was suggested to be stimulation of de novo autoimmune pathogenic CD4 (+) T cell response by epitope-specific autoantibody.

Cellular immune abnormalities

Alteration of T cell subsets and T cell mediated injury is likely to play an important role in pathogenesis of autoimmune POF as evidenced by human studies and animal models of autoimmune oophoritis (Mignot *et al.* 1989b, Melner and Feltus, 1999; Nelson, 2001). This is similar to the pathology in other endocrine autoimmune diseases, such as IDDM, Graves' disease, and Addison's disease. Chernyshov *et al.* (2001) have reported an increase of autoantibody producing B cells and a low number of effector suppressor/cytotoxic lymphocytes in their study comprising 68 patients with POF. Reduced NK cell number and impaired NK cell activity have been documented in women with POF and in murine post-thymectomy autoimmune oophoritis (Pekonen *et al.*, 1986; Hoek *et al.*, 1995; Maity *et al.*, 1997). The role of cytokines has also been described in causing follicular atresia in POF (Coulam and Stern, 1991; Naz *et al.*, 1995).

Animal models

Autoimmune oophoritis and POF can be induced in mice by neonatal thymectomy done 3 days after birth (Taguchi *et al.*, 1980; Kojima and Prehn, 1981; Kalantaridou and Nelson, 1998). The autoimmune damage is primarily mediated by T cells (Sakaguchi *et al.*, 1982; Smith *et al.*, 1991). Humoral

autoimmunity may also play a role as these mice generate a spectrum of antibodies most of which react with antigens in the oocyte cytoplasm. The inciting antigen in autoimmune disease could be a common target of both autoreactive B and T cells. Using immune serum from these mice, Tong and Nelson (1999) isolated and characterized a novel oocyte-specific protein that may play a role in autoimmune POF. Nelson (2001) cloned the gene for the oocyte specific antigen designated 'Maternal Antigen That Embryos Require'. Such studies may lead to recognition of a similar antibody marker for the human disease.

Immunogenetics in POF

The studies investigating genetic susceptibility for autoimmune POF may help understand its pathogenesis.

Animal studies suggest involvement of immune-regulatory regions outside the H-2 locus in determining susceptibility to murine post-thymectomy autoimmune oophoritis (Kojima and Prehn, 1981; Nair *et al.*, 1996). Teuscher *et al.* (1996) identified the locus determining genetic susceptibility to autoimmune POF on mouse chromosome 3. There may be a role of similar predisposing genes for POF in women.

Among human studies, HLA-DQB1*0301 and HLA-DQB1*0603 were shown to be associated with 3β-HSD autoimmunity in POF (Arif *et al.*, 1999). In a study comprising 37 patients with POF and 100 organ donors from the same population, no statistically significant difference was found in the distribution of A, B, Cw, DR and DQ antigens (Jaroudi *et al.*, 1994).

Studies on APS show association of HLA-DR3 with APS type 2 (Farid *et al.*, 1980; MacLaren and Riley, 1986; Weetman, 1995). The most likely genetic candidate in this condition is proposed to be at a locus controlling T cell development. Associations with HLA class II alleles have been reported in PAS type I as well (Betterle *et al.*, 1998). In APS I, mutations of the *AIRE* gene play an important role. The *AIRE* gene is assigned to chromosome 21q22.3 (Aaltonen *et al.*, 1997) and its more than 40 mutations are reported (Wang *et al.*, 1998).

In view of inconsistent findings on clinical and laboratory studies, the mechanism for ovarian autoimmunity remains obscure. Genetic or environmental factors might initiate the immune response. The role of major histocompatibility complex antigen and cytokines has been explored in human autoimmune POF. The relative contribution of cell-mediated immunity and antibody-mediated immunity is controversial. There exists a possibility for disease-specific therapy to prevent further autoimmune ovarian damage in selected POF patients with proven autoimmune aetiology.

