Premature Ovarian Failure
(Primary Ovarian Insufficiency)
An Update

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Primary Ovarian Insufficiency

"…A syndrome characterized by primary ovarian insufficiency" and decreased stature…"

Fuller Albright, *et al.*

American Journal of Medical Sciences 204, 625-648, 1942

Nomenclature

TABLE 1

Terms used in the medical literature to equate with "primary ovarian insufficiency" as originally described by Fuller Albright in 1942 (4).

Term	Count in PubMed
Gonadal dysgenesis	2675
Premature ovarian failure	1461
Premature menopause	799
Early menopause	468
Hypergonadotropic hypogonadism	268
Ovarian dysgenesis	181
Primary ovarian failure	130
Hypergonadotropic amenorrhea	44
Primary ovarian insufficiency	33
Climacterium praecox or menopause praecox	5

Cooper, F&S, 2011

Reproductive Aging - Quantity

The life history of a woman's oocyte endowment

Fetal Life

Conception | 12 wks | 20 wks | Birth | Puberty Age ~12 | Age ~37 | Menopause Age ~51

PGCs ~1,000

PGC migration & proliferation 5-7 million

oogonia enter meiosis & differentiate

1 million oocytes/follicles

Ovulation begins 500,000 oocytes

Fertility declines ~25,000 oocytes

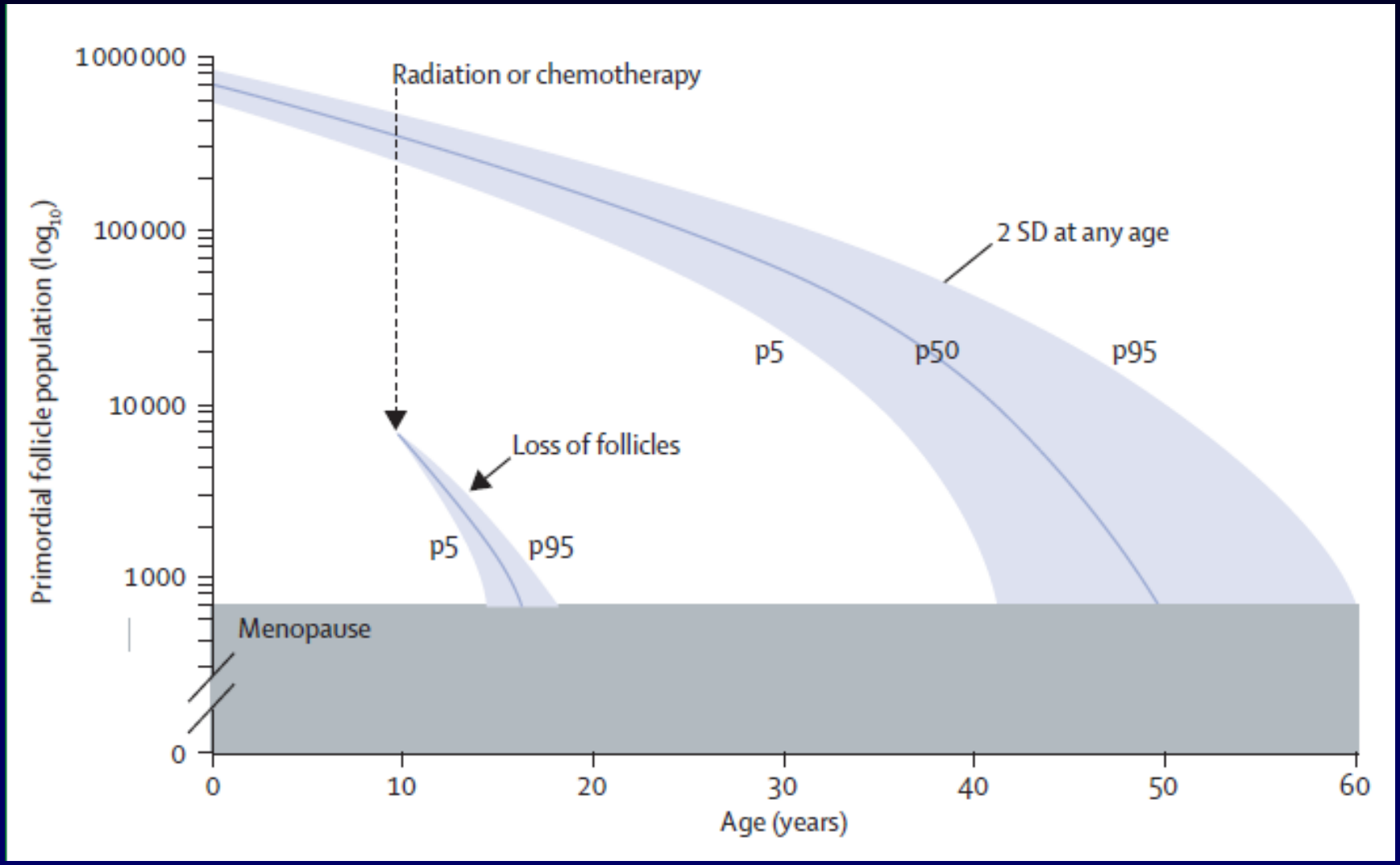
Ovulation ends <1,000 oocytes

POI
Clinical features

- < 40 years age (-2SD of χ(51yrs))
- 4 months of amenorrhoea
- Hypoestrogenism
- Serum FSH > 40 mIU/L on 2 occasions (at least 1 month apart)

- ≈10-28% of women with primary amenorrhea
- ≈ 4-18% with secondary amenorrhea have POI.

Decline of ovarian follicular reserve



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Primary Ovarian Insufficiency (POI)

INCIDENCE

YEARS	INCIDENCE
< 20	1 / 10,000
< 30	1 / 1,000
< 35	1 / 250
< 40	1 / 100

POI

Clinical features

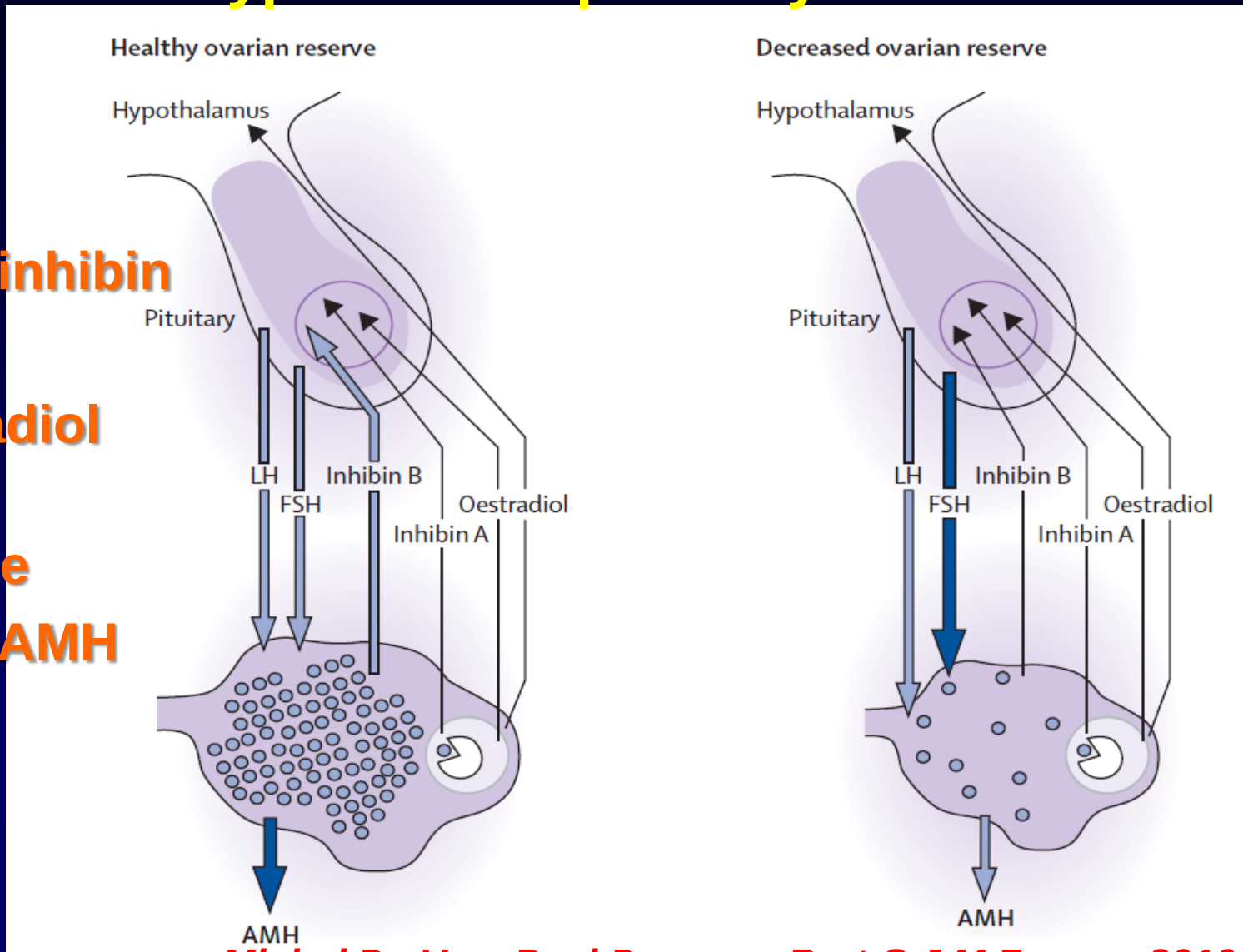
- **NO characteristic menstrual history**
  - **50 % oligomenorrhoea**
  - **25 % postpartum or after OC use**

- **Normal fertility**
  - **15-50 % ovulation**
  - **5-10 % spontaneous pregnancy**

- **Mortality**
  - **All-cause mortality RR: 2.14 (1.15-3.99) (Snowdon 1989)**
  - **Stroke mortality RR: 3.07 (1.34-7.03). (Snowdon 1989)**
    RR: 1.50 (0.97-2.34) (Cooper 1998)

Healthy and decreased ovarian follicular reserve with increased age and changes in concentrations of ovarian and hypothalamopituitary hormones

- Decreasing inhibin
- Rising FSH
- Erratic estradiol
- Decreasing Testosterone
- Decreasing AMH



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JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Anti-Müllerian Hormone, Inhibin B, and Antral Follicle Count in Young Women with Ovarian Failure

