




AETIOLOGY OF PREMATURE OVARIAN FAILURE



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FIRST DEFINITION

- Premature ovarian insufficiency
was first proposed by

A L B R I G H T

1942.

DEFINITION

- **POF is a heterogenous disorder of multifactorial origin defined as the occurrence of amenorrhoea, hypergonadotropism and hypoestrogenism in women under the age of 40 years**

(De Moraes Ruehsen M, Jones GS, 1967)



MORTALITY

- **Two fold age-specific increase in mortality rate in untreated POF has been reported (Snowdon et al, 1989.)**

!!!!!!



DIAGNOSIS

- **<40 y's**
- **FSH>40 IU/L + E2<50 pmol/L**
- **Karyotype- younger than 30. y's of age**
- **Genetic screening for FRAXA premutat.**

INCIDENCE

YEARS	INCIDENCE
20	1: 10 000
30	1: 1000
35	1:250
40	1:100

OVARIAN PHYSIOLOGY

- Follicle atresia from 15. week of gestation;
- 6-7 mil.(20. week) →1-2 mil (on birth) → 300 000 in puberty;
- Fewer than 500 oocytes (0.007%)are released

- **CRITICAL PROCESS: transition**

primordial



primary follicles

AETIOLOGY

- I Genetic aberrations (X chr. or autosome)**
- II Autoimmune ovarian damage**
- III Environmental factors**
- IV Iatrogenic (surgical, radio or chemio Th)**
- V Metabolic changes (galactosaemia ...)**
- VI Defect in structure/effects of gonadotrop.**
- VII Idiopathic**

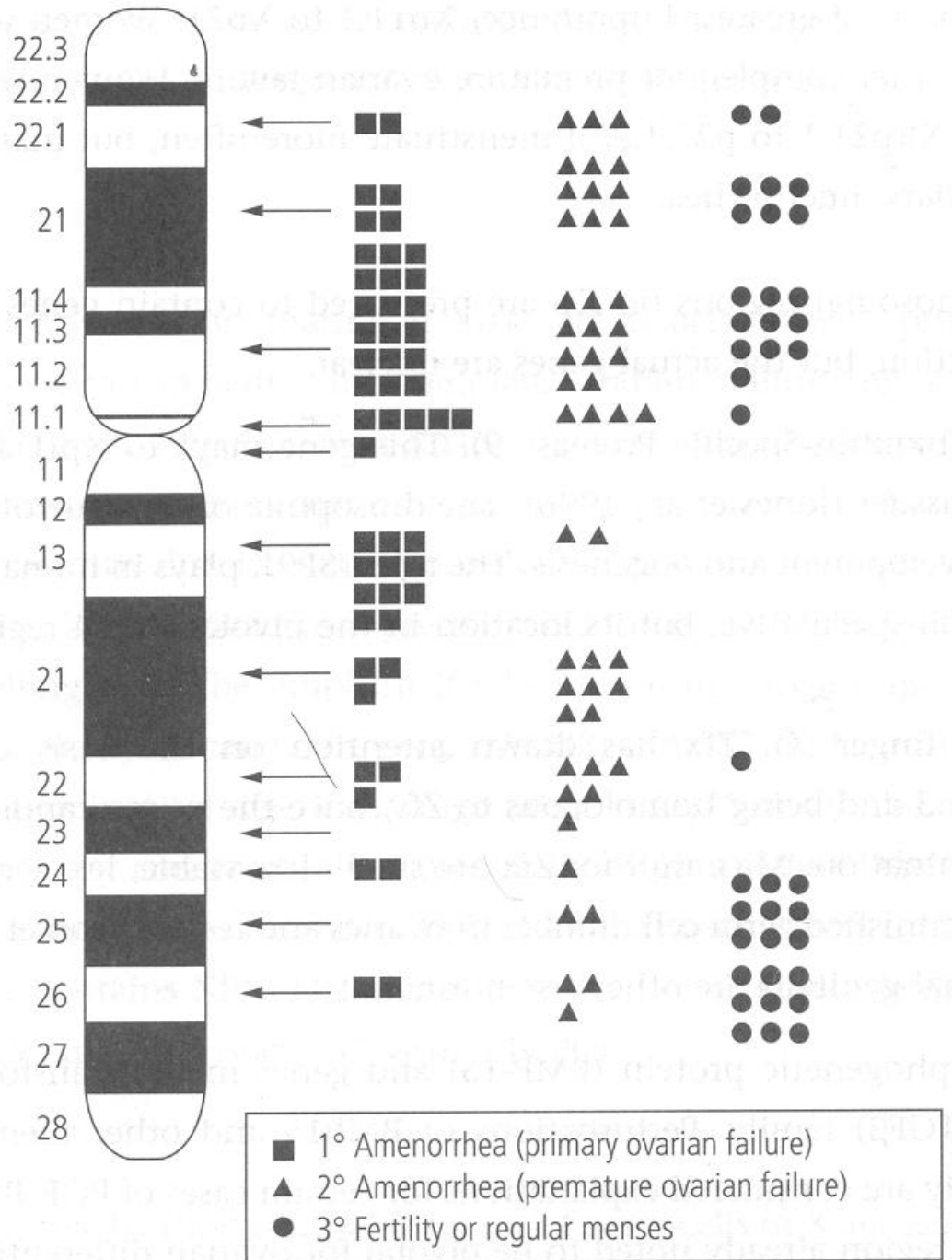
GENETIC ABERRATIONS

Reduced gene dosage

- Non-specific chromosome effects that impair meiosis



- ↓ number of primordial follicles
or
- ↑ atresia due to apoptosis or failure of follicle maturation.