Diagnosis of autoimmune ovarian failure

The gold standard for detecting autoimmune causes of immune ovarian destruction has been ovarian biopsy. However, because there is no treatment proven safe and effective to restore fertility this procedure cannot be advised in routine clinical practice (Khastgir *et al.*, 1994).

Specific defects of expression of cell surface markers on peripheral blood lymphocytes have been shown to identify individuals destined to develop autoimmune pancreatic destruction and type I diabetes mellitus, even before any other evidence of autoimmunity. A similar study exploring cell surface expression in women with POF showed a statistically significant increase in CD8 density on T cells (Yan *et al.*, 2000). Further development of cell surface markers in combination with other diagnostic tests could result in diagnosis of autoimmune POF before the development of complete ovarian failure.

Miscellaneous causes of POF

Galactosaemia

Classic galactosaemia is a rare cause of POF. It is caused by GALT deficiency and leads to a severe disease in the newborn. According to one study, 81% of 47 affected women developed ovarian failure, with primary amenorrhoea noted in eight, and the majority experienced POF shortly after puberty (Waggoner *et al.*, 1990). Intracellular accumulation of galactose metabolites or deficient glycosylation reactions could lead to decrease in the initial number of oogonia through apoptosis. The clinical management essentially includes hormonal replacement therapy (Forges and Monnier-Barbarino, 2003).

Iatrogenic

In patients developing malignant diseases, radiotherapy and chemotherapy can lead to POF (Koyama *et al.*, 1977; Howell and Shalet, 1998). However, there is little risk of premature menopause in women treated with radiation fields that exclude the pelvis (Madsen *et al.*, 1995). Ovarian radiation of 9 Grays render humans infertile, though pregnancies have been reported after significantly higher irradiation exposure (Spinelli *et al.*, 1994). The effect of radiotherapy is also dependent on dose and age and on the radiation therapy field. The prepubertal ovary is relatively resistant to this form of gonadotoxicity (Beerendonk and Braat, 2005). Transposition of the ovaries in young women requiring pelvic irradiation helps in preserving their ovarian function.

POF is important sequelae of cytotoxic chemotherapy given for various malignant diseases in young women. The structure and function of granulosa cells and oocytes are affected by chemotherapeutic agents. The gonadotoxic effect of chemotherapy is largely drug- and dose-dependent and is related to age.

Almost any pelvic surgery has the potential to damage the ovary by affecting its blood supply or causing inflammation in the area. The exact risk is unknown and is thought to be very small for routine operations. Uterine artery embolization, an interventional technique used to manage various gynaecological disorders, also has a potential to result in POF by compromising the vascular supply to the ovary (Amato and Roberts, 2001).

Toxins and viruses

It is popular belief that sperm counts have fallen over recent years because of exposure of the testicle to environmental toxins or drugs. It is possible that the ovary is affected by the viruses or toxins in a similar way. There also exist anecdotal reports of virus infections being followed by ovarian failure (Wood, 1975; Fox, 1992). Mumps oophoritis has been considered to be a cause of POF (Morrison *et al.*, 1975). Cigarette smoking is also

implicated. Female smokers have been shown to experience menopause earlier than non-smokers suggesting a possible detrimental effect of cigarette smoking on ovarian function though further investigations are needed in this field (Di Prospero *et al.*, 2004). Women with epilepsy have also been reported to have an increased risk for developing POF (Klein *et al.*, 2001).

The effects of endocrine disruptors, heavy metals, solvents, pesticides, plastics, industrial chemicals and cigarette smoke on female reproduction has been reviewed (Sharara *et al.*, 1998). The mechanism by which chemicals affect ovarian function may involve hormonal or immune disruption, DNA adduct formation, altered cellular proliferation, or inappropriate cellular death. Data on the association of chemical exposures and adverse reproductive outcomes in humans are, however, equivocal and further studies are needed to clarify which toxicants affect human reproduction and how.