2009

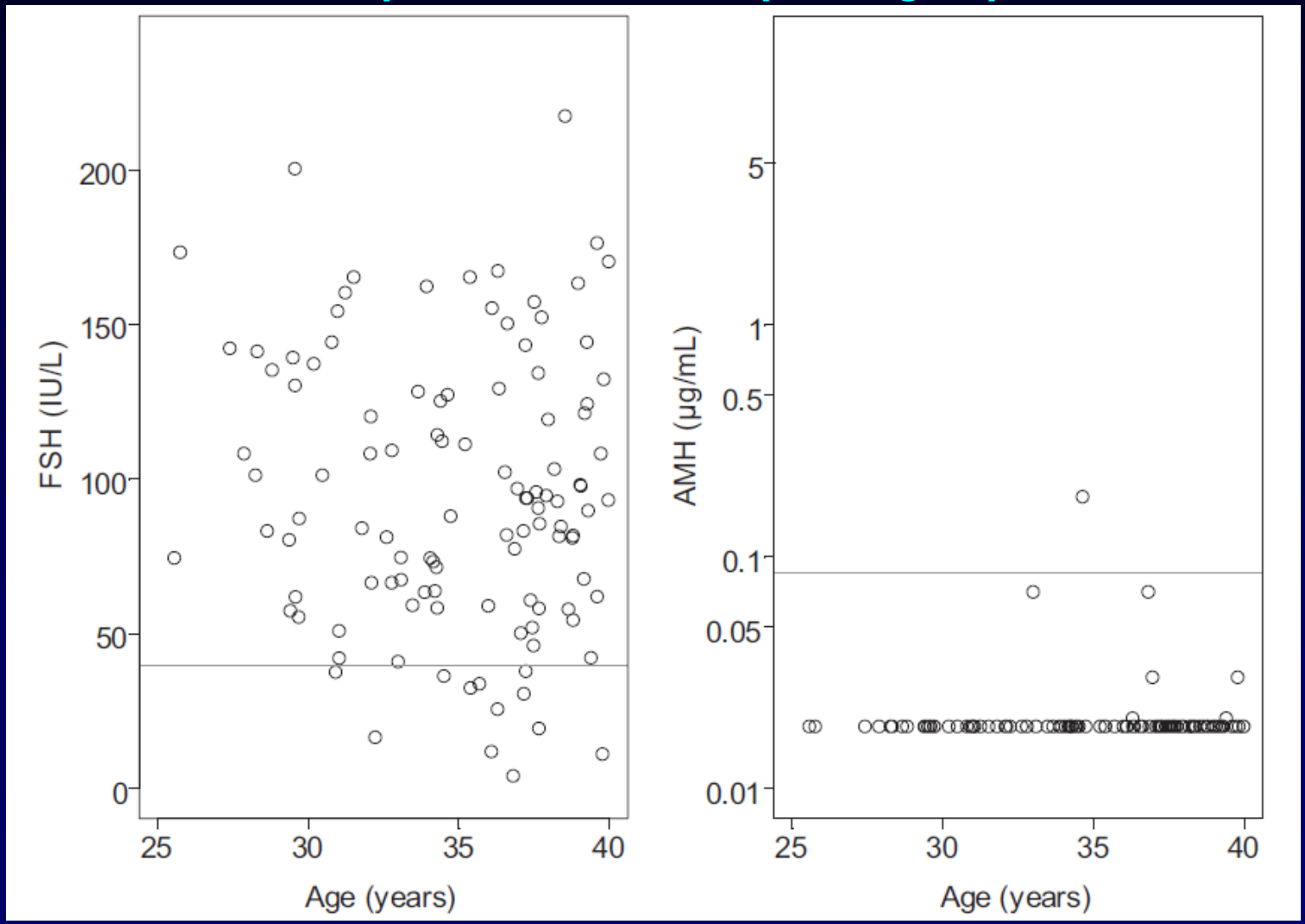
Erik A. H. Knauff, Marinus J. C. Eijkemans, Cornelius B. Lambalk, Marianne J. ten Kate-Booij, Annemieke Hoek, Catharina C. M. Beerendonk, Joop S. E. Laven, Angelique J. Goverde, Frank J. M. Broekmans, Axel P. N. Themmen, Frank H. de Jong, and Bart C. J. M. Fauser, on behalf of the Dutch Premature Ovarian Failure Consortium

Women

1. below age 40 yr with regular menses and normal FSH (controls; 83),
2. regular menstrual cycles and elevated FSH (>10.2 IU/L) [incipient ovarian failure (IOF); 68];
3. oligomenorrhea and elevated FSH (>10.2 IU/L) [transitional ovarian failure (TOF); 79];
4. at least 4 mo. Amenorrhea + FSH levels exceeding 40 IU/L [premature ovarian failure (POF); n112].

FSH (second measurement after diagnosis) and AMH levels (log scale) in relation to age in 112 POF patients

The *lines indicate the cutoff value of 40 IU/L for* FSH and the menopausal threshold (0.086 g/ml) for AMH



Compared with inhibin B and AFC, AMH was more consistently correlated with the clinical degree of follicle pool depletion in young women presenting with elevated FSH levels

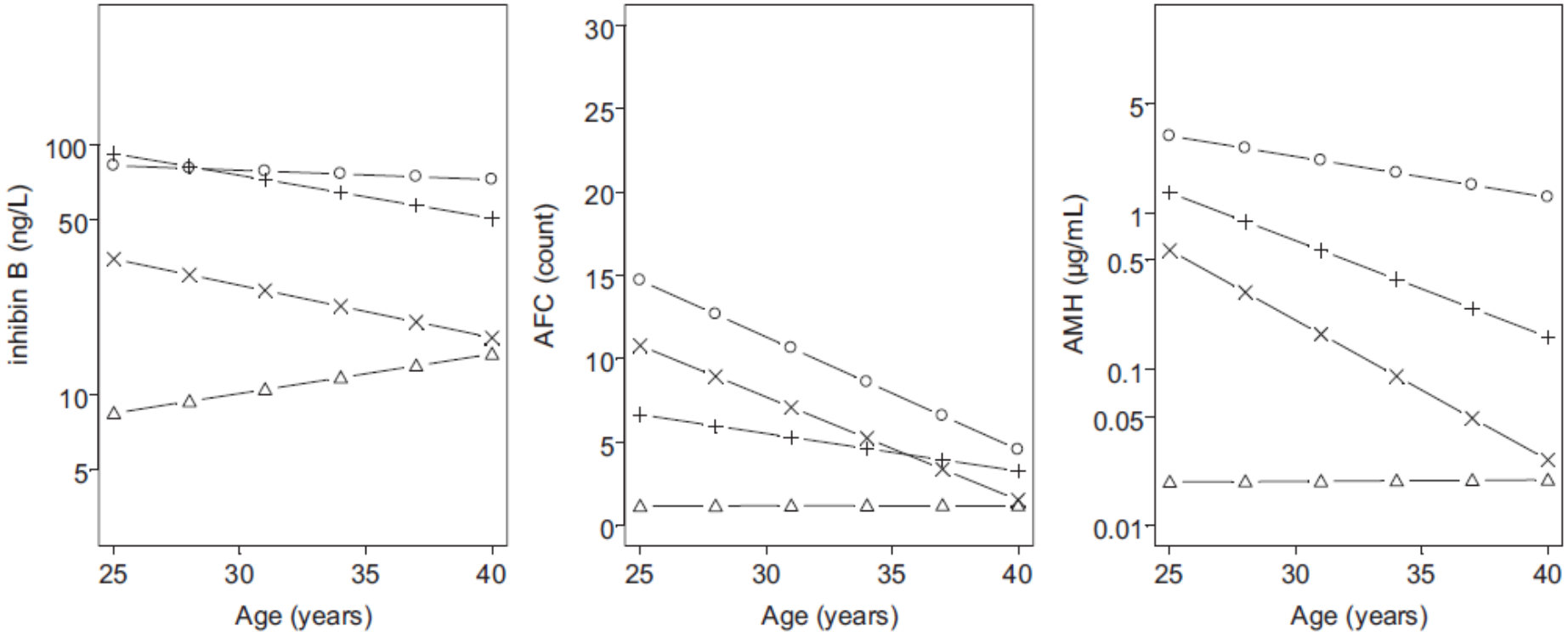


FIG. 3. Regression lines of inhibin B (log scale), AFC, and AMH (log scale) values by age for subgroups of young hypergonadotropic women. °-°-°, Controls; +-+-+, IOF; x-x-x, TOF; Δ-Δ-Δ, POF.

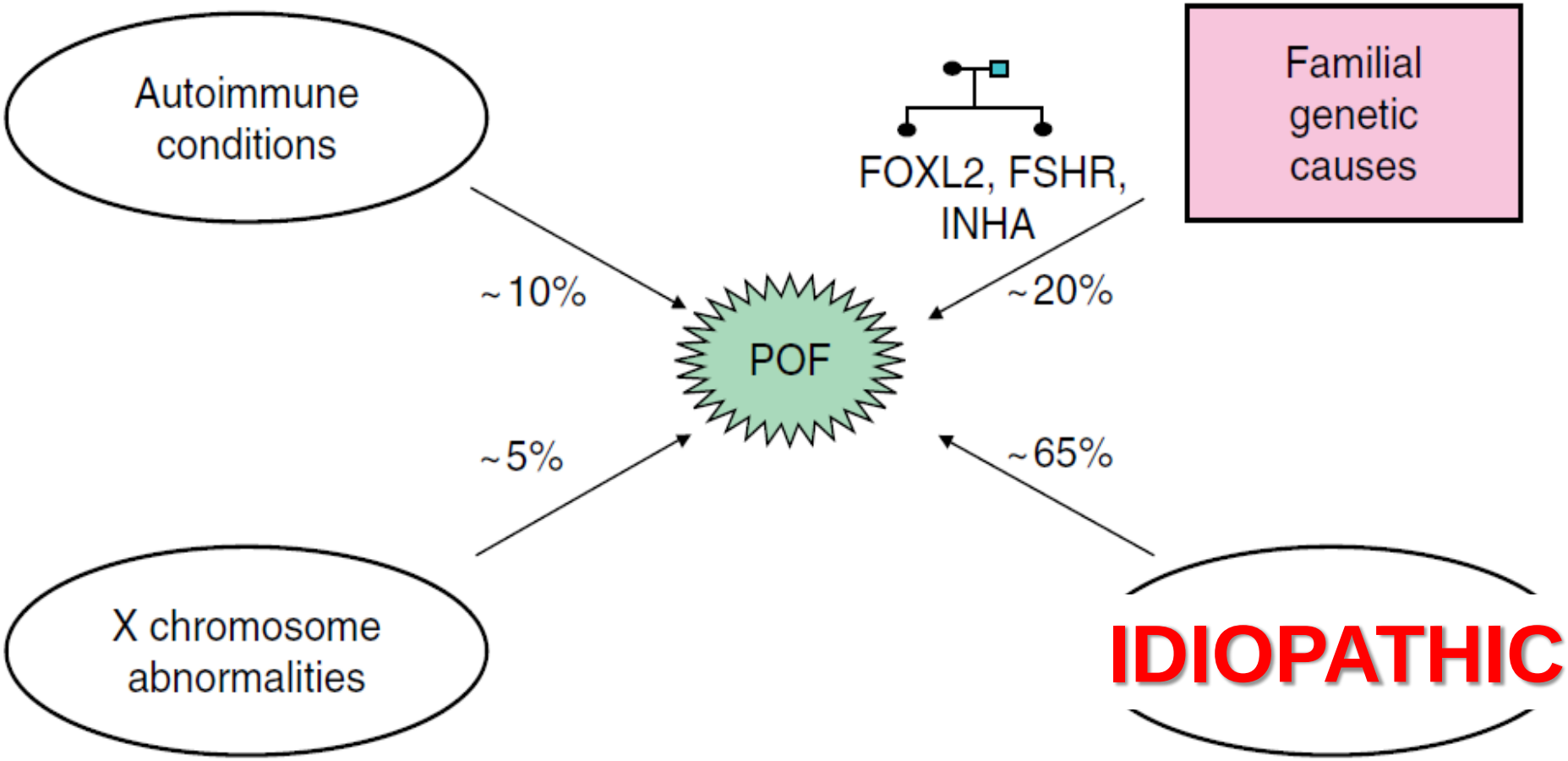
POI

Causes

- **Ovarian follicle depletion**
  - Low initial follicle number
  - Accelerated follicle loss
- **Ovarian follicle dysfunction**
  - Signal defect
  - Enzyme deficiency
  - Autoimmunity

