Recognising the problems of Premature Ovarian Failure (POF)

Nick Panay

Consultant Gynaecologist
Queen Charlotte’s & Chelsea and Chelsea & Westminster Hospitals

WHC Adviser
BMS Council Member
Patron, Daisy Network

www.womens-health-concern.org
www.the-bms.org.uk
www.daisynetwork.org.uk
Recognising the problems of Premature Ovarian Failure (POF)

- Prevalence + symptoms
- Making the diagnosis
  - Presentation
  - Investigations
- Managing the Menopause Aspects
  - Short term
  - Long term
- The POF Database
- Recognising the problems of POF: The Way forward
Prevalence
Premature Ovarian Failure

Prevalence

- Prevalence of premature ovarian failure (<40yrs) ranges between 0.3 and 1% (Coulam CB et al. 1986)

- 2.5% are adolescents (Falsetti L et al. 1999)

- This condition accounts for approximately 25% of women presenting with amenorrhoea
Premature Ovarian Failure

Symptoms

- Ovarian cycle may cease abruptly or fluctuate leading to
  - Amenorrhoea or erratic periods
  - Climacteric Symptoms
  - Cognitive effects
  - Psychological effects
  - May be Family Hx / Iatrogenic interventions / Infections / autoimmune disease
Premature Ovarian Failure

Symptoms

- Ovulation may occur again in spontaneous POF leading to unexpected bleeding and pregnancy

- Premature ovarian dysfunction rather than failure
  - Kalu & Panay Gyne Endocrinol 2007 (submitted)
  - Nelson L et al Fertil Steril 2005 “Spontaneous POF is not early menopause”
Making the diagnosis of POF / predictive tests
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)
Investigations

1. History
   - positive family history
   - concurrent autoimmune disorder

2. Hormone levels
   - min. 2 measurements of FSH and oestradiol four weeks apart; prolactin, testosterone / TFTs. ??Inhibin/AMH

3. Karyotyping
   - women with primary amenorrhea
Investigations

4. Antibody screening  ➔ only a few women show positive immunofluorescence against the ovary

5. Imaging  ➔ pelvic scan (ovarian volume, doppler flow, antral follicles)

6. Ovarian biopsy  ➔ restricted to research

7. Poor response to OI  (v elevated basal FSH)
   Lawson Fert Steril 2003
   Kok et al HR 2003
A model for predicting menopause age in women – polygenic screening
Hefler et al Fertil Steril 2006

- Screening for high risk genes

- Women who have Factor V Leiden mutation can suffer series of microemboli that restricts blood flow to ovaries.
  - Women with the mutation went through menopause a year or two earlier than those without.

- Another mutation in the Apo E2 gene led to women entering menopause up to four years earlier
  - The APO E2 gene is linked to an increased risk of early Alzheimer’s disease
Management – the team & treatment options

“Early assessment of the individual’s risk of developing POF, development of a strategic management plan, and timely commencement of infertility and HRT together with counselling in an integrated management plan should improve both short and long term health for those with POF”

- Meskhi Seif Curr Opin Obstet Gynecol 2006
Premature Ovarian Failure

Multidisciplinary collaboration

- Menopause / Reproductive medicine unit

- Specialist GP’s & Nurses
  - Menopause nurse & GP specialists
  - Gynae oncology nurse specialist (Macmillan)

- Affiliated specialists
  - Haematology (HHNT / Marsden)
  - Gynae Oncology
  - Dietician
  - Psychosexual counsellor
  - Pharmacist
  - Councillor
Information is Vital!

- “No talk of hot flushes and sleepless nights only everything should be alright.”

- “No doctors mention the dry skin or straggly hair, such menopause symptoms only mentioned if the patient dared.”

- “It seems like a long road I have to travel; can I find a companion for this menopause puzzle.”

- Menopause Library / Patient Information booklet
The Daisy Network
Premature Menopause Support Group

PO Box 183
Rossendale
BB4 6WZ

www.daisynetwork.org.uk
membership@media@daisynetwork.org.uk
Information is Vital

- Under 40? Menopausal? It's time to seek specialist help.....
- PRESS RELEASE: 26 April 2007

In the Spring 2007 issue of The Menopause Exchange newsletter, Mr Nick Panay and Mr Emmanuel Kalu, both from the Chelsea and Westminster Hospital in London, discuss the causes, symptoms and management of premature menopause.

“A premature menopause can turn a woman’s life upside down, whether it is brought on by surgery or it occurs naturally,” says Norma Goldman, director of The Menopause Exchange.