Management of POF

Management of POF needs to address the two major medical issues—hormone replacement therapy (HRT) and infertility. Women also require personal and emotional support to deal with impact of diagnosis on their health and relationships. In addition, associated pathology needs to be assessed and managed so that long-term follow-up is essential to monitor HRT and for health surveillance. Various issues of importance in the management of women with POF are summarized in Table III.

HRT

Long-term HRT is needed for relief of menopausal symptoms (including vasomotor instability, sexual dysfunction, mood, fatigue and skin issues) and to prevent long-term health sequel of estrogen deficiency, such as osteoporosis (Davis, 1996). Estrogen replacement is usually continued up to the age of 50 years, when the risk and benefit of continued treatment are reviewed (Armitage *et al.*, 2003). No data are available to evaluate the impact of treatment on risk factors, such as the development of breast cancer or of cardiovascular events in young women with POF and extrapolation from studies in older women may not always be appropriate.

Table III. Issues in the management of women with POF

Education and counselling
Remission: The likelihood of recovery of ovulation is not possible to predict
There is no proven effective treatment for infertility
Adoption and oocyte donation are among the available options but require guidance and counselling
Access to follow-up counselling is important as issues return with life events such as pregnancy in family
Investigations
Thyroid function tests are useful as thyroid involvement is a common association
Autoantibody screen including thyroid and adrenal antibodies
Karyotype for early onset POF and genetic screen for *FRAXA* premutation
Pelvic ultrasound and ovarian biopsy do not alter the management
Treatment
Estrogen and progesterone replacement is usually indicated
There is no comparative data to guide estrogen use in young women as most studies on HRT involve post-menopausal women
Inform on all estrogen preparations—oral, transdermal and implants
Inform on media HRT scares and relevance to young women
Consider vaginal estrogen and testosterone supplements

A wide range of HRT preparations are available for estrogen replacement including oral, transdermal, subcutaneous and vaginal routes of administration. An HRT regimen should be based on the individual preferences of each patient. The dose of estrogen required by young women is titrated to prevent vasomotor symptoms and vaginal dryness and may be higher than that used in an older age group. Serum estradiol (E_2) may be helpful in those women using implants so as to avoid tachyphylaxis, but in the majority symptoms alone are sufficient guide.

Once the choice of estrogen has been made, separate consideration can be given to the progestin in women with an intact uterus. First, the route may be oral, transdermal or uterine. With the oral and transdermal routes there is a choice between continuous or sequential (for 10–14 days each month) delivery. Continuous regimen avoids menstrual flow but break through bleeding may be more common in young women compared to an older age group in whom there is greater uterine atrophy. Sequential regimen ensures monthly menstrual bleed, which may be a psychological benefit to some young women (and absurd to others!). Progestins vary from the more potent such as norethisterone to the weaker such as dydrogesterone. Trial and error will allow the user to find the most suitable progesterone preparation. Uterine delivery with the levonogestrel intrauterine device (Mirena) has a great theoretical advantage allowing 'estrogen only' systemic preparations to be used avoiding the adverse effects of oral progestins highlighted in the WHI and Million women studies of older women (Beral, 2003; Chlebowski *et al.* 2003). Androgen replacement is useful in some instances when persistent fatigue and loss of libido persist despite optimised estrogen replacement (Mazer, 2002; Arlt, 2003; Davis and Burger, 2003; Chu and Lobo, 2004; Shifren, 2004).

To return to oral estrogen choices, conjugated equine estrogen and 17 β-E_2 have consistent and comparable effects on hot flashes and may have similar short-term adverse effects (Nelson, 2004). Transdermal estrogen is very attractive because the avoidance of first-pass liver metabolism, rapid onset and termination of action, non-invasive self-administration, attainment of therapeutic hormone levels with low daily doses and potential for improved patient compliance. (Henzl and Loomba, 2003). Of particular note is the recent data that transdermal estrogen may be free of an excess risk of thrombosis (Scarabin *et al.*, 2003). Lastly, some young women find the combined oral contraceptive (COC) pill to be a 'peer friendly', discrete form of estrogen replacement as opposed to HRT preparations. The COC, however, provides a fixed combination of estrogen and progesterone with a 'pill free week' which contrasts from the greater flexibility and uninterrupted estrogen possible with the HRT alternatives.

