

# Genetic disorders in premature ovarian failure

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This review presents the genetic disorders associated with premature ovarian failure (POF), obtained by Medline, the Cochrane Library and hand searches of pertinent references of English literature on POF and genetic determinants cited between the year 1966 and February 2002. X monosomy or X deletions and translocations are known to be responsible for POF. Turner's syndrome, as a phenotype associated with complete or partial monosomy X, is linked to ovarian failure. Among heterozygous carriers of the fragile X mutation, POF was noted as an unexpected phenotype in the early 1990s. Autosomal disorders such as mutations of the *phosphomannomutase 2 (PMM2)* gene, the *galactose-1-phosphate uridylyltransferase (GALT)* gene, the *FSH receptor (FSHR)* gene, chromosome 3q containing the *Blepharophimosis* gene and the *autoimmune regulator (AIRE)* gene, responsible for polyendocrinopathy-candidiasis-ectodermal dystrophy, have been identified in patients with POF. In conclusion, the relationship between genetic disorders and POF is clearly demonstrated in this review. Therefore, in the case of families affected by POF a thorough screening, including cytogenetic analysis, should be performed.

*Key words:* autosomal disorders/FSH receptor/inhibin/premature ovarian failure/X chromosome abnormalities

## TABLE OF CONTENTS

Introduction
Literature search
X chromosome abnormalities
Autosomal disorders
Inhibin
FSH receptor
Discussion
References

## Introduction

Premature ovarian failure (POF) is defined as cessation of ovarian function at the age of  $\leq 40$  years after normal development (Coulam, 1982). It is characterized by the occurrence of oligomenorrhoea, primary or secondary amenorrhoea with elevated gonadotrophins and low estrogen levels. The incidence of POF is estimated to be 1% per year (Coulam *et al.*, 1986). The following criteria have been suggested for diagnosing POF (Anasti, 1998):  $\geq 4$  months of amenorrhoea and two serum FSH levels of  $\geq 40$  mIU/ml obtained  $\geq 1$  month apart in a woman aged  $\leq 40$  years.

A total depletion of ovarian follicles differentiates POF from the potentially treatable disorder termed resistant ovary syndrome (Metha *et al.*, 1992), in which the ovarian biopsy demonstrates primordial and immature follicles only. Confirmation of the

diagnosis requires histological examination of a full-thickness ovarian biopsy (Metha *et al.*, 1992; Olivar, 1996). Minilaparoscopic surgery allows the performance of bilateral, multiple ovarian biopsy, obtaining a sufficient amount of ovarian tissue for histopathological diagnosis (Pellicano *et al.*, 2000). The diagnostic and prognostic role of ovarian biopsy is controversial, as well as the management of resistant ovary syndrome and POF, though several authors have reported pregnancies occurring in patients with negative biopsies (Sutton, 1974; Polansky and de Papp, 1976; Shangold *et al.*, 1977). A histological separation into follicular and atfollicular types of POF seems logical, but some of the known aetiological factors, such as galactosaemia and blepharophimosis, fit uneasily into these histological types, and some cases of ovarian failure that were originally of follicular type may progress to an atfollicular stage (Eden, 1994; Khastgir *et al.*, 1994).

The aetiology of POF comprises genetic disorders, surgery, or ovarian tissue damage due to radiation or chemotherapy (Coulam *et al.*, 1983). Rare causes, such as galactosaemia, will usually have been identified in early life. With careful analysis of the family history, the prevalence of familial POF has been reported to be 4, 12.7 and 31% in various series (Coulam *et al.*, 1983; Vegetti *et al.*, 1998; Van Kasteren *et al.*, 1999). Among genetic causes, X monosomy as in Turner's syndrome (TS) or X deletions and translocations are known to be responsible for POF (Davis *et al.*, 2000). On the other hand, autosomal abnormalities have been

identified in POF patients such as mutations of the *phosphomannomutase 2 (PMM2)* gene, the *FSH receptor (FSHR)* gene, the *galactose-1-phosphate uridylyltransferase (GALT)* gene, chromosome 3q containing the *Blepharophimosis* gene, and the *autoimmune regulator (AIRE)* gene.

This review details the literature of X chromosome-linked disorders and autosomal disorders related to POF.