The Menopause Exchange at PO Box 205, Bushey, Herts WD23 1ZS, call 020 8420 7245, fax 020 8954 2783 or send an e-mail to norma@menopause-exchange.co.uk
Principles of Hormone Replacement in POF

Estrogen replacement is first line treatment in POF
Committee on Safety of Medicines www.mhra.gov.uk

1) Pre pubertal POF: To induce development of secondary sexual characteristics and development

2) To relieve the immediate sequelae of menopause i.e. symptom relief and quality of life

3) To prevent the long term sequelae of the menopause

4) To create an environment conducive to the successful replacement of donated embryos
Premature Ovarian Failure

Therapeutic Options

- Route / Type HRT

- Choice of oestrogen route of administration must be made on individual basis

- No controlled studies regarding the ideal hormone replacement strategy for women with premature ovarian failure

In principle, non oral E2 / progesterone preparations can be better monitored but what is ideal E2 level?
Premature Ovarian Failure

Therapeutic Options

- Route / Type HRT
  - In the absence of better prospective randomised data…

- GIVE WOMEN WHAT THEY WANT

………..particularly if you want them to use it!
HRT preparations in POF

- Start with standard / ‘high’ dose oestradiol in most cases (“higher” doses if symptomatic++)

- 0.625 - 1.25mg CEE / 2.0mg E2 / 75-100 mcg patch / 1.0 – 2.0 mg E2 gel
  
  - Can use lower doses if asymptomatic? Correct E2 level

- Vaginal route e.g. Vagifem 25mcg vaginal tablets
  
  - Kalentzi Panay TOG 2005
Timing of HRT after malignancy

Management

– Liaise with gynae onc / oncologists / haematologists re time to start

– Immediately if curative procedure (after histol)

– Delay (1 year disease free interval) if advanced oestrogen sensitive tumour e.g. endometrial carcinoma
HRT preparations in POF

- Progestogenic opposition if uterus present
  - Even after radiotherapy

- Aim for minimum effective dose / local opposition with Mirena / Crinone / Cyclogest

- In future SPRMS, SERMS/estrogen, local delivery
SERM/ERT combination (tissue selective estrogen complexes)

- Pickar J.
  - 6th IMS Workshop Pisa, 2006 &
  - 5th AMS 2007

- Phase III studies BZA/CEE

- Improvement in menopause symptoms & bone-sparing effects

- Good endometrial suppression and amenorrhea rates

- No additive increase in VTE & no effect on breast symptoms
Previous Gynaecological Malignancy

- Cervical Cancer (squamous)
  - Not Oestrogen sensitive
  - No evidence of excess risk

- Cervical Cancer (adenocarcinoma)
  - No evidence
  - But, more cautious approach
Previous Gynaecological Malignancy

- Endometrial Cancer – 3 retrospective studies
  - Stage 1 & 2 & 3 Endometrial Cancer
  - 2/75 (1%) recurrences in HRT group v 11/75 (14%) in non users
  - Hormone users had a statistically longer disease free interval than non users
    - Suriano et al Obstet Gynecol 2001
Previous Gynaecological Malignancy

- Ovaries
  - “HRT does not seem to have a noteworthy effect on the progression of epithelial carcinoma of the ovary”
  - 31 patients with 55 month follow up

- Bebar et al Eur J Gynecol Oncol 2000
Previous Gynaecological Malignancy

Vagina / Vulva (squamous)

No evidence

Vaginal Adenocarcinoma

No evidence
HRT: Don’t Forget Testosterone!

- Women have more testosterone receptors in the forebrain than men!
- Levels drop by 50% after a surgical menopause and 20% after a ‘natural’ menopause
- This can lead to problems such as lack of energy, headaches & libido
- Only implanted pellets licensed in women until recently
“Some patients report persistent tiredness, lack of energy, reduced libido or sexual function despite apparently adequate doses of oestrogen replacement. This may be more common in oophorectomized women, and consideration should be given to additional treatment with testosterone.”