Subcutaneous estrogen replacement involves placement of 25–50 mg E_2 pellets usually in the lower abdomen or buttocks. Insertion is a minor office procedure and can also include testosterone implants if indicated. Return of symptoms, combined with serum levels of E_2, can be used to determine the timing of redosing, which is about every 6 months for most women (Jones, 2004).

Topical vaginal estrogen is often neglected and may be used as an adjunct to systemic estrogen. Creams, pessaries, tablets

and vaginal ring appear to be equally effective for control of symptoms (Suckling *et al.*, 2003).

Natural estrogens do not prevent any spontaneous ovulatory activity. Moreover, ovulation and pregnancy may occur in women with POF who use the COC. Barrier contraceptives are therefore recommended for women with POF who wish to avoid pregnancy.

The general measures advised for prevention of bone loss include improved physical activity, adequate diet, calcium and vitamin D, and avoidance of behaviours that promote bone loss, such as smoking and alcohol abuse. Monitoring bone mineral density with dual energy X-ray absorptiometry scan helps identify the women with osteoporosis who require specific additional intervention such as with bisphosphonates.

The efficacy of non-estrogen treatment modalities including other hormonal preparations, non-hormonal drugs, homeopathic preparations and non-drug treatments is not well documented (Bachmann, 1994), but may find favour in women who are intolerant to exogenous estrogen.

Infertility

Women with POF have a 5–10% chance of conceiving at sometime after diagnosis. Pregnancy loss in these circumstances is reported at 20%, which is similar to that of normal population (van Kasteren and Schoemaker, 1999). There are many case reports and small series reporting use of various medical therapies in an attempt to induce fertility in women with POF; however, the few randomized therapeutic trials that are available fail to demonstrate any significant improvement in ovulation and pregnancy rates. In a systematic review of the various therapeutic interventions thought to restore ovarian function in POF, the authors concluded that interventions were equally ineffective and unlikely to be an improvement on expectant management (van Kasteren and Schoemaker, 1999). Only IVF and embryo transfer using donor oocytes has demonstrated high success rates and is considered to be the fertility treatment of choice in patients with POF (van Kasteren, 2001).

The likelihood of recovery of ovulation is not possible to predict. However, it cannot be assumed that infertility in women with POF is permanent or irreversible as in some cases hormone levels and disease activity fluctuate and return to biochemical normality. In a study of the effectiveness of gonadotrophins suppression using gonadotrophin-releasing hormone agonist (GnRHa) 4/26 (17%) women appeared to ovulate over 4 months and the intervention had no effect on this outcome (Nelson *et al.*, 1992). In a similar study using E_2 instead of GnRHa, 17/37 (46%) women were found to ovulate at least once during the 12 week study (Taylor *et al.*, 1996).

There are several isolated cases of spontaneous pregnancies in women with POF taking both estrogen and, interestingly, the COC (Polansky and De Papp, 1976; Szlachter *et al.*, 1979; Ohsawa *et al.*, 1985; Varma and Patel, 1988; Boulieu and Bully, 1993; Menashe *et al.*, 1996). Alper *et al.* reported six women who conceived after a diagnosis of POF. Two pregnancies occurred while the women were receiving conjugated estrogen therapy, two while taking oral contraceptives and two women conceived spontaneously. There may be differences in fertility outcome in cases with ovarian failure depending on the age of onset. In a retrospective analysis of 86 ovarian failure patients, none of the 23 patients with primary amenorrhoea due to ovarian failure ovulated while seven of 63 (11.1%) with secondary amenorrhoea due to ovarian failure ovulated, and three of them conceived and delivered normal, healthy infants (Kreiner *et al.*, 1988). The authors recommended a trial of E_2 replacement with close monitoring for ovulation in the women with secondary amenorrhoea due to POF before oocyte donation. In another series of 115 women with POF, those with secondary amenorrhoea continued to have intermittent ovarian function. Ovulation was detected in 24% and pregnancy occurred in 8% while ovulation was not detected in any of the women with primary amenorrhoea (Rebar and Connolly, 1990).