### Literature search

A Medline and Cochrane Library search of English literature on POF and genetic determinants, cited between the years 1966 and February 2002, was performed. The medical subject headings (MESH) terms and established abbreviations of premature ovarian failure, genetic disorders, Turner's syndrome, fragile X syndrome, carbohydrate-deficient glycoprotein syndrome type 1, galactosaemia, blepharophimosis and polyendocrinopathy-candidiasis-ectodermal dystrophy as POF-related disorders were included to collect the relevant citations, completed by search-results of the MESH terms 'inhibin' and 'FSH receptor'.

In addition, a hand search of pertinent references was performed.

### X chromosome abnormalities

X and autosomal chromosomal abnormalities, mutations of autosomal or X-linked genes and polygenic/multifactoral determinants are pertinent to different genetic mechanisms. Several studies have shown that ovarian differentiation requires only one X (Schwartz *et al.*, 1987; Ogata and Matsuo, 1995; James *et al.*, 1998; Zinn *et al.*, 1998). If two intact chromosomes are not present, ovarian follicles in 45,X individuals usually degenerate by birth. Genes on the second X chromosome are responsible for ovarian maintenance, rather than ovarian differentiation (Simpson and Rajkovic, 1999). Until now, there is no evidence of a gene directing primary ovarian differentiation. Several studies have shown that proximal Xp and proximal Xq contain regions of importance to ovarian maintenance, among them Xq13 and Xp11. Deletions in this area are believed to result equally in primary amenorrhoea and POF (Simpson and Rajkovic, 1999).

### Turner's Syndrome

TS is the phenotype associated with complete or partial monosomy X in human females. The pathogenesis of the TS phenotype is complex, and most authors believe that growth retardation, ovarian failure and other physical abnormalities are separate and distinct genetic defects. Ultrasound assessment in patients with TS shows either 'streak' or 'non-streak' ovaries. Non-streak ovaries range from small glands, sometimes containing minute cysts, to ovaries indistinguishable from those which are normal for age. Such ovaries retain a range of function, as evidenced in some cases by spontaneous breast development and uterine enlargement (Massarano *et al.*, 1989). A study of 17 patients with TS investigated the presence of sexual differentiation structures. All gonads were constituted by rudimentary ovarian stroma with different states of hyalinization. Primordial follicles were noted in two patients, sexual cords were seen in six, and medullary tubules in nine. Different amounts of hilar cells were also found (Rivelis *et al.*, 1978). Growth failure may result

from deficiency of X-linked gene(s), perhaps together with non-specific effects of aneuploidy. Similarly, ovarian failure may be due to inadequate dosage of X-linked genes (Krauss *et al.*, 1987) and/or incomplete meiotic chromosome pairing (Burgoyne and Baker, 1985). Most X-linked genes are subject to X inactivation during early embryogenesis and are thus functionally haploid in both 45,X and 46,XX fetuses during critical developmental stages (Lyon, 1961). These genes are unlikely to be involved in the TS phenotype, with the possible exception of ovarian failure, since the inactive X is reactivated during oogenesis. Furthermore, it appears that the Y chromosome supplies the second dose of critical TS genes in normal males; therefore, TS genes are predicted to be X-Y homologous and to escape X inactivation (Zinn *et al.*, 1993). There are presently only 18 such candidate genes. Cytogenetic and molecular studies suggest that most TS physical features map to the short arms of the X and Y chromosomes (Ferguson-Smith, 1965; Kalousek *et al.*, 1979; Fryns *et al.*, 1981; Goldman *et al.*, 1982; Jacobs *et al.*, 1990; Temtamy *et al.*, 1992; Lahn and Page, 1997). The 2.6 Mb Xp-Yp pseudoautosomal region may appear to play a role in TS since X and Y copies of the region are identical, and all genes within the region seem to escape X inactivation (Ogata *et al.*, 1992b). However, short stature is the only clinical finding consistently associated with deletions of just this region (Ogata *et al.*, 1992a; Rappold, 1993; Ogata and Matsuo, 1995). Nonetheless, there is evidence that a locus (loci) for short stature, ovarian failure, autoimmune thyroid disease and high-arched palate might be mapped to another region of the X chromosome, Xp11.2-p22.1 (Zinn *et al.*, 1998). The human sex-linked genes *RPS4X* and *RPS4Y* encode distinct isoforms of ribosomal protein S4. When insufficiently expressed, this protein may play a role in the development of TS (Lahn and Page, 1997).