POI

Causes

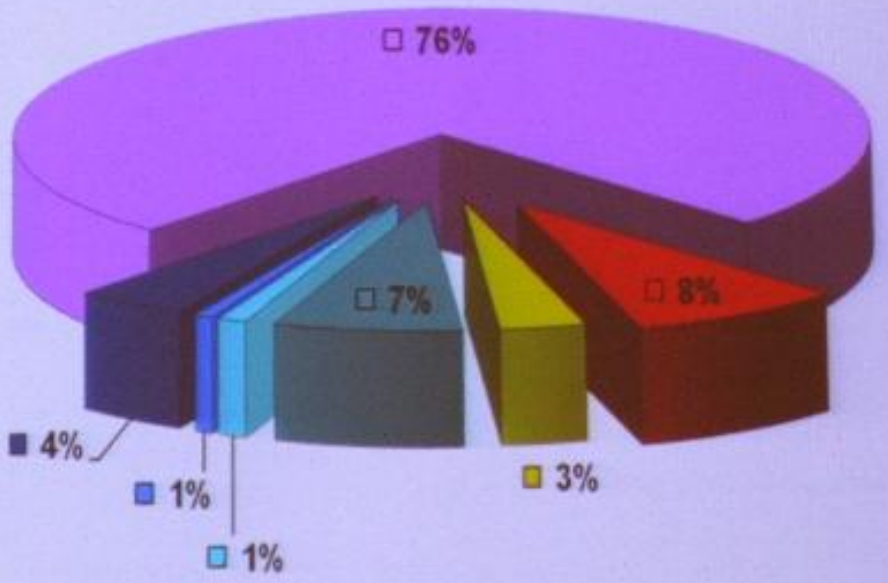


Shelling AN, Reproduction 140: 633, 2010

POI

Etiological factors in Dutch Consortium

(N = ~ 480)



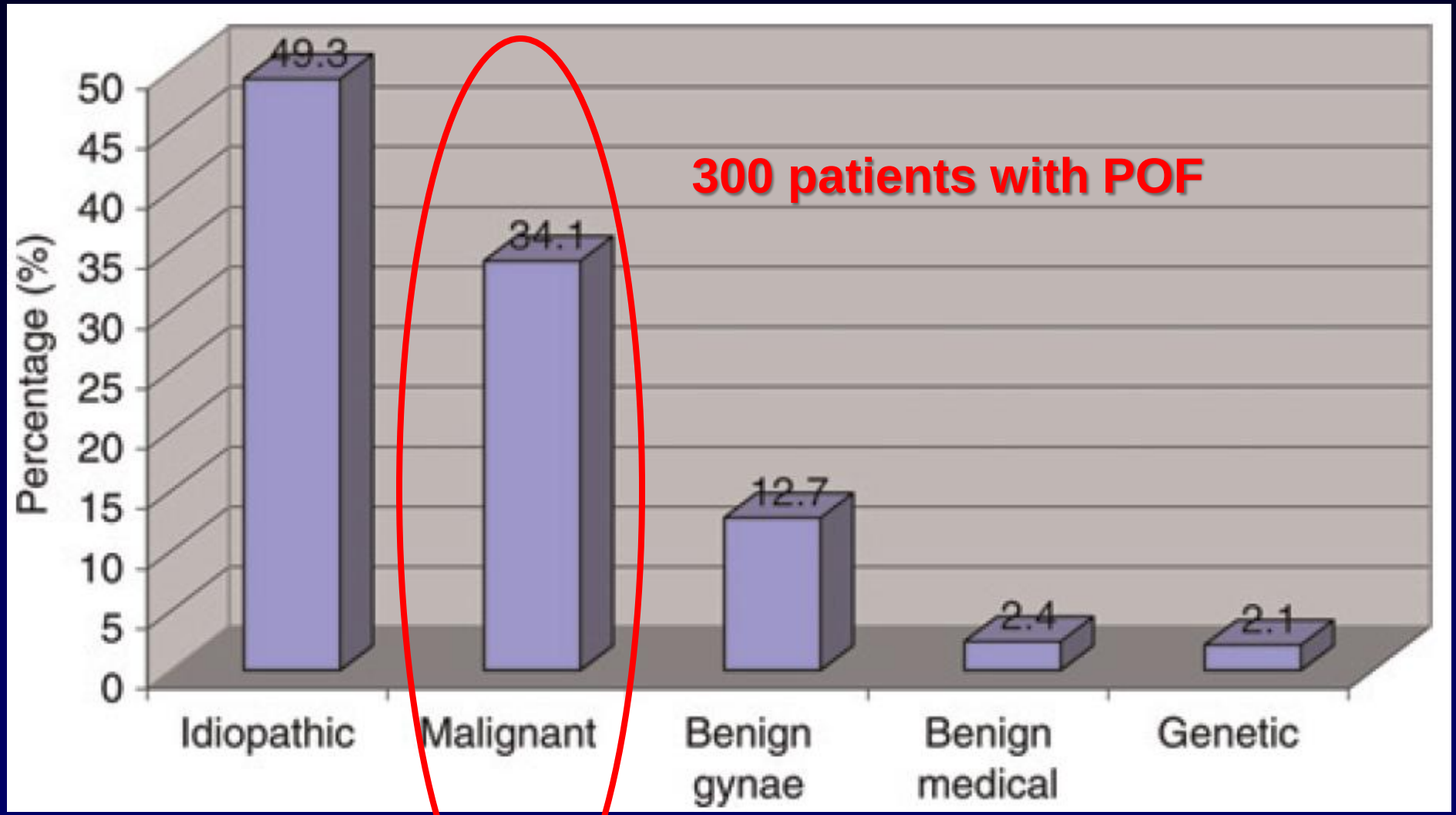
- Abnormal Karyotype
- Fragile X Premutation
- Anti-Thyroid
- Anti-Adrenal
- Anti-Ovarian
- Anti-Parietal
- Idiopathic

Causes of premature ovarian failure in 352 women attending the Middlesex Hospital, London, UK

	n	%
Idiopathic (including autoimmune)	204	58
Turner's syndrome	82	23
Chemotherapy	24	7
Familial premature ovarian failure	15	4
Pelvic surgery	8	2
46XY gonadal dysgenesis	7	2
Galactosaemia	6	2
Pelvic irradiation	6	2

Gerard S Conway, 2000

Aetiology of POF at the West London Menopause Centre



Kate Maclaran, 2010

Character of the disorder	No. (%) N = 75
1. Familial	18 (24)
Autosomal dominant inheritance, sex-limited transmission or X dominant inheritance	17 (22.6)
X chromosome abnormality [46,X,del(X)(q22)]	1 (1.3)
2. Chromosomal disorders	16 (21.3)
a) X chromosome deletions	8 (10.6)
Xq deletion[a]	7 (9.3)
Xp deletion	1 (1.3)
b) Numerical chromosomal rearrangements	6 (8)
47,XXX	2 (2.7)
mos 45,X[30]/46,XX [70]	1 (1.3)
mos 45,X [54]/46,XX [46]	1 (1.3)
mos 45,X[20]/46,XX[48]/47,XXX[32]	1 (1.3)
mos 45,X[36]/46,XX[30]/47,XXX[34]	1 (1.3)
c) Translocations	2 (2.7)
X to autosome translocation 46,X,t(3;X)(q23;q24)	1 (1.3)
Autosomal translocation 45,XX,t(13:14)(q10;q10)	1 (1.3)
3. Swyer syndrome	2 (2.7)
4. Autosomal recessive inheritance[b]	1 (1.3)
5. Fragile X premutation carrier	2 (2.7)
Total No. of patients with sporadic or familial genetic abnormalities	39 (52)

[a] Three of these 7 patients had mosaic mutations.
[b] This patient had galactosemia.

Genetic abnormalities in Turkish women with premature ovarian failure

A genetic cause of POF was identified in 39 (52%) of 75 patients (5yrs.)

Gulay Ceylaner, 2010

POI

Cerrahpasa experience (2002-2009)

- N=78
- 66% w/oligomenorrhoea
- 14% w/primary amenorrhoea
- Mean BMI 23
- Mean FSH 67
- Mean LH 27
- Mean E2 25
- 33 pts. karyotype'd: 1 (3.03%)→(45,XO)
- 53 pts. chk'd w/DEXA: 6 (11.3%) osteopenia cases
- 20 pts chk'd for thyroid Abs: + in 10 (50%) cases

Oral, E

POI Causes

Panel 1: Disorders leading to ovarian insufficiency*

Ovarian follicle dysfunction

Signalling defect

- Follicle-stimulating-hormone-receptor mutation (*FSHR*)
- Luteinising-hormone-receptor mutation (*LHR*)
- Pseudohypoparathyroidism type 1a (*GNAS*)

Enzyme deficiency

- Isolated 17-α-hydroxylase or 17,20-lyase deficiency (*CYP17A1*)
- Aromatase deficiency (*CYP19*)

Autoimmunity

- Autoimmune lymphocytic oophoritis
- Polyglandular autoimmune syndrome, including adrenal, thyroid, or thymic disease
- Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (*AIRE*)

Associated with insufficient follicle number

- Luteinised graafian follicles

Ovarian follicle depletion

Insufficient initial follicle number

- Blepharophimosis, ptosis, and epicanthus inversus syndrome (*FOXL2*)
- 46,XY gonadal dysgenesis (*SRY* and others)
- Other syndromes and genes associated with an insufficient initial follicle number that have not been described

Spontaneous accelerated follicle loss

- Turner's syndrome: full blown and mosaic variants (unknown)
- Trisomy or polysomy X, or mosaic variants
- Macrodeletions Xp or Xq
- Autosomal or X translocations

Adapted from Nelson.[28] *Genes associated with primary ovarian insufficiency are shown in parenthesis.