X CHROMOSOME DEFECTS

- **Monosomy**
- **Trisomy**
- **Mosaicism**
- **Deletions**
- **Translocations**

X monosomy – Sy Turner

- Follicle degenerate by birth as a result of a lack of a diploid dosage one or more vital genes both alleles of which are active in oogenesis – follicle atresia
- **PROBLEM:** diplotene oocyte incorporation into nascent follicle
- In 80% paternally derived X is lost (Longlin SA)

TRISOMY/MOSAICISM

- Affects 1 in 900 women
- No effects on fertility
- Jacobs (1959): XXX+POF

MOSAICISM

- 45X/46XX & 45X/47XXX
- Mixed germ lines and manifest phenotypic abnorm, & POF
- 12% menstruate (Simpson,1975)

DELETIONS

- **Distal deletions – preserved ovarian functions**
- **Proximal deletions – ovarian failure**
- **Deletion in Xp11- 50% primary & 50% secondary amenorrhoea**
- **Deletion in Xq13 – primary amenorrhoea**

TRANSLOCATIONS- POF I i II

The most frequent breakpoints involve

- POF I: Xq 26-qter (24-39y), fragile X
- POF II: Xq 13.3-21.1 (16-21 y's)

Impaired chromosomes provoke a pachytene checkpoint during meiosis leading to oocyte apoptosis.

Transcriptional factor FOXL2

- **Earliest marker of ovarian differentiation**
- **Can ↑: StAR expression, follicle differentiation & initial recruitment**
- **In homozygous mutation: no differ. of granulosa cell from squamose to cuboid →no secondary follicles, oocyte atresia (Pisarka MD,2004)**

IDENTIFIED MUTATIONS

CHROMOSOME	GENE
X	FMR 1,2 BMP15
AUTOSOME	FOXL2,FSHR,LHR, INHIBIN A,AIRE, NOGGIN,POLG,GALT

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•
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POF GENES ON THE X - FRAGILE X SY

- FMR1 gen – responsible for FRAGILE X due to expansion of CGG repeats more than 55x at the 5'UTR Xq27.3
 - "gene silency" resulting in
 - *male mental retardation
 - *POF in female carriers

MONOGENIC DEFECTS

A) SYNDROMIC DEFECTS

- Congenital disorders of glycosylation
- Galactosemia (recessive)
- Blepharophymosis-ptosis-epicanthus inversus syndrome
- Pseudohypoparathyroidism Ia

MONOGENIC DEFECTS

B. ISOLATED DEFECTS

- **FSR receptor mutation**
- **LH receptor mutation**
- **FOXL2**
- **Bone morphogenic protein 15 mutation**

CURRENT TREND

- **None of candidate genes is accepted as a genetic marker for POF!**

AUTOIMMUNE CAUSE

AIRE gene responsible for autoimmune polyendocrinopathy-candidiasis sy

-abnormal self recognition

-20%POF has autoimmune disorder

- ↓natural killer cell activity, altered T cell regulation, oophoritis**

AUTOIMMUNE ASSOCIATION

- **ENDOCRINE**

- Hypothyroidism 25%

- Addison disease 3%

- Diabetes 2.5%

- Hypophysitis

- Hypoparathyroidism

(M.Rees,2006)

- **NON ENDOCRINE**

- Vitiligo, ITP, SLE, RA

- alopecia, cirrhosis,

- hepatitis, Sjogren sy,

- haemol. anaemia

- pernicious anaemia,

- chr.candidiasis

(Hoek,'97,Betterle,'02)

AUTOIMMUNE POLYGLANDULAR SYNDROME

TYPE	INHERITANCE	AUTOIMM. INVOLVEM.	AGE
I	Autos. reces.mut. in AIRE gene	Candidia.+Addison +Hypoparathyroid	3-5
II	Polygenic domin. HLADR3	Addison+Autoim. thyroid (Schmidt) & or DMI (Carpenter)	III decade
III	Apart from the absence of adrenal failure	Hypothy. + other immune sy NO Addison	Adult

PH

- In 60% POF no follicles, fibrosis
- 10% with follicles=Resistant ovary sy (Savage sy): receptor disorder (for gonadotropins, E2)

PH

- ↓ number of germinal cells, atretic follicles, lymphocyt. oophoritis, ↓ T Ly, ↓ B Ly, a lot of macrophages, plasma cells & NK cells.

ENVIRONMENTAL FACTORS

- Alkalyzing drugs toxic (Meirow,2000)
- POF: acute myeloid leukemia –15%; NonHodgkin lymphom – 32%; Hodgkin disease – 45%, Breast carcinoma – 50% (Benedetti P,2004)
- 100 girls receiving cytostatics before age of 5 y's – 17% POF

INFECTIONS

- **Mumps oophoritis (Rees M,2008)**
- **TBC**
- **Malaria**
- **Varicella**
- **Shigella**
- **CMV**
- **Herpes simplex virus**

METABOLIC

A) 17 OH deficiency

↑ FSH, LH, DOC, Progesteron

Hypertension, hypokaliemic alkalose

B) Def.galactosae-1-phosphate uridil

transferase: intracellular accumulation of galactosae metabolits → defficiency of granulosa cell pool (Forges T,2003)

GALT gene on 9p13

CURRENT TREND

- **To diagnose POF on time**
- **Loss of menstrual regularity of 3 or more consecutive months should be evaluated**
- **Screening for associated autoimmune disorders and karyotyping –part of Dg**
- **No role for ovarian biopsy!**