The identification of genes or critical regions responsible for individual TS features other than short stature has turned out to be problematic. Most studies have only used cytogenetic, rather than molecular, techniques to define X chromosome abnormalities, but the precision and accuracy of cytogenetics may not be adequate for genotype correlations (Ferguson-Smith, 1965). Mosaicism, which is frequently present in TS patients, may confound karyotype/phenotype associations. Literature reviews with large sample sizes are subject to interobserver variation in phenotypic evaluation (Zinn *et al.*, 1994). The variability of TS features, even among 45,X patients, necessitates appropriate statistical methodology for genotype/phenotype correlations. A more recent study (Ross *et al.*, 2000) examined the critical region of Xp for neurocognitive aspects and psychosocial profile, described in TS females. The phenotype was seen with either paternally or maternally inherited deletions and with either complete or incomplete skewing of X inactivation. Fine mapping of informative deletions implicated a critical region of <2 Mb within the pseudoautosomal region (PAR)-1. The authors therefore concluded that haploinsufficiency of *PARI* gene(s) is the basis for susceptibility to the TS neurocognitive phenotype (Ross *et al.*, 2000).

### Fragile X syndrome

Fragile X syndrome (FRAXA) is an X-linked dominant condition with incomplete penetrance (Fu *et al.*, 1991). The molecular basis of the disease is the expansion of a CGG trinucleotide repeat in

the 5' untranslated region (UTR) of the *fragile X mental retardation (FMR1)* gene located at Xq27.3 (Verkerk *et al.*, 1991; Warren and Ashley, 1995). It was proposed that micro-deletions within *FMR2*, the gene associated with FRAXE, might be a significant cause of POF, and is found in 1.5% of women with the condition, and in only 0.04% of the general female population (Murray *et al.*, 1999a). In the normal population, the CGG repeat size is highly polymorphic and usually stably inherited (Fu *et al.*, 1991). In carriers, the size of the repeated tract is between 60 and 200 repeats; this condition is termed premutation, since premutated alleles are susceptible to expansion when passed from a carrier to offspring. An expansion of >200 repeats (called full mutation) causes hypermethylation of the CpG island upstream of the *FMR1* gene and, consequently, its transcriptional inactivation (Pieretti *et al.*, 1991; Verkerk *et al.*, 1991; Warren and Ashley, 1995). However, more recent data have suggested that these processes may be altered—at least in male premutation carriers (Tassone *et al.*, 2000). Among heterozygous carriers of the fragile X mutation, POF was noted as an unexpected phenotype in the early 1990s (Shermann, 2000). Only premutation carriers have been found to have an increased risk for POF (Cronister *et al.*, 1991; Schwartz *et al.*, 1994; Partington *et al.*, 1996; Allingham-Hawkins *et al.*, 1999; Kornman *et al.*, 2002), whereas full-mutation carriers and their non-carrier sisters appear to have the same risk as seen in the general population (~1%) (Shermann, 2000). Additionally, results obtained in another study indicated that the prevalence (6/106; 6%) of POF is significantly higher in women affected by a FRAXA premutation than expected, suggesting a phenotypic consequence of the premutation alleles (Marozzi *et al.*, 2000).

In a study including 108 subjects with POF, 6.5% of women were found to carry the FRAXA premutation (Uzielli *et al.*, 1999). These authors were able to demonstrate an 18.8% incidence of POF in fragile X females with premutations, and confirmed normal ovarian function in all examined females with a full mutation. None of 63 women with full mutations had POF (Uzielli *et al.*, 1999).

A three-generation family in which POF segregates in association with the FRAXA premutation has been described (Vianna-Morgante *et al.*, 1996). The data acquired from this family further supported the hypothesis of the non-random nature of the association, when the premutation was documented in the three investigated patients with POF. A fourth female was also identified as a FRAXA carrier having a son affected by FRAXA syndrome (Vianna-Morgante *et al.*, 1996). Others (Conway *et al.*, 1998) screened 132 women with POF for FRAXA premutations; in 23 pedigrees with POF, 13% showed an association between FRAXA and POF, while among 106 women with sporadic POF, only 3% were found with FRAXA premutations.