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POI Causes

Panel 2: Genes associated with primary ovarian insufficiency

Known human X chromosome-located functionally relevant genes

- Basic helix-loop-helix protein (*BHLHB9*)
- Bone morphogenetic protein 15 (*BMP15*)
- Homologue of the *Drosophila* dachshund gene (*DACH2*)
- Second human homologue of the *Drosophila* diaphanous gene (*DIAPH2*)
- Fragile X mental retardation syndrome (*FMR1*)
- X-linked mental retardation, associated with fragile site FRAXE (*FMR2*)
- Premature ovarian failure 1B (*POF1B*)
- X-inactivation-specific transcript (*XIST*)
- X-prolyl aminopeptidase 2 (*XPNPEP2*)

Known human autosomal functionally relevant genes

- Autoimmune regulator (*AIRE*)
- Deleted in azoospermia-like (*DAZL*)
- Homologue of yeast disrupted meiotic cDNA 1 (*DMC1*)
- Eukaryotic translation initiation factor 5B (*EIF5B*)
- Oestrogen receptor 1 (*ESR1*)
- Homologue of murine factor in germline α (*FIGLA*)
- Forkhead transcription factor (*FOXL2*)
- Forkhead box O1A (*FOXO1A*)
- Forkhead box O3A (*FOXO3A*)
- β chain of follicle-stimulating hormone (*FSHB*)
- Follicle-stimulating-hormone receptor (*FSHR*)
- Galactose-1-phosphate uridyltransferase (*GALT*)
- Growth-differentiation factor 9 (*GDF9*)
- G protein-coupled receptor 3 (*GPR3*)
- Type II 3-β-hydroxysteroid dehydrogenase deficiency (*HSD3B2*)
- Inhibin alpha (*INHA*)
- Luteinising hormone, β polypeptide (*LHB*)
- LIM homeobox gene 8 (*LHX8*)
- Homologue of *Escherichia coli MutS*, 5 (*MSH5*)
- Homologue of *Drosophila Nanos3* (*NANOS3*)
- Homologue of murine newborn ovary homeobox (*NOBOX*)
- Homologue of murine noggin (*NOG*)
- Nuclear receptor subfamily 5, group A, member 1 (*NR5A1*)
- Progesterone receptor membrane component 1 (*PGRMC1*)
- DNA polymerase γ (*POLG*)
- Transforming growth factor-β receptor, type 3 (*TGFBR3*)
- Y box-binding protein 2 (*YBX2*)

Data from Broekmans and colleagues[29] and Knauff and colleagues.[30] See webappendix for more on the genes listed.

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Smoking - POI

An exposure of mice to PAHs (Polycyclic aromatic hydrocarbons) induces the expression of Bax (pro-apoptosis gene) in oocytes, followed by apoptosis, thus, oocyte destruction and ovarian failure occur

Matikainen T, Nature Genet, 2001

Smoking - POI

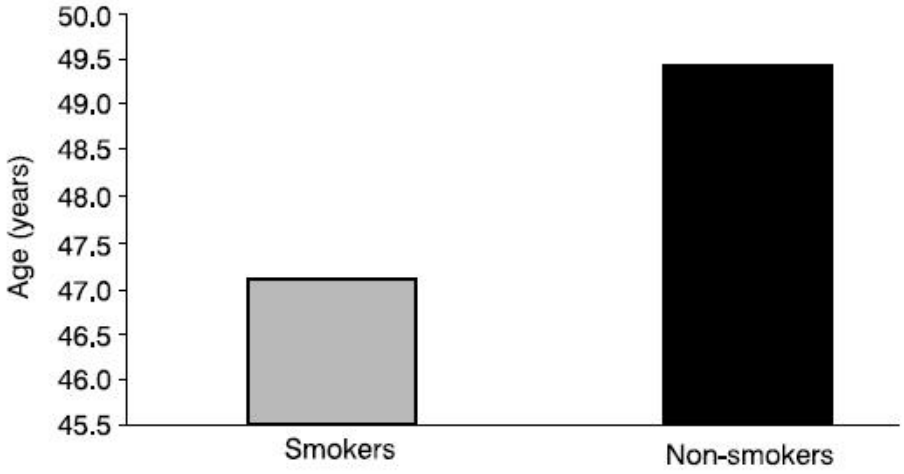


Figure 1. Age at menopause in smokers (n = 87) and non-smokers (n = 263). The two groups were significantly different ($P < 0.000001$).

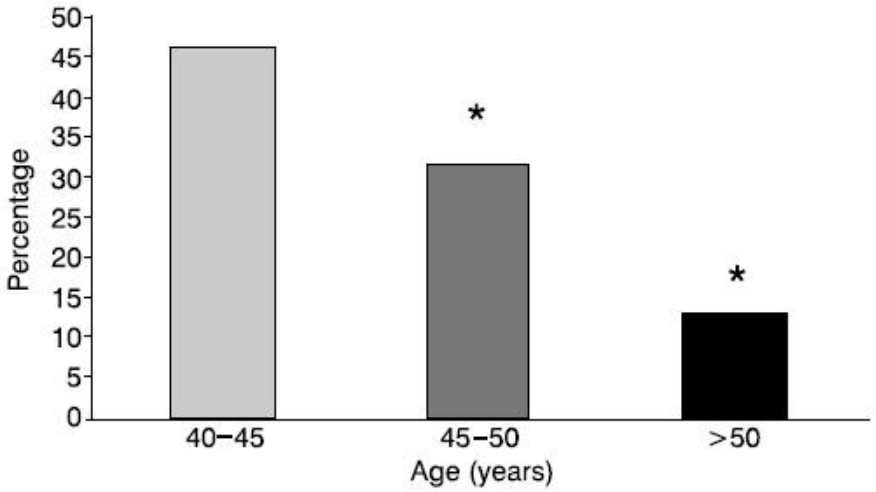


Figure 2. Smokers (%) in different age groups at menopause. * indicates significantly different from youngest age group ($P < 0.0001$).

Di Prospero F, 2003

POI among hairdressers (mail survey)

Among 443 hairdressers and 508 women in other occupations, 14 (3.2%) and 7 (1.4%) developed POI, resp.

Table II RRs and 95% CIs for POF among hairdressers compared with non-hairdressers estimated using Cox proportional hazards regression

	POF cases	Person years[a]	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[b]
All ages				
All races				
Non-hairdressers	7	20 887	1.00 (reference)	1.00 (reference)
Hairdressers	14	18 719	2.06 (0.83, 5.09)	1.90 (0.76, 4.72)
Caucasian women				
Non-hairdressers	4	17 963	1.00 (reference)	1.00 (reference)
Hairdressers	14	16 264	3.53 (1.16, 10.74)	3.24 (1.06, 9.91)
Ages 40–55 years				
All races				
Non-hairdressers	5	14 539	1.00 (reference)	1.00 (reference)
Hairdressers	12	14 232	2.46 (0.87, 6.97)	2.31 (0.81, 6.62)
Caucasian women				
Non-hairdressers	2	12 891	1.00 (reference)	1.00 (reference)
Hairdressers	11	12 352	5.78 (1.29, 25.82)	5.58 (1.24, 25.22)

95% CI = 95% confidence interval; RR = relative risk; POF = premature ovarian failure.

[a]Calculated from age 0 (birth) to either age at menopause for those women who reported having undergone menopause (including those who had been diagnosed with POF) or age at the time of survey completion for those women who were still menstruating.

[b]Adjusted for age and current smoking (yes/no).

L. Gallicchio, 2009

POI
Family history

- **4-31%** (Conway 1996, Vegetti 1998, Van Kasteren 1999)
- **Mother's menopause age** (Torgerson 1994)
- **Sister's menopause age** (Cramer 1995)

- **Twin studies**
  - **MZ % 58, DZ % 39** (Snieder 1998)
  - **MZ % 53, DZ % 33** (Treolar 1998)

Early menopause
Family history

- 129 early menopause cases (<46 years old)
- Overall 129 (37.5%) of the early menopause cases reported a family history of menopause before age 46 years in a mother, sister, aunt, or grandmother compared to 31 (9.0%) of controls yielding an odds ratio (OR) of 6.1 (95% [CI] of 3.9 to 9.4) after adjustment for smoking history, education, parity, and body mass index.

Cramer DW, 1995

POI

Autoimmune (≈in 20% of POI)

25.0 % Hypothyroidism

3.0 % Adrenal insufficiency

2.5 % Diabetes (Kim 1997)

POI
Autoimmune

- POI in up to 60% (39% at the age of 15 years and 72% at 40 years) of women with the autoimmune polyglandular syndrome (APS) type 1 (hypoparathyroidism, adrenal insufficiency, and chronic mucocutaneous candidiasis)

Ahonen P, 1988; Wheatcroft N, 1997

- APS type 2 (adrenal insufficiency, insulin dependent diabetes mellitus, and hypothyroidism) is less frequently associated with POI (10%)

Wheatcroft N, 1997

POI

Chromosome abnormalities

- Rare in secondary amenorrhea (13%)

  Rebar, 1982

- 50% in women with primary amenorrhea

  Rebar, 2009

- It is nevertheless useful to obtain a karyotype in all women with POI, to reveal a Y chromosome or chromosomal fragment, mandating the need for gonadectomy given the known association with subsequent malignancy

  Manuel, 1976

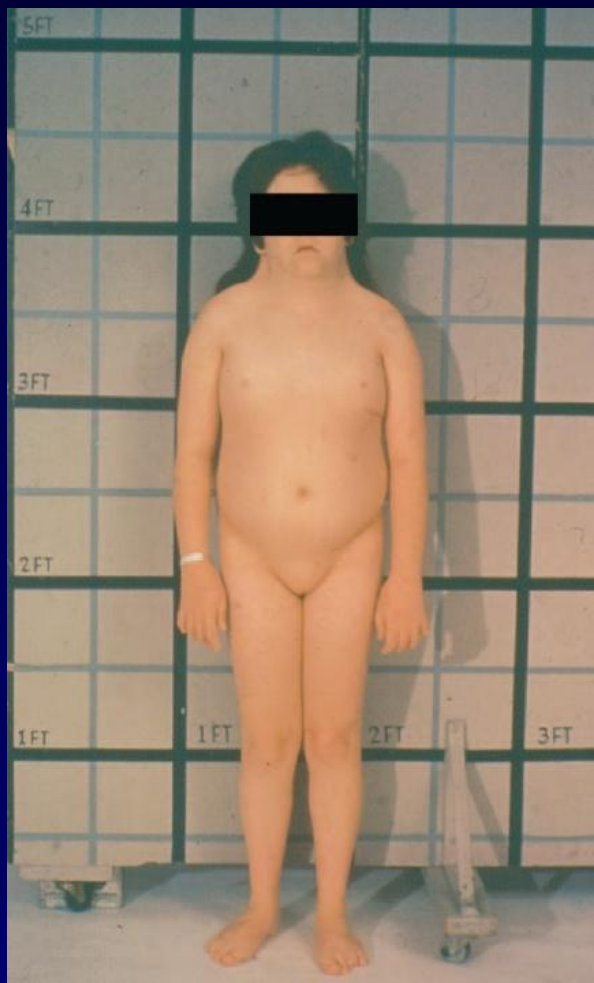
POI

X chromosome abnormalities

- 5-40%
- X-mosaicisms (45 XO, 45,XO/46,XX, 46,XX/47,XXX)
- X chromosome deletions
- X chromosome balanced translocations
- Xq13-q26 (Critical region for normal ovarian function) (Sarto 1973)
- POF1 Xq21.3-q27 Xq26.1-q27 (24–39 yrs) (Krauss 1987)
- POF2 Xq13.3-q21.1 (16–21 yrs) (Powell 1994)

Monosomi X (Turner's sy)

- One of the most common chromosomal anomalies with a prevalence of about 1:2000 live female births
- 50 % of gonad dysgenesis,
- 25 % mosaicisms (45,XO/46,XX)
- 80 % of them paternal X is missing
- 3% spontan menses,
- 5% breast development (mosaicisms 12-18%)
- Fertility ????



