

management of the young woman with premature menopause

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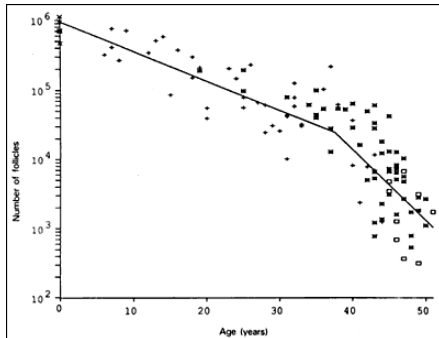


definition

- menopause before the age of 40
- menopause at an age >2 SDs below mean for reference population (average age for Western populations 51)
- premature menopause before age 45
BMS Consensus Statement 2007

age-related decrease in primordial follicles

Faddy MJ, Gosden RG, Gougeon A et al Hum Reprod 7:1342, 1992



prevalence

- 1% of women under the age of 40
- 0.1% of women under 30
- 0.01% of women under 20

10 - 28 % of women with 1^{ary} amenorrhoea
4 - 18 % of women with 2^{ary} amenorrhoea

Coulam 1986, Anasti 1998

management

- make - and explain - diagnosis
- treat symptoms
- prevent long-term consequences
- address psychological needs
- genetic counselling if appropriate
- treat infertility
- offer long-term follow-up and support

make the diagnosis!

- diagnosis of POF is often delayed, even with classic symptoms of menopause

Alzubaidi 2002

- POF is often a fluctuating condition
ovarian dysfunction precedes POF

presentation

- amenorrhoea
- oligomenorrhoea / menstrual dysfunction
- infertility
- oestrogen-deficiency symptoms

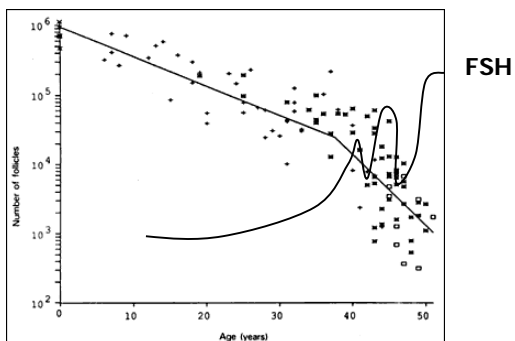
- pubertal delay / primary amenorrhoea

diagnostic tests

- elevated FSH levels in menopausal range (usually above 40iu/l) on at least two occasions a few weeks apart
- ultrasound not required for diagnosis
- no role for ovarian biopsy

Khastgir 1994

age-related rise and fluctuation in FSH



investigations

- FSH, LH, oestradiol (prolactin) (androgens)
- thyroid function
- autoantibody screen
- karyotype (young patients)
- FRAXA screen
- pelvic ultrasound
- bone mineral density

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autoimmunity and POF

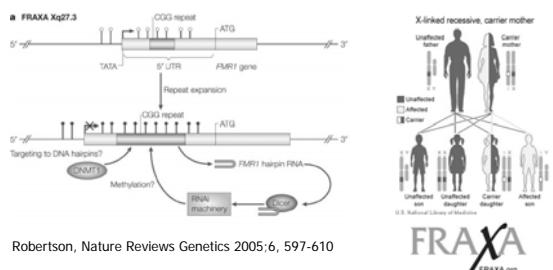
- autoimmune disorders in 20%
- wide range
- adrenal autoimmunity 2-10%
may precede Addison's disease (Bakalov 2002,2005)
- thyroid autoimmunity 20-40%
(Mignot 1989, Belvisi 1993)

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FRAXA pre-mutations found in 13% familial POF and 3% sporadic cases
 Conway 1998

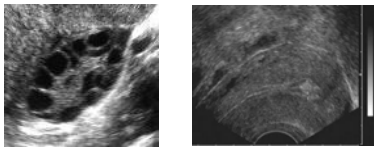
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ultrasound

- ovarian activity commonly seen in POF
- may be seen in primary amenorrhoea
- associated with higher BMD
- higher chance of pregnancy

Conway 2006



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clinic profile

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

	<i>n</i>	%
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

consequences of POF

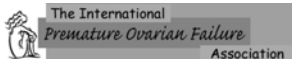
- oestrogen-deficiency
 - symptoms
 - long-term effects
- infertility

psychological needs

- counsellor is key member of clinic staff
- information
 - from health professionals
 - from support groups

<http://www.pofsupport.org/>

www.daisynetwork.org.uk



symptoms

- flushes
- night sweats and sleep disturbance
- vaginal dryness
- loss of libido
- stiffness and muscle pain
- mood changes
- fatigue
- poor concentration and memory

HRT

- which type?
- what dosage?
- what duration?