In premenopausal women from FRAXA families, a significant increase in serum FSH level was found in premutation carriers, suggesting that as a group these women will enter menopause before full mutation carriers and unaffected controls (Murray *et al.*, 1998, 1999b). Furthermore, there is a statistically significant difference ( $P < 0.05$ ) in the median age of precocious menopause in patients with sporadic and familial POF (31.0 and 37.5 years respectively) (Vegetti *et al.*, 1998). Studies showed that 16% of 395 women carrying FRAXA premutated alleles entered menopause before the age of 40 years (Allingham-Hawkins

*et al.*, 1999). These subjects had a median age of menopause 6–8 years earlier than women in the general population, experiencing POF in 28% of cases (Partington *et al.*, 1996).

FRAXA is the most common inherited cause of developmental disability and the second most common cause after Down's syndrome. The molecular mechanism underlying the link between FRAXA premutation and POF is unknown at present, although an imprinting effect was described in POF confined to paternally inherited fragile X permutations. The occurrence of POF and age at menopause in women with a paternally inherited fragile X permutation (PIP) were compared with those in women with a maternally inherited fragile X permutation (MIP). Some 28% of patients with PIP had POF, compared with only 3.7% with MIP. Age at menopause was significantly lower ( $P = 0.003$ ) in women with PIP than in those with MIP. The authors hypothesized that this may be caused by a paternal genomic imprinting effect (Hundscheid *et al.*, 2000). However, there was no evidence for any parent-of-origin effect influencing POF in fragile X premutation carriers in a similar cohort of women. This study showed no evidence to support the suggestion that there is imprinting of the *FMR1* gene (Murray *et al.*, 2000). This is in contradiction to other results not supporting the hypothesis of a parent-of-origin effect of the *FMR1* premutation on ovarian function, such that only the paternally inherited premutation is significantly associated with POF in Brazilian families (Vianna-Morgante and Costa, 2000).

So far, there is no information available from randomized controlled trials to indicate whether or not non-selective screening for fragile X in women desirous of pregnancy, or already pregnant, confers any benefit over the existing practice of selectively screening those thought to be at increased risk (Kornman *et al.*, 2002). However, screening for FRAXA premutation in women with a familial condition of POF may be used to prevent the transmission of mental retardation syndrome.

## Autosomal disorders

### *Carbohydrate-deficient glycoprotein syndrome type 1 (CDG1)*

The search for the carbohydrate-deficient glycoprotein syndrome type 1 (CDG1, or Jaeken syndrome), an autosomal recessive disorder characterized by defective glycosylation, has revealed the existence of a family of *phosphomannomutase (PMM)* genes in humans (Schollen *et al.*, 1998). Most patients show a deficiency of phosphomannomutase (PMM), the enzyme that converts mannose 6-phosphate to mannose 1-phosphate in the synthesis of GDP-mannose. *PMM1* is located on chromosome 22q13, and *PMM2* on chromosome 16p13 (Matthijs *et al.*, 1997). Mutations have recently been identified in the *PMM2* gene in CDG1 patients with a PMM deficiency (CDG1A) (Matthijs *et al.*, 1998). The patients show a severe encephalopathy with axial hypotonia, abnormal eye movements and pronounced psychomotoric retardation, as well as a peripheral neuropathy, cerebellar hypoplasia and retinitis pigmentosa. They exhibit a peculiar distribution of subcutaneous fat, nipple retraction and hypogonadism. There is a 20% lethality in the first years of life due to severe infections, liver insufficiency or cardiomyopathy (Matthijs *et al.*, 1997).

### **Galactosaemia**

Galactosaemia is a rare autosomal recessive disorder due to an impairment in galactose 1-phosphate uridylyltransferase (GALT) metabolism (Beutler *et al.*, 1965; Segal and Berry, 1995). Despite adequate dietary control of the metabolic disorder, women with galactosaemia have a lower IQ, dyspractic speech, delays in growth and development, neurological dysfunction and POF. The prevalence of POF is 70–80% in female patients with galactosaemia (Donnell *et al.*, 1961; Hoefnagel *et al.*, 1979; Kaufman *et al.*, 1979, 1981; Waggoner *et al.*, 1990; Robertson *et al.*, 2000). According to another study, 81% of 47 affected female patients developed ovarian failure, with primary amenorrhoea noted in eight, and the majority experienced POF shortly after puberty (Waggoner *et al.*, 1990).