Exogenous estrogen could act by sensitizing the granulosa cells to the effect of FSH leading to ovulation and conception (Alper *et al.*, 1986). Oral contraceptives may act similarly by down-regulating the LH and FSHRs (Check *et al.*, 1989). However, interventional studies using oral contraceptives for gonadotrophin suppression in POF failed to show resumption of follicular activity (Buckler *et al.*, 1993). Successful attempts at ovulation induction have been reported with clomiphene (Nakai *et al.*, 1984) and gonadotrophins (Check *et al.*, 1991; Blumenfeld *et al.*, 1993; Chatterjee *et al.*, 1993). Recently, pregnancy was reported after stimulation with recombinant FSH of a galatosaemia patient with ovarian failure (Menezo *et al.*, 2004). It was suggested that the impact of galactosaemia on the ovary could be due to the absence of recognition of circulating FSH by its receptor and not to a toxic alteration of the ovary by itself. Combination of different modalities of treatment has also been tried (Davis and Ravnikar, 1988).

Suppression of gonadotrophin secretion using GnRH analogues has been tried in an attempt to reverse POF but was not successful (Ledger *et al.*, 1989; Surrey and Cedars, 1989). Similarly no benefit could be demonstrated from the immunomodulatory and gonadotrophin-suppressing effects of danazol in patients with karyotypically normal spontaneous POF (Anasti *et al.*, 1994).

Recovery of ovarian function may occur after regression of the autoimmune status and control of coexistent endocrine disease. In women with myasthenia gravis and ovarian failure, thymectomy has resulted in resumption of menses, with or without recovery of fertility (Lundberg and Persson, 1969; Bateman *et al.*, 1983; Chung *et al.*, 1993). Finer *et al.* (1985) reported a 32-year-old woman with POF associated with ovarian autoantibodies, autoimmune Addison's disease and primary hypothyroidism who became pregnant following the treatment of her thyroid and adrenal deficiencies.

There also exist a few reports on a successful ovulation-inducing treatment of selected women with POF (those with other autoimmune phenomena) with immunomodulating therapies, such as corticosteroids (Rabinowe *et al.*, 1986; Taylor *et al.*, 1989). Pregnancy after corticosteroid administration has been reported in POF occurring in a patient with polyglandular endocrinopathy syndrome (Cowchock *et al.*, 1988). In another study, 11 consecutive women with POF were given prednisone 25 mg four times per day for 2 weeks. Two women demonstrated normalization of their serum gonadotrophins, an increase of serum E2, and ultrasonographic visualization of follicular growth, and both conceived (Corenblum *et al.*, 1993). Despite these case

reports none of immunosuppressive therapies is proven to be safe and effective by prospective randomized placebo-controlled study and may be associated with complications such as osteonecrosis (Kalantaridou *et al.*, 1999).

Several novel strategies have been tried including combined pentoxifylline–tocopherol treatment using 800 mg of pentoxifylline combined with 1000 IU of vitamin E given daily for 9 months (Letur-Konirsch and Delanian, 2003) and growth hormone-releasing hormone given in a dose of 1000 mg/day (Busacca *et al.*, 1996).

Assisted conception with donated oocytes has been used to achieve pregnancy in women with POF since 1987 (Asch *et al.*, 1987; Oskarsson *et al.*, 1990; Rotsztejn *et al.*, 1990). Presently it remains the only means for fertility treatment in POF that carries high success rate (Anonymous, Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine. Assisted reproductive technology in the United States, 2002). Cryopreserved embryos have also been used for ovum donation in POF with a high pregnancy rate of 30% per transfer (Abdalla *et al.*, 1989).