HRT type

- cyclical (sequential) usually preferable to “no bleed” (continuous combined) HRT
breakthrough bleeding common
- choice of progestogen
- route of administration is patient’s choice
unless contra-indications to oral HRT

OCP vs HRT

- synthetic
- more potent
- Pill-free week
- like peer-group
- reminder of infertility
- physiological
- may be safer for long-term use
- continuous estrogen
- stigma of HRT
- not contraceptive

HRT dosage

- standard HRT doses may be suboptimal
- monitor by symptoms and BMD
(oestradiol levels useful only for implants)

urogenital symptoms

in young women HRT may not be enough

- vaginal moisturisers
- topical oestrogen
e.g. vagifem 25mcg

testosterone

- androgen levels ↓ in POF
(half of testosterone supply from ovaries) Hartmann 1997
- reduced libido, sexual function, ?energy ?BMD
- worse in oophorectomised women
- replacement – patches (Intrinsa)
- s/e excess hair growth and acne
Braunstein 2005, Shifren 2007



alternatives to HRT

- efficacy lower than HRT:
 - serotonin and noradrenaline re-uptake inhibitors
 - clonidine
 - gabapentin
- efficacy unproven:
 - progesterone transdermal creams
 - phyto-oestrogens (soy, red clover)
- safety unproven:
 - herbal preparations
eg black cohosh, dong quai

Panay and Rees RCOG 2006

lifestyle

- smoking increases risk of POF Chang 2007
- exercise, especially weight-bearing,
improves bone mass Wallace 2000
- diet, calcium and vitamin D Jackson 2006
- alcohol and caffeine



long-term risks of POF

life expectancy reduced

Rocca et al Lancet Oncol 2006

cohort of >12,000 women

- 2 years less life expectancy if menopause <40
- increased mortality ischaemic heart disease
- reduced uterine and ovarian cancer

Ossewarde et al Epidemiology 2005;16:556

long-term risks of POF (2)

Mayo clinic cohort study – bilateral oophorectomy
1950-1987 followed to 2006

- premature death HR 1.67 [1.16-2.40]
- cardiovascular disease
- cognitive impairment, dementia, Parkinsonism
- osteoporosis & fractures
- ↓ psychological wellbeing
- ↓ sexual function

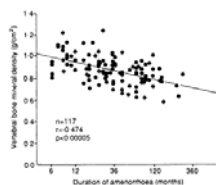
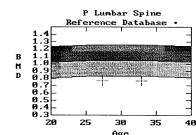
Shuster et al Menopause Int 2008

bone loss

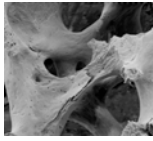
- failure to achieve peak BMD
- increased loss

- fracture rate OR 1.5 [1.2-1.8]

Davies 1990, Notelovitz 1993, Vega 1994
Van der Voort 2003



osteoporosis prevention



- HRT prevents bone loss
- HRT improves BMD in POF

- little evidence on alternatives in POF
 - bisphosphonates used in breast cancer
 - calcium and vitamin D

Gulekii 1994

cardiac disease

- increased risk of ischaemic heart disease following BSO HR 2.62 [2.05-3.35] Atsma 2006 Lokkegaard 2006

- subclinical coronary artery disease x 2 following TAH+BSO (OR2.0, 95%CI: 1.2-3.4)

- modified by HRT within 5 years of oophorectomy

Allison 2008

cardiac disease (2)

- vascular endothelial dysfunction associated with oestrogen-deficiency
 - improved by HRT Kalantaridou 2004, Ostberg 2007