Ovarian damage has been attributed to a toxic effect of galactose, or one of its metabolites, on follicular structures during fetal life (Levy *et al.*, 1984; Fraser *et al.*, 1986). It has been suggested that the oligosaccharide moieties on the gonadotrophin subunits may be altered in such way as to render them biologically inactive (Rebar *et al.*, 1982, 1987). Experimental studies on rats have shown that high maternal galactose levels inhibit the migration of primordial germ cells to the gonadal ridge (Chen *et al.*, 1981), suggesting that ovarian failure in patients with galactosaemia might be due to a galactose-induced decrease in the initial number of oogonia.

It was also found that the FSH isoforms from female galactosaemic sera had a neutral isoelectric point (Prestoz *et al.*, 1997); this neutral form of FSH had a higher affinity for its receptor, but was unable to stimulate adenylate cyclase. Other investigators observed normal biological activity of the gonadotrophins from galactosaemic patients. In some patients with galactosaemia a genetic marker has been identified, *GALT Q188R*, and individuals heterozygous for *GALT Q188R* mutations are not at increased risk of developing ovarian dysfunction (Kaufman *et al.*, 1994). Cloning and sequencing of human *GALT* resulted in the finding of >150 documented mutations associated with galactosaemia, and raised the possibility of genotype–phenotype relationships. The many genes and their enzyme products involved in carbon dioxide production are considered ‘epigenetic’ to the *GALT* gene (Guerrero *et al.*, 2000). The development of POF in females with galactosaemia is more likely if the patient’s genotype is Q188R/Q188R, if the mean erythrocyte galactose 1-phosphate level is >3.5 mg/dl during therapy, and if the recovery of <sup>13</sup>C<sub>2</sub> from whole-body <sup>13</sup>C-galactose oxidation is reduced below 5% of administered <sup>13</sup>C-galactose. This study also confirmed that hypergonadotrophic hypogonadism occurs in prepubertal girls with galactosaemia (46,XX) (Guerrero *et al.*, 2000).

Histological studies of ovarian tissue in galactosaemia complicated with POF described follicular depletion (Beauvais and Guilhaume, 1984; Robinson *et al.*, 1984). In a report of two sisters with galactosaemia and POF (Fraser *et al.*, 1986), ovarian biopsy in the younger showed an appearance consistent with resistant ovary syndrome, whilst the ovary of the elder showed follicular depletion. This indicated that follicular resistance may precede follicular loss, but the exact mechanism of ovarian failure has not yet been elucidated in patients with galactosaemia and POF.

### **Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES)**

Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) is an autosomal dominantly inherited disorder, whereby the affected patients exhibit characteristic facial abnormalities, i.e. small palpebral fissures, ptosis and a skinfold running inward and upward from the lower lid. Two forms of BPES exist. In type I, infertility in the form of ovarian failure is an adjunct to the condition and is sex-limited, i.e. only females are affected. In type II, only facial abnormalities are present (Zlotogora *et al.*, 1983).

Patients with this syndrome have a high incidence of menstrual irregularities, and this condition appears to be associated with POF (Jones and Collin, 1984; Fraser *et al.*, 1988). BPES types I and II were each mapped on the long arm of chromosome 3 (Panidis *et al.*, 1994; Amati *et al.*, 1996; De Baere *et al.*, 1999). Ovarian biopsy in two patients showed a resistant ovary appearance in one patient, and a premature menopause characterized by follicular depletion in the other (De Baere *et al.*, 2001).

Two novel genes were identified within the breakpoint region (Crisponi *et al.*, 2001). One of these genes, termed *FOXL2*, shared common features with members of the winged helix/forkhead protein family. Both novel genes were successfully sequenced in a number of BPES type I and type II families, and genetic modifications were identified in all affected BPES patients but not in unaffected family members and a healthy control group. All mutations were exclusively localized in the *FOXL2* gene (Crisponi *et al.*, 2001). However, bearing in mind the potentially high promise of *FOXL2* for elucidating ovarian failure, no *FOXL2* mutations were detected in a group of 30 women with non-syndromic POF (De Baere *et al.*, 2001). A position effect and thus *FOXL2* involvement in non-syndromic ovarian failure cannot be excluded.