(Management, Section 2. Hormone replacement therapy)
Intrinsa data: Intimate I & II

Total Satisfying Activity

Mean Change From Baseline

Sexual Desire

Mean Change From Baseline

Distress

Mean Change From Baseline

Analysis combined
Intimate SM1 & SM2

* p < 0.05

West London Menopause & PMS Centre, United Kingdom NP/June 2007
Long term Risks of POF & Benefits of HRT
Premature Ovarian Failure
Long term effects

- Mean Life Expectancy
  - 2 years shorter than women with menopause >= 55 years of age
  - CVS & Bone effects of chronic hypoestrogenaemia

- Ossewarde et al Epidemiology 2005
Premature Ovarian Failure
Osteoporosis

- Young women who have not received oestrogen treatment are at high risk for osteoporosis of trabecular bone of the spine with associated compression fractures and height loss
  
  - Bondy CA et al. 2006
Premature Ovarian Failure
Osteoporosis

- Rate of bone loss is the same as following natural menopause but consequences more severe as longer life expectancy

- Dimitriou et al. Maturitas 2003
  - 514 women studied in total
  - Women with POF exhibited lower BMD compared with normally menopausal women @ ages 45-55
Premature Ovarian Failure
Osteoporosis

Van der Voort et al Ost Int 2003
– Cross sectional population based study

– 4725 postmenopausal women in 50-70yr olds
  (2757 controls) filled in questionnaires

– Those with early menopause had significantly higher fracture rates OR 1.5 (CI 1.2-1.8)
Premature Ovarian Failure
Coronary artery disease

Related to number of years past menopause rather than age
Hormonal changes at menopause and risk of coronary event

- Age of menopause and Coronary Heart Disease risk: Nurse’s Health Study

- Significant correlation between younger age of menopause & CHD in non HRT users

- Beneficial effect of E2 in younger users on CHD risk

Hu/Stampfer Arch Int Med 1999; Grodstein 2006
Cardiovascular disease & HRT in premature ovarian failure

- Endothelial dysfunction impaired due to hypo-estrogenic state

- 6 months HRT restored endothelial dysfunction

  • Kalantaridou J Clin Endoc Metab 2004
WHI study

Combined analysis CEE / CEE + MPA v Placebo

50-59yr age group - 30% reduced risk of all cause mortality (10:10000 less deaths)

Effect of POF (Surgical) on CNS

- Mayo Clinic Minnesota (BBC Website April 8th 2006) American Academy of Neurology

- 1209 women BSO and 1302, 1 ovary removed (1950 – 1987)

- 260% increase risk of Dementia following removal of at least one ovary by age 38

- 70% increased risk if both ovaries removed by age 46

- **HRT was used inconsistently and probably not for long enough**
HRT DANGER FOR WOMEN

‘Huge increase’ in killer disease risk

MILLIONS of women on hormone replacement therapy are in danger of getting heart disease or breast cancer, a study showed yesterday.

The US research programme revealed such huge increases in risk that it was stopped three years early.

In clinical HRT pills taken in steps
Premature Ovarian Failure
Therapeutic Options

- Impact of Alarmist Media on HRT use for Premature Menopause
  - Ng C., Reddy N., Panay N. 2004 ESHRE Berlin
    - All aware of adverse publicity
    - Majority continuing with HRT BUT 37% (1/3) were contemplating stopping HRT because of breast cancer fears
    - Less than half realised that risks did not apply to their age group
Now experts say hormone therapy can CUT heart attack danger

U-TURN ON THE RISKS OF HRT

By Jenny Hope
Medical Correspondent

MILLIONS of women may have been scared into abandoning HRT unnecessarily, it was revealed yesterday.

A USA report which linked the treatment to breast swelling and spots has fuelled alarm in the international press.

A non-faulty was issued at the research meeting revealing that hormone replacement therapy has actually proved much safer for women than once thought.

It has surprised that women over 47 and women taking a relative dose of the hormone have been excluded, raising fears that the treatment may be harmful. Women who have been using HRT for years have been in the UK, with some being prescribed a hormone.

Should hostage Britons be allowed to turn captivity into cash?

SEE PAGES 6-7
Jacques Roussouw NIH WHI Architect

"It goes some way toward settling the issue for an important group of women and their physicians -- that is, women who have menopausal symptoms around the age of menopause who have been avoiding hormone therapy when it may not have been necessary for them to do so."
Pill v HRT
Choice of HRT for post-pubertal women with premature ovarian failure Bath et al 2001 Clin Endocrinol

European Soc Paediatric Endocrinology 42 questionnaires (28 responses)

- COCP 18 (64%) Loestrin (20-30) 12 (67%)
- Oral HRT (sequential) 5 (18%) Prempak C 5 (100%)
- Transdermal HRT (sequential) 3 (11%) Estracombi 2 (66%)
- Ethinyloestradiol (sequential) 2 (7%)

- Two respondents had no preferred HRT preparation!
- “No consensus for prescribing in POF to optimise skeletal & cardiovascular health”
Premature Ovarian Failure
Therapeutic Options

- Combined pill
  - “Use of ethinylestradiol has been driven by practicalities rather than science”
Premature Ovarian Failure
Therapeutic Options