Monosomi X (Turner)

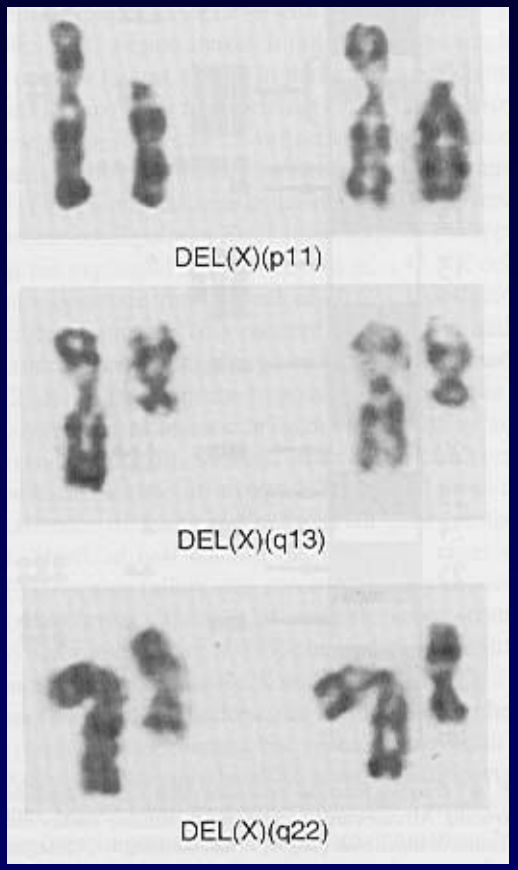
- Women in Turner syndrome have normal follicular development up to the 18th week IU development
- The follicles start to disappear, but up to 40% of Turner girls may have them as teenagers
- Premature menopause is expected… but at which ages and how to make individual prognosis ???
- Onset of spontaneous puberty, mosaic Turner syndrome and normal serum concentrations of FSH and AMH are positive prognostic signs for the presence of ovarian follicles at the ages of 12-14 yrs, where they can be cryostored
- Oocyte donation is a good treatment , but the risks for pregnancy have to be considered (Aortic rupture)

Hovatta, Outi, 2011 (TANTEM)

POI

X-chromosome deletions

- **Complete**
  - Xp11
  - Xq13
  - Xq22
- **Partial**
  - Xp21
  - Xp22
  - Xq26
  - Xq28



Prevalence of the Triple X syndrome in phenotypically normal women with POI

- In the general population, the syndrome affects 1 in 900 women
- its relative prevalence among women with POI is not known

- High prevalence of psychological disturbances but normal phenotype and reproductive competence in the majority of cases.

Ravinder Goswami, 2003

X Chromosome

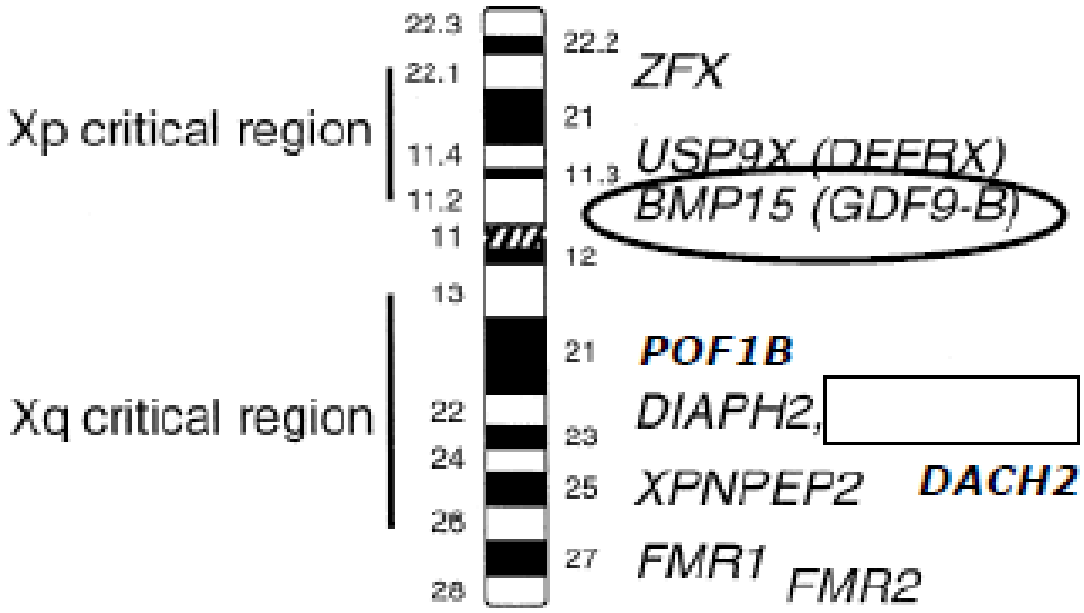


Figure 1. POF critical regions and candidate genes on the human X chromosome.

Bone Morphogenetic Protein 15 Gene (BMP15)

encodes for an oocyte-derived growth and differentiation factor which is involved in follicular development as a critical regulator of many granulosa cell processes

Table 2 Frequency of *BMP15* gene variants in patients with primary ovarian insufficiency (POI) and controls of different ethnicity

	Size of POI cohort	Patients with nonsynonymous variations (%)	Size of control population	References
Origin				
Japan	15	0	–	Takebayashi *et al.* (2000)
New Zealand	38	0	51	Chand *et al.* (2006)
Europe and USA (Caucasian)	166	4·2[a]	211 (0%)[a]	Di Pasquale *et al.* (2006)
Europe and North Africa	203	1·5[a]	54 (0%)[a]	Laissue *et al.* (2006)
India	202	8·9[a]	197 (0%)[a]	Dixit *et al.* (2006*a*)
Italy and USA (Caucasian)	300	4·3[a]	216 (0%)[a]	Rossetti *et al.* (2009)
China	100	6[a]	100 (1%)[a]	Wang *et al.* (2010)
Europe, North Africa and Asia	50	12[a]	214[a] (1·9%)	Tiotiu *et al.* (2010)

[a]After exclusion of p.ins263L, p.N103S found in 3–12% of POI patients and controls.

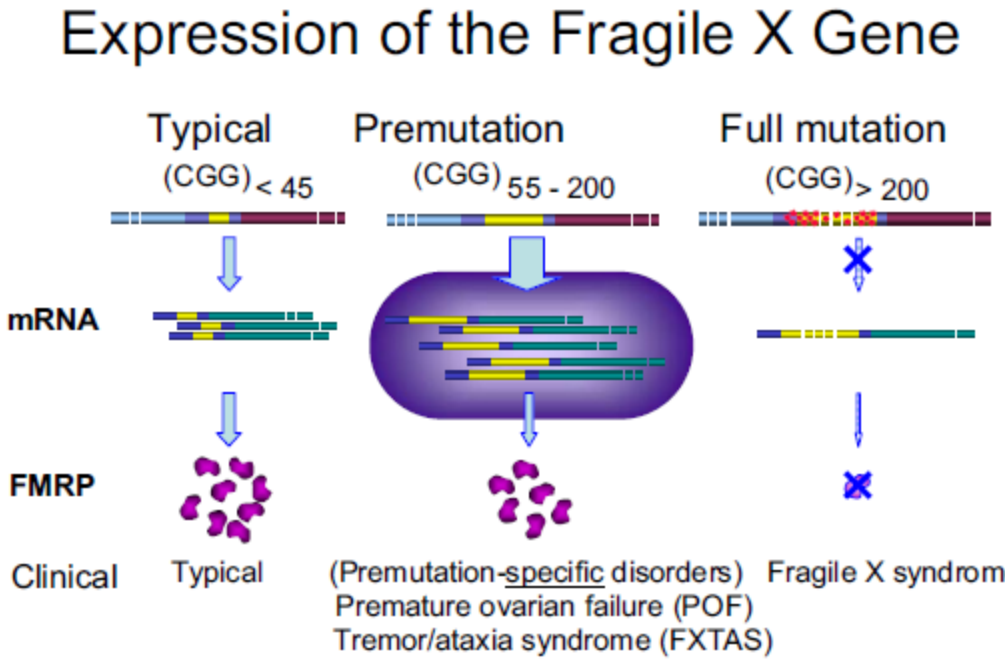
POI

Fragile X syndrome (FRAXA)

X-linked dominant

- FMR1 (Fragile X Mental Retardation Gene 1 (Xq27.3)) an expansion of a trinucleotide (CGG) repeat located at the 5' UTR region of the gene FMR-1.
- normal (6-40), gray-zone (41-60), premutated (61-200), and fully mutated (>200).

Expression of *FMR1* in normal women, premutation carriers, and full mutation carriers. Figure adapted from Hagerman and Hagerman (10).



Wittenberger. FMR1 premutation. Fertil Steril 2007.

POI

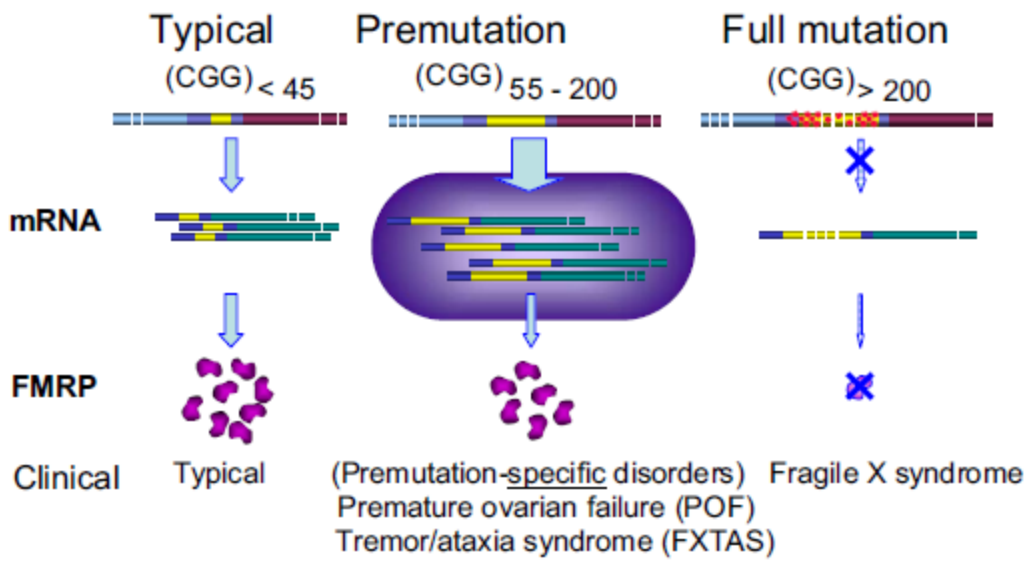
Fragile X syndrome (FRAXA)

FRAXA: FULL MUTATION (>200)

the most common cause of inherited mental retardation as well as the most common known genetic cause of autism.