### **Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)**

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is an autosomal recessive disorder manifesting as a widely variable pathology of three components: (i) autoimmune destruction of tissues, predominantly endocrine glands; (ii) chronic superficial candidiasis; and (iii) ectodermal dystrophy. APECED is caused by mutations of a single gene, named the *autoimmune regulator (AIRE)* gene which has been mapped to chromosome 21q22.3 (Nagamine *et al.*, 1997; Bjorses *et al.*, 1998). To date, >40 *AIRE* gene mutations—including several nonsense and missense mutations as well as frameshift mutations—are known (Rosatelli *et al.*, 1998; Cihakova *et al.*, 2001; Heino *et al.*, 2001; Saugier-veber *et al.*, 2001), and more have recently been identified (Meloni *et al.*, 2002). In a Finnish survey of 72 patients, hypogonadism was present in 60% of female patients aged >12 years; half of the females with ovarian atrophy failed in pubertal development (Perheentupa, 1996).

### **Inhibin**

Due to its role in the negative feedback control of FSH, the glycoprotein inhibin plays a pivotal role in the recruitment and development of ovarian follicles during folliculogenesis. Structurally, it is related to the transforming growth factor- $\beta$  superfamily, a gene group of multifunctional growth and

differentiation (Shelling *et al.*, 2000). Its main function in women is the regulation of pituitary FSH secretion. When the ovarian follicular reservoir begins to subside, a decline in serum inhibin concentrations has been observed (MacNaughton *et al.*, 1992). Recent results of different study groups show changes in inhibin secretion to be responsible for an increase in FSH, and also perhaps to act as a marker of ovarian reserve (Christin-Maitre *et al.*, 1998). An increase in FSH secretion coincides with an increased rate of follicular depletion during the menopausal transition (Richardson *et al.*, 1987). Several other studies have confirmed the finding of a close relationship of inhibin genes to the pathogenesis of POF (Pampfer and Thomas, 1989; Buckler *et al.*, 1991; Lindstedt *et al.*, 1997). *Inhibin alpha (INHA)*, *Inhibin beta A (INHBA)* and *Inhibin beta B (INHBB)* are responsible for coding for inhibin. Furthermore (Shelling *et al.*, 2000), it was shown that a transition in the *INHA* gene occurred in ~7% of POF patients.

### FSH receptor

An inactivating mutation of the *FSH receptor (FSHR)* gene in connection with hypergonadotrophic ovarian failure has been reported (Aittomäki *et al.*, 1995). This study was initiated by a population-based investigation (Aittomäki, 1994) in Finland of patients with XX gonadal dysgenesis (XXGD). Segregation analysis confirmed the recessive mode of inheritance of the disease, as well as the existence of several kindreds with two or more affected sisters. A locus for ovarian failure related to hypergonadotrophic ovarian failure was mapped to chromosome 2p, and two particularly interesting genes with respect to gonadal function were localized to this chromosome, i.e. *FSHR* (Rousseau-Merck *et al.*, 1993) and the *LH receptor* gene (Rousseau-Merck *et al.*, 1990). An inactivating mutation in either gene could potentially cause ovarian failure. However, the role of FSH in the early events of ovarian development, including follicular development and maturation, as well as the absence of pseudohermaphroditism in the affected families, suggest FSH mutation as a more likely explanation for the syndrome (Rousseau-Merck *et al.*, 1993). In some of these patients, histological studies of the ovaries showed a streak or hypoplastic aspect and the presence of primordial and primary follicles with impaired follicular development at further stages (Aittomäki *et al.*, 1996). In a study with ovarian biopsies of a woman with molecular *FSHR* alterations, histological and immunohistochemical examinations reflected normal numbers of healthy primordial and primary follicles. Secondary follicles also displayed a normal morphology (Touraine *et al.*, 1999). FSH effects on follicular growth and maturation differ markedly at various developmental stages. There is evidence indicating that initiation of follicular growth in mice and rats, when a resting follicle enters the growth phase, does not require FSH (Nakano *et al.*, 1975; Halpin *et al.*, 1986), and the absence of *FSHR* expression in non-growing human follicles confirmed this point (Oktay *et al.*, 1997). FSH is needed for further follicular development between the primary and antral stages. In rat models, hypophysectomy or GnRH antagonist administration leads to an almost complete absence of follicular growth beyond the secondary stage (McGee *et al.*, 1997). The same pattern has been obtained in xenografts of human ovarian tissues in hypogonadal *severely compromised*