- lack of long-term data on HRT for POF

benefits and risks



- WHI and Million Women studies are not applicable to young women
- breast cancer less common in untreated POF
? effect of physiological HRT
- ischaemic heart disease : HRT might benefit
- osteoporosis : clear benefit

HRT duration

- until expected age of menopause

"In women who have experienced a premature menopause (due to ovarian failure, surgery or other causes) HRT may be used for treatment of menopausal symptoms and for prevention of osteoporosis until the age of 50 years. After this age, therapy for prevention of osteoporosis should be reviewed and HRT considered a second choice"

MHRA April 2007

fertility

"the sudden switch from fertile woman to irrevocably infertile woman was the biggest blow of all"

spontaneous pregnancy

- pregnancy rate 5-10%
- can occur on HRT
- miscarriage rate ? 20%

Van Kasteren 1999

- prognostic factors:
 - recent diagnosis – short period of amenorrhoea
 - fluctuating FSH
 - ovarian activity on ultrasound
 - POF due to autoimmunity or chemotherapy

fertility treatment

- treatment strategies unproven:
 - stimulation after FSH suppression
 - corticosteroids
- review in 194 patients 3 pregnancies

Van Kasteren 1999

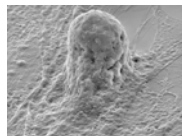
fertility horizons

- germ cells in BM – unproven

"Bone marrow transplantation generates immature oocytes and rescues long-term fertility in a preclinical mouse model of chemotherapy-induced premature ovarian failure"

Johnson & Tilly 2005, Lee 2007

- cloning?
- artificial gametes?



egg donation

- good success rates (up to 50%)
- wide variation in availability

- recipient needs HRT to prepare uterus
- donor undergoes IVF stimulation cycle

risks to egg donor

- risks of stimulation
 - OHSS
 - (hormone-dependent conditions)
- pregnancy
- risks of egg collection
 - bleeding
 - infection

reproductive tourism



pregnancy risks

- multiple birth
- pre-eclampsia
- Turner syndrome: cardiac death, GDM, PIH
- cancer survivors:
 - cardiac / renal toxicity of chemotherapy
 - uterine irradiation: misc, IUGR, pre-term

surrogacy

may be required after gynaecological cancer or uterine irradiation

- IVF with “full” surrogacy (donated eggs)
- insemination (surrogate is egg donor)



prevention of POF

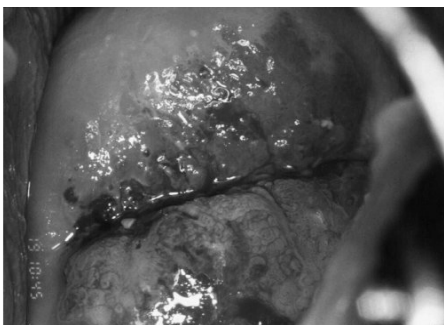
- lower hysterectomy rate
- fertility-preserving surgery for cancer
- less gonadotoxic chemotherapy regimens
- ? hormonal protection (GnRH-a)
- embryo, egg and tissue freezing

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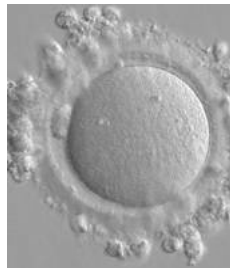
embryo freezing

- well established
- no long-term risks demonstrated
- success rate rising
LBR 20% per cycle HFEA 2005
use of vitrification



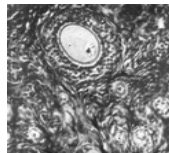
egg freezing

- pregnancy rate
10-20% per transfer with
conventional freezing
- higher with vitrification
no long-term safety data
- ? 500 births in total
Tur-Kaspa ASRM 2007



ovarian tissue freezing

- still experimental
- cycle-independent
- possible in pre-pubertal patient
- requires laparoscopy
- 4 live births reported
- future ?IVM ?whole ovary graft



POF recommendations

- improve awareness and information
- multi-disciplinary clinical services
 - incorporate psychology & associate with "late effects" service in cancer centres
- multicentre research collaboration
- ? guidelines



Thank you