- **approximately 1/4,000 males (IQ↓↓↓)**
- **1/4,000-8,000 females (IQ≈↓)**

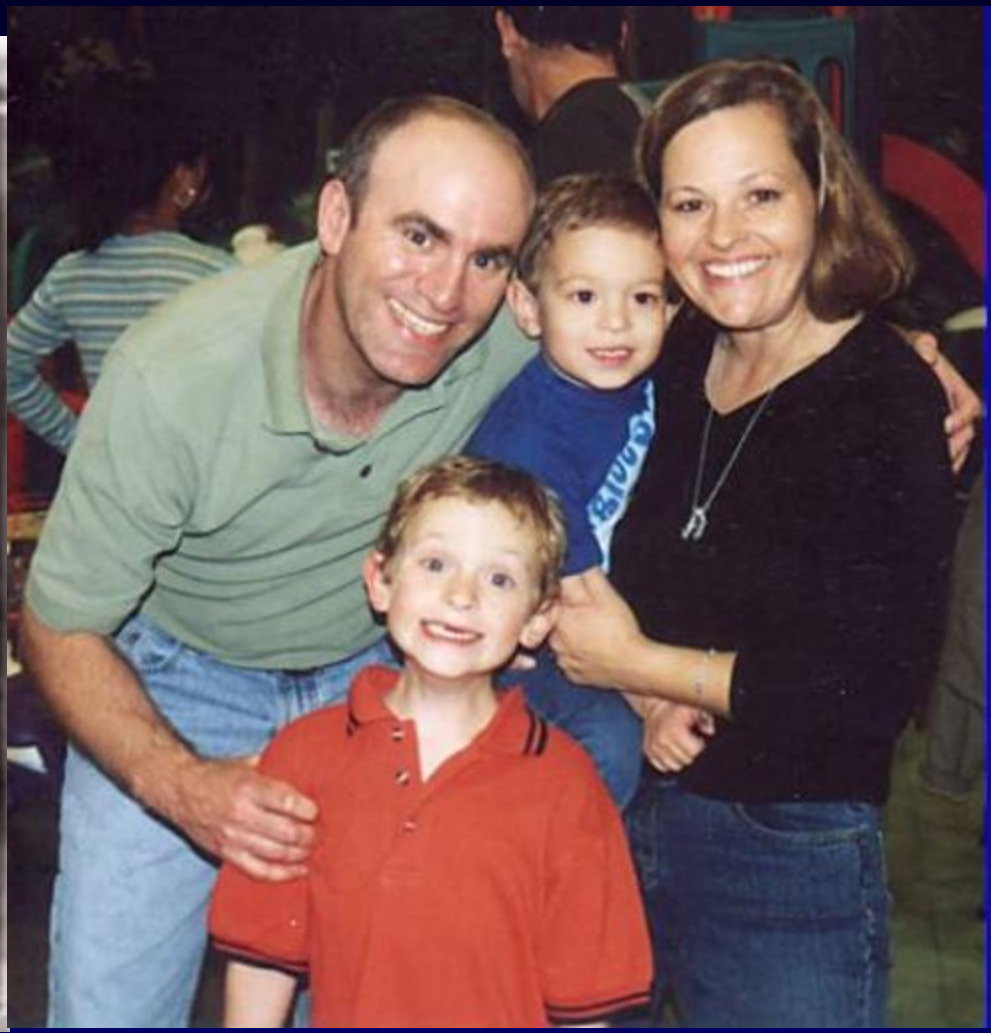
Expression of *FMR1* in normal women, premutation carriers, and full mutation carriers. Figure adapted from Hagerman and Hagerman (10).



Wittenberger. FMR1 premutation. Fertil Steril 2007.

POI

Fragile X syndrome (FRAXA)



Corrigan, et al, FS 84: 1508, 2005

POI

FXTAS / POI

PREMUTATION (61-200)

1. FXTAS

An adult onset neurologic disorder

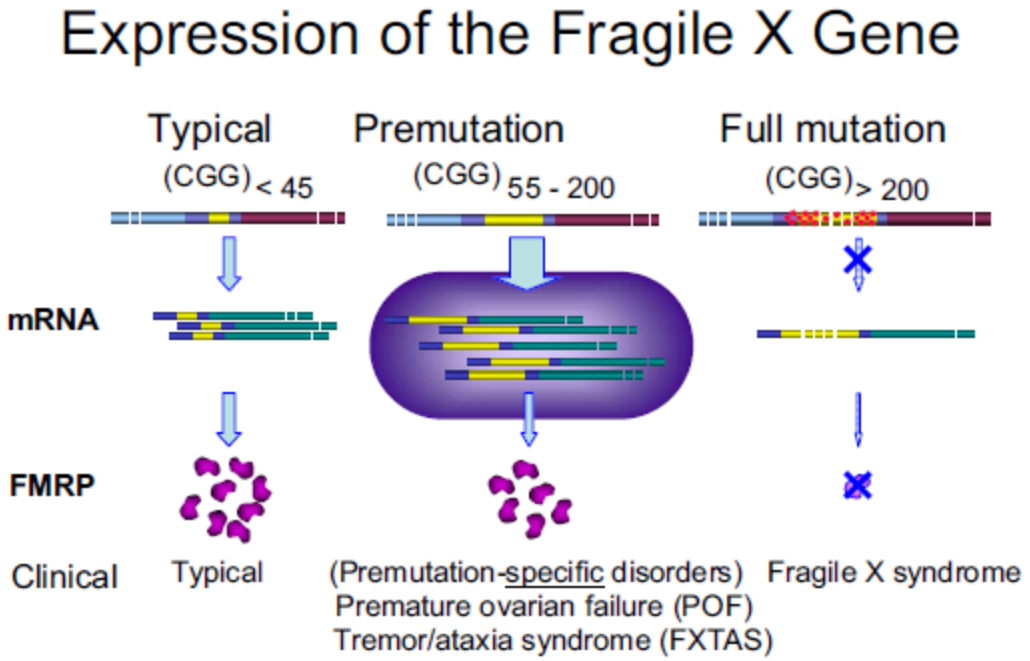
“Fragile X–associated tremor/ ataxia syn.”

X linked recessive

Primarily affects males

Incidence increases w/age

Expression of *FMR1* in normal women, premutation carriers, and full mutation carriers. Figure adapted from Hagerman and Hagerman (10).



Wittenberger. FMR1 premutation. Fertil Steril 2007.

POI

FXTAS / POI

PREMUTATION

(61-200)

2. POI:

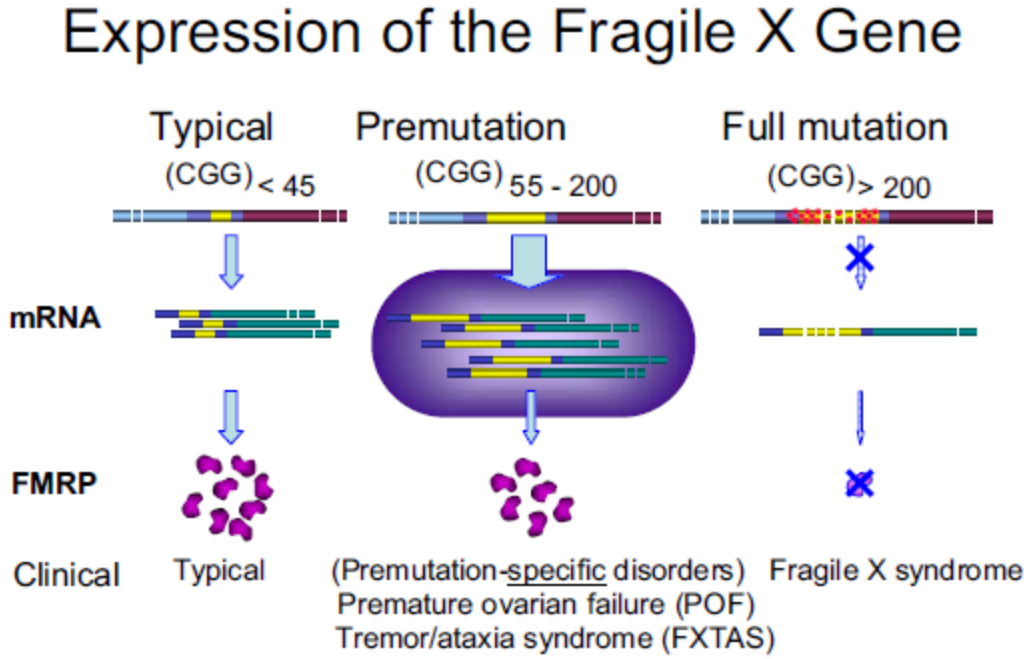
13-26% of women who carry the premutation

Premut. Incidence

Sporadic POI: 0.8-7.5%

Familial POI: up to 13%

Expression of *FMR1* in normal women, premutation carriers, and full mutation carriers. Figure adapted from Hagerman and Hagerman (10).



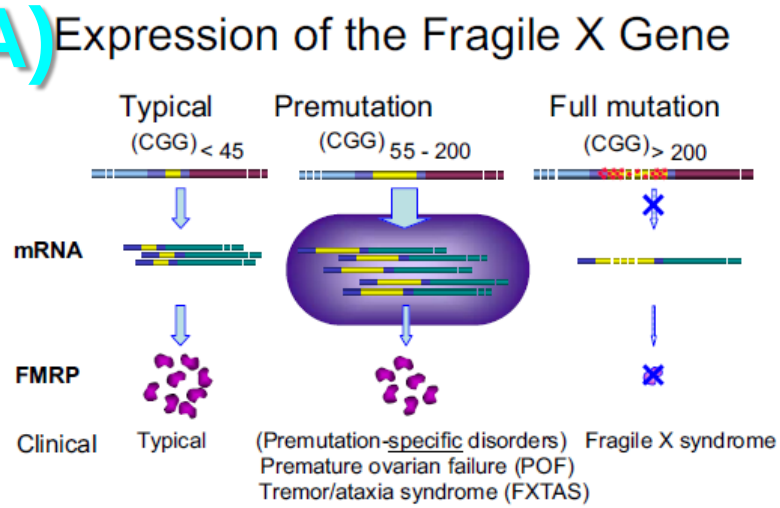
Wittenberger. FMR1 premutation. Fertil Steril 2007.

POI

Fragile X syndrome (FRAXA)

- X-linked inheritance.
- Women who carry the mutation transmit it to 50% of their offspring.
- Men who carry the mutation transmit it to all of their daughters and to none of their sons.
- As the mutation is passed from mother to offspring, it has the tendency to expand in size

Expression of *FMR1* in normal women, premutation carriers, and full mutation carriers. Figure adapted from Hagerman and Hagerman (10).



Wittenberger. FMR1 premutation. Fertil Steril 2007.