*immunodeficient (SCID)/hpg* mice (Oktay *et al.*, 1998). Finally, in mice bearing a homozygous invalidation of either *Fsh $\beta$*  (Kumar *et al.*, 1997) or *Fshr* (Dierich *et al.*, 1998), development was blocked before the antral stage. In humans, clinical observations also suggest FSH independence during the first steps of follicular development. In situations where low levels of circulating gonadotrophins are present, i.e. prepubertally or in women with hypogonadotrophic hypogonadism or with mutations of the FSH- $\beta$  subunit, morphological examination of the ovaries revealed the existence of small pre-antral follicles but few antral follicles, indicating that gonadotrophin deficiency is associated mainly with a disruption of the final stages of pre-ovulatory folliculogenesis (Rabin *et al.*, 1972; Goldenberg *et al.*, 1976; Rabinowitz *et al.*, 1979; Matthews *et al.*, 1993).

No mutations in the gene for FSH- $\beta$  were identified in women with POF, but this does not entirely exclude the possibility that smaller deletions, insertions or point mutations of *FSHB* could be aetiological in some women with POF (Laymann *et al.*, 1993; Themmen *et al.*, 1997). All affected individuals displaying the disease were homozygous for the mutation, and all parents that could be studied (obligatory heterozygous) were shown to be heterozygous. One group (Tong *et al.*, 2001) screened the entire coding region of *FSHR* for pathogenic mutations in women with POF and polycystic ovarian syndrome (PCOS) and found no mutations in these patients. In Japanese women with POF and PCOS, no inactivating mutations in exons 6, 7, 9 and 10 of the *FSHR* gene were identified (Takakura *et al.*, 2001).

In North America, the *FSHR* gene mutation is uncommon in women with POF (Conway *et al.*, 1997; Shelling *et al.*, 2000), and it needs to be determined whether the incidence of this entity is as high in other populations as in Finland. A well known feature of the Finnish population is a considerable enrichment of mutations for certain recessively inherited disorders (Salonen *et al.*, 1981; de la Chapelle, 1993). However, the incidence of the condition may be seriously underestimated in clinical practice (Aittomäki, 1994).

### Discussion

This review raises the importance of considering the relationship between POF and genetic disorders for every POF patient and her affected relatives. Cytogenetic analysis should be considered for women presenting with unexplained POF, even when there are no other clinical features suggestive of chromosomal abnormality. It has been suggested that chromosome studies could be limited to those women with onset of hypergonadotrophic amenorrhoea prior to the age of 30 years (Rebar and Cedars, 1992). However, in one study, two of four chromosome abnormalities were found in women with onset-age  $\geq 30$  years (Devi and Benn, 1999), while three of six chromosome abnormalities detected by another group (Rebar and Conolly, 1990) also had a later onset. Thus, limitation of cytogenetic studies to those cases that are apparent by the age of 30 years appears too restrictive. Therefore, it is suggested that karyotypes are obtained from all patients with POF.

Gonadectomy is indicated in those patients whose karyotypes demonstrate Y chromosome material, in order to prevent gonadoblastoma. In families with POF, the risk of other females developing POF will depend on the mode of inheritance and the mode of transmission. Whereas in case of autosomal recessive

inheritance the risk involved in the recurrence of the disorder is lower, there is a similar genetic risk with both autosomal dominant and X-linked patterns of inheritance. In families with maternal transmission, the risk of recurring POF is 50% (39.5% corrected by penetrance), regardless of whether the pattern of inheritance is X-linked or autosomal dominant. In contrast, in families with paternal transmission the risk is 100% (79.1% corrected by penetrance) when the disorder has an X-linked pattern of inheritance, but decreases to 50% (39.5% corrected by penetrance) when the dominant pattern of inheritance is autosomal. If a POF patient appears to be a sporadic case, the risk of other female relatives developing POF will probably be equal to the risk of the general population, at ~1%. An adequate family history can distinguish between familial or sporadic premature POF.