- Combined pill
  Pros:
  - Convenient
  - “Peer Friendly”
  - Free
Premature Ovarian Failure
Therapeutic Options

- Combined Pill
  Cons
  - Un-physiological
  - Difficult to monitor – what is correct dose anyway?
  - Pill free week can lead to symptom resurgence
  - ?Risks of long term ethinylestradiol v “natural hormone replacement
Premature Ovarian Failure

- Combined Pill v HRT
  - Guttmann et al 2001 Clin Endocrinol
  - 0.625mg v 30mcg EE in 17 adult women with Turner’s Syndrome
  - 6 month cross over study: Hormones, Lipids, Bone Turnover etc
  - FSH most suppressed by EE, BUT HRT was superior at minimising hyperinsulinaemia & bone turnover
Alternatives
Alternatives to HRT in POF

- Pharmaceutical Alternatives
  - SNRIs
    - No data in POF
  - Progestogens
    - No data in POF

- Complementary Medicines
  - Phytoestrogens
    - No data in POF
    - Inappropriate for POF women with severe symptoms
  - Black Cohosh
    - No data in POF

Panay & Rees SAC Paper RCOG 2006

West London Menopause & PMS Centre, United Kingdom NP/June 2007
Alternatives to HRT in POF

- Pharmaceutical Alternatives for Bone
  - SERMS (raloxifene)
  - Bisphosphonates (Evista)
  - Strontium Ranelate (Protelos)
  - NO EVIDENCE
Audit - database
Management of Women with Premature Ovarian Failure (POF) at Teaching Hospitals - EMAS Istanbul 2006

Etienne Horner, Emmanuel Kalu, Adam Kay, Elsa Mohan, Nick Panay
Menopause/POF clinics at Queen Charlotte’s & Chelsea and Westminster Hospitals

Prospective evaluation of POF patient notes attending tertiary referral menopause clinics

2006 onwards

n= 148 (at time of audit – now>200)
Aetiology

Diagnosis in patients with POF

- Cancer: 52%
- Idiopathic: 31%
- Benign: 14%
- Genetic: 3%
<table>
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<th>Cancer Diagnoses</th>
<th>Count</th>
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<tr>
<td>CML</td>
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<td>Hodgkins disease</td>
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</tr>
<tr>
<td>Myeloma</td>
<td>1</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>1</td>
</tr>
</tbody>
</table>
Mean age at diagnosis by aetiology

- Idiopathic → 32 years  
  (range 16-39)
- Cancer → 27 years
- Genetic → 28 years
- Benign → 32 years
Investigations performed

- Hormone assay: 100%
- U/S pelvis: 57%
- DEXA: 55%
- Karyotyping: 14%
- Auto-antibodies: 10%
HRT Preparations

- Tablet: 71%
- Patch: 61%
- COC: 12%
- Other: 25%
Summary of Audit

- 64% cancer / surgery patients v 31% with spontaneous POF
- One third had mood and sleep disturbances
- 91% were using HRT; 9% had discontinued HRT
Spontaneous POF audit
Kalu et al BMS Bournemouth 2007

82 / 202 (40%) - of these 90% nulliparous

4.7% Spontaneous conception (4/84),
3.6% following oocyte donation

50% will not consider oocyte donation.
Recognising the problems of Premature Ovarian Failure (POF)

**Future Objectives - Audit**

- Need to merge data with those from other units over the long term to look at quality of life / fertility outcomes / osteoporosis / CVS disease

- POF patients should therefore remain under long term follow up
Recognising the problems of Premature Ovarian Failure (POF)

The Way Forward

- Health Professionals……..

- BMS / RCOG working group to be convened early 2008 to:
  - Identify clinics seeing POF patients & Develop National Register of POF patients
  - Establish National Guidelines for Mx of POF
  - Propose future research: particularly to determine optimum therapeutic regimens
Recognising the problems of Premature Ovarian Failure (POF)
The Way Forward

- Women with POF.............
  - Need Improved access to information

- CONSUMERS FORUM @ RCOG:
  - Premature Menopause Public Meeting
  - “A change too soon”
  - Saturday 3rd November 2007
Further Information on POF

- www.thebms.org.uk
  - BMS Consensus Statements: Title: Premature Menopause

- www.imsociety.org
  - Updated Recommendations on HRT use. Climacteric June 2007

- www.daisynetwork.org.uk

- www.menopausematters.co.uk

- www.earlymenopause.org

- Premature Menopause – A Multidisciplinary Approach: Singer & Hunter 2000