- A repeat size of 59–79 expands to the full mutation <50%,
- a repeat size of 90 expands to the full mutation more than 90% of the time

Recommendation for FRM1 genes

- The American College of Obstetricians and Gynecologists(ACOG) (2006) in their most recent committee opinion on the subject stated, "If a woman has ovarian failure or an elevated follicle-stimulating hormone level before the age 40 years without a known cause, fragile X carrier screening should be considered to determine whether she has a premutation"

- The European Societ for Human Genetics and the European Society of Human Reproduction and Embryology (2006) suggest that testing *FMR1* as part of the diagnostic workup of female infertility may be relevant, but specific recommendations were not provided

POI

Galactosemia

- Autosomal recessive disorder due to an impairment in galactose 1-phosphate uridyltransferase (GALT) gene mutation (9p chromosome)

  Beutler et al., 1965; Segal and Berry, 1995)
- 1/60,000 newborns. Early mental retardation, hepatomegaly, cataracts, and POI.
- 47 women with galactosemia (81 % POI)

  Waggoner 1990
- Ovarian damage has been attributed to a toxic effect of galactose, or one of its metabolites, on follicular structures during fetal life

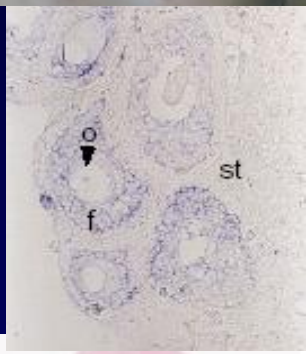
  Levy et al., 1984; Fraser et al., 1986
- Individuals heterozygous for GALT Q188R mutations are not at increased risk of developing ovarian dysfunction

  Kaufman 1993

Blepharophimosis, Ptosis, Epicantus Inversus Syndrome (BPES) - POI

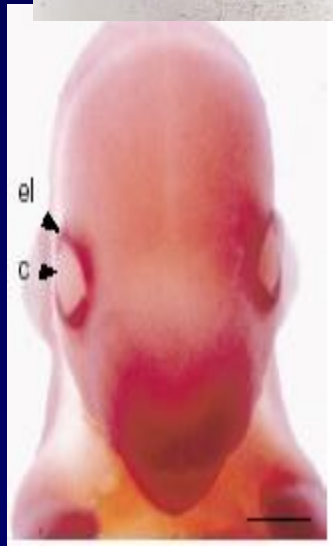
- **Autosomal dominantly inherited disorder,**
- **Characteristic facial abnormalities:**
  - Small palpebral fissures,
  - Ptosis
  - skinfold running inward and upward from the lower lid.
- **Two forms of BPES exist:**
  - Type I: ovarian failure. Only females are affected.
  - Type II: only facial abnormalities are present

Zlotogora et al., 1983



- **3q22-q23**
- **FOXL2 gene mutation.**
- **FOXL2: important role in the early stages of ovarian differentiation and ovarian function**
- **A role in cholesterol metabolism and steroidogenesis in the ovary???**

Crisponi 2001



Blepharophimosis, Ptosis, Epicantus Inversus Syndrome (BPES)

Woman with BPES - POI

POI - Gonadotrophin receptors

- KAL (Kallman's syndrome)
- DAX-1 (X-linked adrenal hypoplasia, cause deficiency of GnRH results in defective pituitary production of gonadotropins)
- FSH-β chain mutation Layman 1997
- FSH receptor gene mutation 2p Aittomaki 1996
- LH receptor gene mutation 2p Latronicon1996
- Inhibin alpha gene mutation 2q Shelling 2000

Premature Ovarian Failure
Making the Diagnosis

- Vital to make the diagnosis of idiopathic premature ovarian failure in a timely manner

50% of women with secondary amenorrhea saw three or more clinicians before any laboratory testing was performed

(Aluzubaidi NH et al. 2002)

In 25%, the time to diagnosis was more than 5 years

POI
Summary of evaluation - 1

1. Initial assessment and investigations

- **Good history, including family history**
- **Tests: serum FSH, LH, prolactin, TSH and E2. If FSH in menopausal range, repeat**
- **AMH and inhibin B – especially if fertility is an issue**

Panay N, 2009

POI

Summary of evaluation - 2

2. Further investigations

- **Chromosomal and genetic studies (karyotype, FMR1 gene mutation if family history of POI, fragile X syndrome or mental retardation, *(ACOG rec.)*)**

- **Auto-antibodies: Auto-immune screen for polyendocrinopathy (thyroid antibodies, anti-adrenal antibodies,?ovarian antibodies???)**

- **Estimation of bone mineral density through DEXA. Repeated every 2 to 5 yrs**

Panay N, 2009

Management of POI - 1

Inform

- **Discuss the test results on a special visit (not by phone).**
- **The diagnosis of POI can be particularly traumatic for young women.**
- **Use of appropriate terminology is important (use of premature ovarian failure or insufficiency is preferred instead of premature menopause or early menopause)**
- **Explain the nature of the disease and advise the patient of sources of information and support.**

Management of POI - 2

Counsel

- The ovary is not only a reproductive organ but also is a source of important hormones that help maintain strong bones. Adequate replacement of these missing hormones, a healthy lifestyle, and a diet rich in calcium are essential. DEXA bone scan every 2 years may be needed.
- POF is not menopause. Spontaneous ovarian activity and pregnancies are possible.
- Allow the patient enough time to accept the diagnosis. Discuss fertility plans later, after the patient has come to terms with her condition.
- No proven therapies exist to restore fertility, and an experimental treatment should be performed only under a review board–approved research protocol.
- Currently available options to resolve infertility include change of plans, adoption, and ovum donation.

Management of POI - 3

Replace Deficient Hormones

- Cyclic/continuous oral/transdermal estrogen and cyclic oral progestin are needed.

- **Full replacement dose** is needed to alleviate symptoms and maintain age-appropriate bone density.

Follow-up

- Adequacy of hormone replacement therapy (HRT) should be followed yearly.
- **TSH and adrenal antibodies** (expert opinion) should be followed yearly.
- **ACTH stimulation test** should be performed yearly if the adrenal antibodies are positive.
- **DEXA bone density** scan should be performed as needed

Management of POI - 4

Consultations

- Consultation with an endocrinologist may be indicated in some cases because of concerns of hypothyroidism or adrenal insufficiency.

- Patients with infertility due to POF usually have a grief response after hearing the diagnosis. They benefit from a baseline psychological evaluation and appropriate counseling.

- Genetic counseling may be needed in some cases.

Management of POI - 5

Diet

- Patients with ovarian failure should consume 1200-1500 mg of elemental calcium per day in their diet. If this is not feasible, calcium supplementation is appropriate. An adequate intake of vitamin D also is important.

Activity

- Women with POF should be encouraged to engage in weight-bearing exercises for 30 minutes per day, at least 3 days per week, in order to improve muscle strength and maintain bone mass. Participation in outdoor sports is strongly recommended.

Sexual function of women – POI

TABLE 2. *Mean FSFI scores of the women with POF and the women in the control group (n = 58 in each group)*

	POF group		Control group		
Domain	Mean ± SD	Median	Mean ± SD	Median	*P*
Desire	3.5 ± 1.1	3.6	3.6 ± 1.1	3.6	NS
Arousal	3.7 ± 1.2	3.8	4.2 ± 1.0	4.4	0.0176
Lubrication	4.2 ± 1.3	4.2	5.0 ± 1.2	5.4	0.0012
Orgasm	4.0 ± 1.3	4.0	4.6 ± 1.2	4.8	0.0136
Satisfaction	4.3 ± 1.3	4.8	4.9 ± 1.1	5.0	0.0124
Pain	4.3 ± 1.3	4.4	5.0 ± 1.0	5.2	0.0037
Total	24.0 ± 6.0	24.0	27.3 ± 4.8	27.7	0.0047

All cells/data refer to Wilcoxon signed-rank test.
FSFI, Female Sexual Function Index; POF, premature ovarian failure; NS, not significant.

- **more difficulties in relation to satisfaction, lubrication, orgasm, pain, and arousal;**
- **however, there were no differences between the two groups with respect to desire.**

de Almeida DMB, 2011

POI
Hormone Therapy - 1

- **Transdermal estradiol at a dose of 100 mcg/day**
- **the most physiological HT because it achieves circulating E2 levels of 100 pg/mL**
- **bypassing the hepatic first-pass metabolism**
  - avoiding gastrointestinal side effects
  - decreased risk of venous thromboembolism compared with oral regimens
- **oral estrogen: estradiol at 1 to 2 mg/day**
- **Dose equivalents**
  - 1 mg micronized 17 beta estradiol
  - 50 mcg/day transdermal 17 beta estradiol
  - 0.625 mg conjugated equine estrogens

POI
Hormone Therapy - 2

- **Progesterone**
  - micronized progesterone 100 mg-200 mg daily, for 10 days each month
  - medroxyprogesterone acetate 10 mg daily for 10 days each month
  - LNG-IUS

POI

Hormone Therapy -3

- In the girls failing pubertal development, HT can be started between 12-13 years of age
- Very low doses of estrogen (either 25 mcg of transdermal patches of 17betaE2 or 0.3 mg of CEE orally) and continue this therapy for no longer than 6 months or until breakthrough bleeding occurs
- Then a progestogen (MPA 2.5 to 5.0 mg or micronized progesterone 100 mg orally) is added for 12 to 14 days every 30 to 60 days to induce regular withdrawal bleeding.
- The dosage of estrogen then can be increased to adult levels gradually at 6-month intervals, with the progestin continued for 12-14 days at 30- to 60-day intervals

POI

Hormone Therapy - 4

Androgen replacement ??? **(symptomatic despite estrogen replacement)**

- **oral methyl testosterone,**
- **oral dehydroepiandrosterone,**
- **testosterone sprays, creams, gels, and testosterone patch.**
- **Combined esterified estrogen-methyl testosterone tablets**

Osteoporosis - fracture risk

- **weight bearing exercise**
- **smoking cessation**
- **daily intake of 1200 mg of calcium + 800 to 1000 Vit D3**

POI

Hormone Therapy - 5 - contraception

- Combined hormonal contraception, does not reliably prevent ovulation and pregnancy
- related to the extremely elevated Gn levels in POI, which are not fully suppressed by COCs and may allow for breakthrough ovulation on occasion.
- Because of the small risk of spontaneous pregnancy, cyclic COC use (as opposed to continuous) is preferable because an unexpected spontaneous pregnancy may go unrecognized for longer
- Barrier contraception should be recommended
- LNG-IUS

POI

Hormone Therapy – 6- fertility

- Although there is a 5-10% chance of spontaneous conception among women with POI, in vitro fertilization using donated oocytes or embryos represents the best chance for fertility.

- In those women with POI due to Turner's syndrome or Turner's mosaics, pregnancy can be particularly dangerous due to structural abnormalities of the aortic root, predisposing these patients to aortic rupture during pregnancy.
- the risk of fetal and maternal morbidity and mortality in the setting of undiagnosed adrenal insufficiency, particularly in the postpartum period

DHEA - Proposed mechanism

- ***Barad and Gleicher (2006)*** **postulated that the effect of DHEA was due to the *creation of PCOS-like characteristics in the aging ovary:***

  - ***Better oocyte & embryo quality***

    Gleicher, 2007

  - ***Higher pregnancy and lower miscarriage rates***

    Gleicher, 2009

  - ***Likelihood of bearing male off-spirng is increased in patients who received DHEA to improve ovarian response***