The only means of obtaining a pregnancy in patients with POF is fertilization of a donor oocyte (Franco Junior *et al.*, 1994), and the efficacy of this procedure is at least as good as conventional IVF. A recent investigation (Hovatta *et al.*, 2002) achieved pregnancies after oocyte donation in women with severely decreased FSH action because of an inactivating point mutation (Ala189Val) in the FSH receptor which causes primary ovarian failure.

The necessity of identifying FRAXA premutations in an era of ovum donation, when women with POF are seeking ovum donation, has also been emphasized (Conway *et al.*, 1998). However, many of these women may be tempted to use ova from a relative who may also carry a FRAXA premutation and who would therefore be at risk of donating an ovum with a full FRAXA mutation.

The cryopreservation of oocytes is successful in animals, but awaits refinement before it can be applied routinely to humans with prodromal POF in order to save their oocytes for future fertilization (Matthews *et al.*, 1993). At present, it is possible only to advise females in affected families to have children at an early age—if possible, several years before the earliest menopause reported in the family.

Several different genetic mechanisms are known to affect the pathogenesis of POF, and the exact locations and number of loci on chromosome X responsible are currently under investigation. However, as yet no gene responsible for directing the primary ovarian differentiation has been detected. In addition, genes along the X chromosome must be involved, but so far these remain unidentified. The reasons for the difficulty in identifying such genes are a lack of candidate genes mapping on chromosome X, a scarcity of patients with fortuitous autosomal translocations, and small pedigrees, which hinders mapping of the loci (Simpson and Rajkovic, 1999). Learning to understand the influence of gene products on ovarian physiology and pathology and focusing on this dissection of essential genes might be helpful for future concepts in therapy.

Absolute numbers of the relative importance of different aetiological factors are difficult to calculate, mainly because of a lack of published studies with sufficient patient numbers that allow conclusions to be drawn. However, a detailed consideration of the literature, as provided by this review, suggests that the use of a routine diagnostic procedure would be valuable in identifying the aetiological factors for POF. Whereas the POF therapy is not affected, counselling of patients with regard to the risk of

recurrence must depend on the aetiology. The suggested diagnostic steps are given according to their assumed importance (Table I): a detailed analysis of the history of the patient and their family will allow identification of iatrogenic factors, and can also provide evidence of autoimmune diseases, the basis behind the initiation of further laboratory investigations, and of putative infections. A detailed investigation of the clinical phenotype, probably with additional consultation of a specialist, may render possible a diagnosis of X chromosome-linked as well as autosomal disorders. It is believed that if clinical signs provide evidence of only one of the genetic syndromes listed in Table I, then further molecular genetic investigation is warranted. The only possibility of detecting chromosomal aberrations which might be causative for POF but are without any other clinical phenotype (e.g. Turner-mosaicism, X chromosome deletions), would be to perform cytogenetic analyses. Accordingly, it is suggested that cytogenetic investigation should become part of the routine management associated with POF, independent of the patient's age. Based on findings from the current literature, it remains questionable as to whether further molecular investigations related to either *inhibin* or *FSHR* genes are warranted in case all other described aetiological factors are excluded.

**Table I.** Aetiological factors of premature ovarian failure

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1. Iatrogenic
Pelvic surgery
Pelvic irradiation
Chemotherapy
2. Association with other autoimmune diseases
Hypothyroidism
Addison's disease
Type I diabetes
Myasthenia gravis
Crohn's disease
Vitiligo
Pernicious anaemia
Systemic lupus erythematosus
Rheumatoid arthritis
3. Toxins and infections
Smoking
Varicella
Mumps
Cytomegalovirus
4. X chromosomal abnormalities
Turner's syndrome
Fragile X
5. Autosomal disorders
CDG1
Galactosaemia
Blepharophimosis
APECD
6. <i>Inhibin</i> gene
7. <i>FSHR</i> gene

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APECD = autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; CDG1 = carbohydrate-deficient glycoprotein syndrome type 1; *FSHR* = FSH receptor gene.

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