In some cases, it is possible to foresee premature menopause as in patients undergoing anticancer treatment with chemotherapy. Because dividing cells are more sensitive to the cytotoxic effects of these drugs, it has been hypothesized that inhibition of the pituitary–gonadal axis using GnRHa would render the germinal epithelium less susceptible to the cytotoxic effects of chemotherapy (Ataya and Moghissi, 1989). Subsequent studies confirmed that GnRHa cotreatment protects against POF during cytotoxic chemotherapy (Blumenfeld *et al.*, 1996, 2002). This approach has also been advocated for young women requiring gonadotoxic treatments for SLE, organ transplantation and other autoimmune diseases (Blumenfeld and Haim, 1997; Blumenfeld *et al.*, 2000). Use of oral contraceptives during chemotherapy has also been studied but the results failed to show protective effect on ovarian function (Longhi *et al.*, 2003).

Use of apoptotic inhibitors, such as sphingosine-1-phosphate, is also been suggested as radioprotective and chemoprotective agent against germ cell death. This agent may act by inhibiting the signalling events involved in apoptotic process and protect the patient from POF (Morita *et al.*, 2000; Spiegel and Kolesnick, 2002; Tilly and Kolesnick, 2002). The various attempts at preventing POF in young women exposed to gonadotoxic chemotherapy have been reviewed (Blumenfeld, 2003).

Other fertility options for women diagnosed with cancer include IVF followed by cryopreservation of embryos, cryopreservation of mature oocytes and cryopreservation of ovarian tissue (Poirot *et al.*, 2002). The first option is not feasible in all cases. Pregnancies and life births have been reported after oocyte cryopreservation and subsequent intracytoplasmic sperm injection (Chen, 1986; Borini *et al.*, 2004). Preservation of the structural complexity of the ovum is an important factor in determining the outcome (Falcone *et al.*, 2004). The use of ovarian tissue cryopreservation for later use has been explored in women undergoing anticancer treatment. Similarly, adolescent girls with Turner's syndrome still have follicles in their ovaries (Hreinsson *et al.*, 2002) and could be candidates for ovarian cryopreservation.

Cryopreserved ovarian tissue could be used in two ways—autograft and *in vitro* folliculo–oocyte maturation. Cryopreserved human ovarian tissue has been found to be functional after retransplantation (Oktay and Karlikaya, 2000; Radford *et al.*, 2001; Gook *et al.*, 2001). The first live birth after orthoptic transplantation of cryopreserved ovarian tissue has been reported recently (Donnez *et al.*, 2004). Successful pregnancy is possible following *in vitro* maturation of oocytes from antral follicles (Cha *et al.*, 1991). Human preantral follicles have been isolated and cultured in humans and several animal species (Roy and Treacy, 1993; Gutierrez *et al.*, 2000). However, the vast majority of follicles in human ovarian cortical tissue are primordial, which do not grow well in culture (Abir *et al.*, 2001) and it is not practical to isolate primordial follicles from the cortical tissue before cryopreservation. Maturation of oocytes from primordial follicles after cryopreservation of ovarian tissue for use in IVF would be a further step in management of infertility due to cancer treatment or genetic causes (Hovatta, 2004).

A woman's age would be a determining factor when considering ovarian cryopreservation. Children are most likely to benefit from it as their ovary contains more primordial follicles than adult women and other alternatives of oocyte or embryo cryopreservation are unavailable for them. It is also expected that by the time these children grow up and need their ovarian tissue, the modalities for its optimal use would become available (Aubard *et al.*, 2001).

Ovarian tissue cryopreservation and oocyte cryopreservation thus hold promise for fertility preservation in the women likely to undergo ovarian failure following cancer treatments. This treatment may, however, be contraindicated in cases with possible metastasis to the ovaries where oocyte donation and IVF would be safer (Shaw *et al.*, 1996).

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