    Ryan *et al.*, 2008

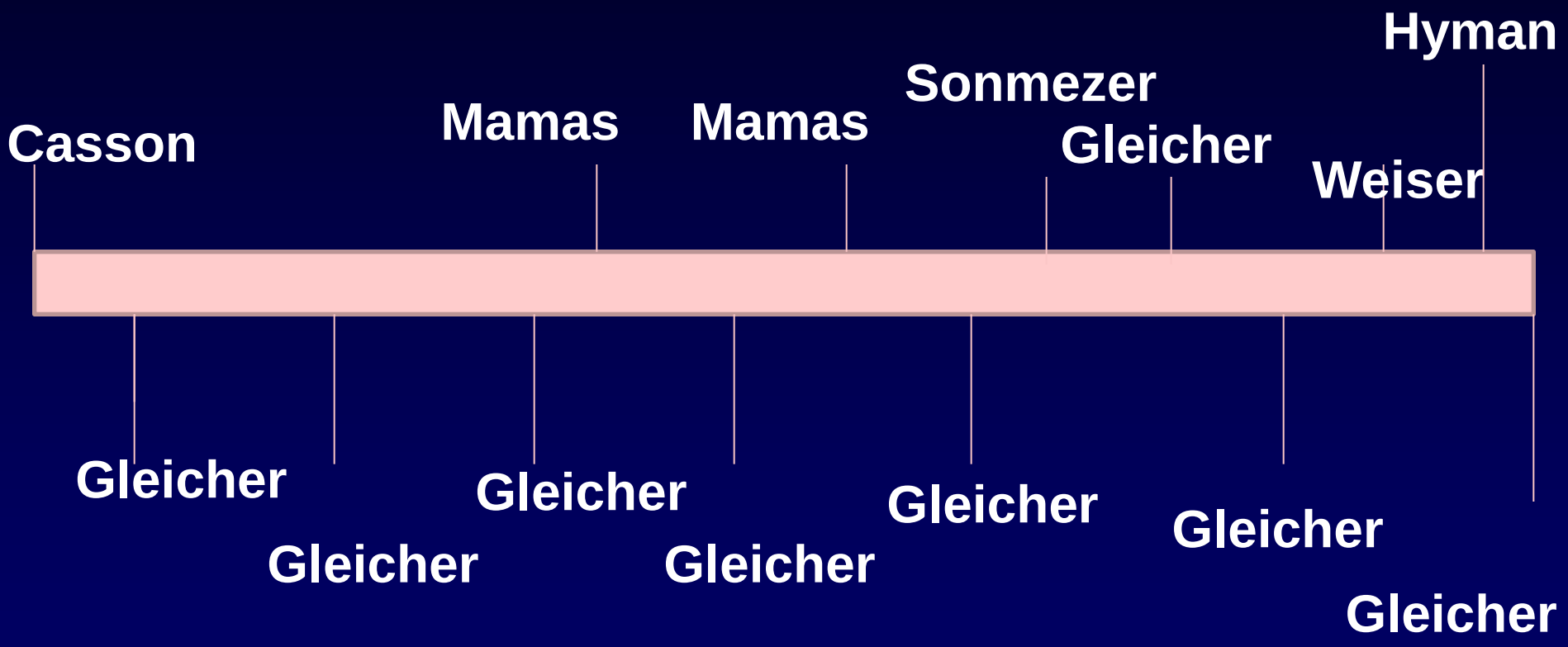

Hyman
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Table IV Comparison between the two groups for both treatment cycles.

Variables	DHEA ($n = 26$)	Control ($n = 25$)	P-value
Mean E2[a] on hCG (pg/ml)	732 ± 337	917 ± 487	0.2
Mean E2 per retrieved oocyte (pg/ml)	239 ± 120	335 ± 150	0.35
Mean progesterone on hCG (ng/ml)	0.8 ± 0.6	0.7 ± 0.4	0.71
Endometrial thickness on hCG (mm)	10.5 ± 2.5	10.8 ± 2.8	0.74
Mean number of retrieved oocytes	3.2 ± 1.6	3.5 ± 2.4	0.65
Fertilization rate (%)	58.20%	56.30%	0.42
Mean no. of embryo transfer	2.1 ± 1.0	2.2 ± 0.7	0.73
Mean scoring of leading embryo transfer	3.1 ± 0.5	3.3 ± 0.4	0.42
Clinical Pregnancy (%)	7 (26.9%)	3 (12.0%)	0.07
Live birth rate	6 (23.1%)	1 (4.0%)	0.05

P=0.099

DHEA - Conclusions

- DHEA supplementation showed a beneficial effect on the live birth rate.
- Should be considered for poor responder patients due to its simplicity of use and lack of side effects.
- Additional, larger studies, using different protocols are needed to reinforce our findings.

Growth Hormone

- Improved the response to gonadotropins (Adashi 1985)
- Enhances gonadotrophin-induced steroidogenesis (Doldi et al., 1996)
- Increase the DNA repair capacity in oocytes (Thompson 2000).
- Related with oocytes' ability to evolve in morphologically normal embryos (Menezo 2002).
- Increased follicular levels of IGF-1 and 2 IGF-2 which play a crucial role in the cytoplasmic maturation (Fraser 2006, Pereira 2011, Menezo 2006).
- Act possibly thorough stimulation of growth differentiation factor 9 and bone morphogenic protein 15 production (Hall 2007, Otsuka 2011).

TABLE 1

Meta-analyses, randomized controlled trials, and other studies retained for analysis.

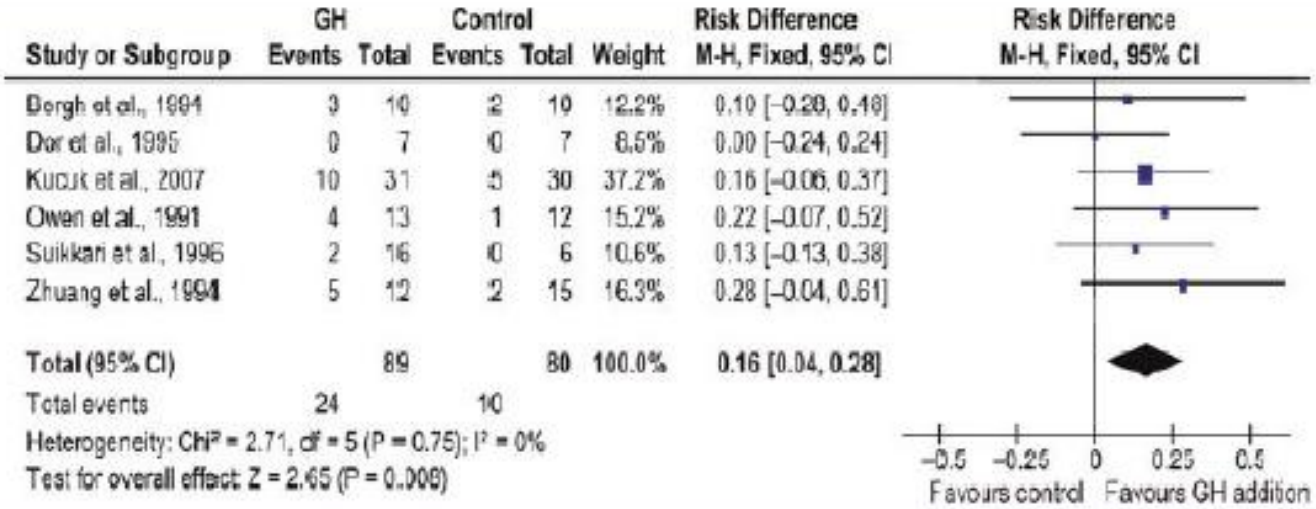
No.	Study type	First author	Published year	Included in Meta-analysis	Reference
1	Meta-analysis	Kolibianankis	2009		(4)
2		Duffy	2010		(3)
3	Meta-analysis + RCT	Kyrou	2009	3	(2)
1	RCT	Owen	1991	1, 2, 3	(6)
2		Zhang	1994	1, 2, 3	(40)
3		Bergh	1994	1, 2, 3	(38)
4		Dor	1995	1, 2, 3	(39)
5		Suikkari	1996	1, 2, 3	(41)
6		Kucuk	2008	1, 2	(43)
7		Tapanainen	1992	2	(44)
8		Younis	1992	2	(45)
9		Hazout	2003	2	
10		Tesarik	2005	2	(42)
11	Other trials	Owen	1991		(5)
12		Schoolcraft	1997		(88)
13		Hazout	2009		(90)
14		Yovich	2010		(90)

Note: RCT = randomized controlled trial.

de Ziegler. Growth hormone in poor COS responders. Fertil Steril 2011.

GH in IVF: *Clinical Pregnancy Rate*

Kolibianakis et al, Hum Reprod Update, 2009



Study or Subgroup	GH Events	GH Total	Control Events	Control Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bergh et al., 1994	3	10	2	10	12.2%	0.10 [-0.20, 0.40]
Dor et al., 1995	0	7	0	7	0.0%	0.00 [-0.24, 0.24]
Kucuk et al., 2007	10	31	5	30	37.2%	0.16 [-0.06, 0.37]
Owen et al., 1991	4	13	1	12	15.2%	0.22 [-0.07, 0.52]
Suikkari et al., 1995	2	16	0	6	10.6%	0.13 [-0.13, 0.38]
Zhuang et al., 1994	5	12	2	15	16.3%	0.28 [-0.04, 0.61]
Total (95% CI)		89		80	100.0%	**0.16 [0.04, 0.28]**
Total events	24		10			

Heterogeneity: Chi² = 2.71, df = 5 (P = 0.75); I² = 0%

Test for overall effect: Z = 2.65 (P = 0.008)

Risk Difference M-H, Fixed, 95% CI

−0.5 −0.25 0 0.25 0.5

Favours control Favours GH addition

Rate Difference +16%
95% CI +4 to +28

Growth Hormone in IVF

- Meta-analysis of 10 studies (440 subfertile couples) demonstrated a statistically significant difference in both
  - Pregnancy rates OR 3.28 (95% CI 1.74 to 6.20)
  - Live birth rates OR: 5.39 (95%CI:1.89-15.35)

Duffy et al. Cochrane Database Syst Rev 2010

Induced (iatrogenic) ovarian failure

If the treatment occurs

- after the onset of puberty **(RR 2.32),**
- in survivors of Hodgkin lymphoma **(RR 3.25),**
- in patients treated with combined chemotherapy and radiation therapy below the diaphragm (RR 8.56-9.6).
- After bone marrow transplant and therapy with busulfan, almost 100% of women develop ovarian failure.

Estimated risk of gonadal dysfunction with cytotoxic drugs

High risk

- Cyclophosphamide
- Ifosfamide
- Chlormethine
- Busulfan
- Melphalan
- Procarbazine
- Chlorambucil

Medium risk

- Cisplatin
- Carboplatin
- Doxorubicin

Low risk

- Vincristine
- Methotrexate
- Dactinomycin
- Bleomycin
- Mercaptopurine
- Vinblastine

Michel De Vos, Paul Devroey, Bart C J M Fauser, 2010

Ovarian Tissue and Oocyte Cryopreservation

- In conclusion, ovarian tissue and oocyte cryopreservation hold promise for fertility preservation. However, cryopreservation of ovarian tissue and oocytes is investigational

- At this time, these procedures may be offered only with appropriate informed consent in a research setting and under the auspices of an institutional review board. Further research is necessary to determine patient selection, methods of tissue collection, and optimal cryopreservation protocols.

ACOG COMMITTEE OPINION, Number 405 • May 2008

Oocyte Cryopreservation

The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 584 • January 2014

Committee on Gynecologic Practice

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Oocyte Cryopreservation

ABSTRACT: In 2013, the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology published a joint document, *Mature Oocyte Cryopreservation: A Guideline*, which addresses advances in techniques to freeze human eggs that have resulted in significant recent improvements in pregnancy success. Based on the current state of evidence, modern procedures to cryopreserve oocytes should no longer be considered experimental. The American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice endorses the joint document and encourages its use by Fellows. There are not yet sufficient data to recommend oocyte cryopreservation for the sole purpose of circumventing reproductive aging in healthy women.

ACOG COMMITTEE OPINION, Number 584, Jan 2014

Primary ovarian insufficiency

(Premature ovarian failure)

Thank you. . .

Cooper, Fertil Steril, 2011

Primary ovarian insufficiency

(Premature ovarian failure)

Thank you. . .

Cooper, Fertil Steril, 2011

The X chromosome and its regions