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Premature Menopause
– who, when and how long to treat?



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Definitions

- Premature Menopause (PM)
 - Cessation of menses for at least 12 months prior to the age of 40 years of age (WHO)
 - Spontaneous and induced menopause
- Premature Ovarian Failure (POF)
 - Spontaneous cessation of menses after puberty (deMoraes-Ruehsen and Jones, 1967)
- Early Menopause
 - Menopause occurring between age of 40-45 years

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Epidemiology

- 1% women < 40 years of age experience spontaneous PM (Coulam et al, 1986; Luborsky et al, 2002)
 - ethnic variation (Luborsky et al, 2002)
 - lower prevalence in Asian women
- Early menopause affects ~5-10% women

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Epidemiology

- 10-15% women presenting with infertility
- 10-28% women with primary amenorrhoea (Falsetti et al., 1999)
- 4-18% women with secondary amenorrhoea (Falsetti et al., 1999)
- Following medical intervention
 - 20-40% post hysterectomy develop PM
 - rate of chemotherapy induced PM ranges from 20-100% (Bines et al, 1996; Blumenfeld, 2000)
 - depending on age/ drug and dose

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Aetiology

- Heterogenous disorder
 - Idiopathic – karyotypically normal spontaneous POF
 - Medically – induced
 - Chemotherapy, radiotherapy, pelvic surgery
 - Enzyme deficiencies
 - Genetic
 - Gene mutations or cytogenetic abnormalities
 - Autoimmune
 - Infections
 - Viral oophoritis

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Aetiology: Risk factors

- Spontaneous POF
 - Positive family history
 - FRAXA mutation
 - Smoking
 - Poor responses to IVF
 - Epilepsy
- Medically Induced
 - Age
 - Dose
 - Duration of therapy
 - Drug type
 - Irradiation site
 - Combined chemo+radiotherapy
 - Pelvic surgery
 - Hysterectomy
 - Ovarian transposition
 - Uterine artery embolisation

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Aetiology

- Autoimmune disease associated with POF:

Autoimmune disorder	Prevalence
Thyroid	14-27%
Adrenal insufficiency	2-10%
Autoimmune Polyglandular Syndrome	Type I 60% Type II 10%
Type 1 Diabetes	2%
Myasthenia Gravis	2%
Pernicious Anaemia	<1%
SLE	<1%

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Clinical Presentation

- Menstruation disturbance/ amenorrhoea
 - no characteristic antecedent menstrual history
- Infertility
- Oestrogen deficiency symptoms
 - 50% women with POF report vasomotor symptoms
 - hot flushes can occur with regular menstrual cycles
 - abrupt onset of severe symptoms in women post oophorectomy
- Non-specific symptoms
 - fatigue, arthralgias, myalgias

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Symptoms: spectrum

N
O
S
Y
M
P
T
O
M
S

- hot flushes
- night sweats
- formications
- anxiety, irritability
- sleep disturbances
- lessened memory, concentration
- vaginal dryness, low libido
- fatigue
- muscle/joint pains
- overall diminished wellbeing

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Diagnosis

- History
 - presenting symptoms
 - gynaecological history
 - history or symptoms of autoimmune disorders
 - past history
 - medications
 - family history
 - lifestyle behaviours

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Diagnosis

- Examination
 - general physical examination
 - assess secondary sexual characteristics
 - gynaecological examination
 - evidence of oestrogen deficiency

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Diagnosis

- Diagnostic criteria
 - > 4 months amenorrhoea
 - X 2 FSH levels > 40mIU/ml at least one month apart (off all hormone treatment and OCP)
 - progesterone challenge test not helpful
- Exclude secondary causes of amenorrhoea including pregnancy

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Causes of Secondary Amenorrhoea

- Pregnancy
- Systemic
 - Thyroid disease
 - Polycystic ovary syndrome
 - Chronic renal failure
 - Adrenal disease
- Ovarian
 - POF/PM
- Uterine
 - Asherman's syndrome
- Medication
 - Post OCP
- Anterior pituitary
 - Pituitary tumours
 - Hyperprolactinaemia
 - Empty sella syndrome
 - Sheehan's syndrome
 - Lymphocytic adenohypophysis
- Hypothalamic
 - Weight loss
 - Exercise
 - Stress
 - Drugs (via altered prolactin secretion)
 - CNS disorders including tumors, trauma, irradiation

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Diagnosis

- Vaginal US
 - exclude outflow obstruction
 - detect presence of follicles
 - Present in up to 60% patients with spontaneous POF (Conway et al., 1996)
 - assess endometrial thickness and determine ovarian volume
- Day 3 FSH and E2 if still menstruating
 - to assess ovarian reserve
 - abnormal if FSH > 10 and E2 < 300

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Diagnosis

- Precise timing of onset often impossible to determine
- Often delay in diagnosis
 - interview survey of 48 women with POF (Alzubaidi et al., 2002)
 - median 2 years from onset of disordered menses to diagnosis POF
 - 61% women consulted 3 or more different clinicians before the diagnosis was made

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Investigations

- TFTs, thyroid antibodies
- Adrenal antibodies (Bakalov et al., 2002)
 - if positive Abs or Sx : am cortisol+ ACTH or SST
- Fasting glucose
- FBE, serum B12, gastric parietal cell antibodies
- ANA, RF
- Ovarian antibodies not helpful
 - presence and activity of POF does not correlate with antibodies (Hoek et al., 1997)

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Investigations

- Karyotype
 - case reports of genetic abnormalities in women > 30 years with PM
 - case report of co-existing autoimmune disease and 46XXX (Holland, 2001)
- FRAXA
 - implications for female family members
 - risk of POF and suitability as a oocyte donor
 - ?elevated FSH levels predictive of POF in menstruating premutation carriers (Murray et al., 1999)

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Investigations

- Se T, SHBG, FAI
- Fasting lipids
 - women with POF demonstrated ↑ total cholesterol, ↑ LDL and ↓ HDL compared with controls (Falsetti et al., 1999)
- DEXA
- Calcium
- 25OH Vitamin D if osteopaenic

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Management: Fertility

- Spontaneous remission observed in POF
 - 5-10% lifetime chance of conception (Kasteren and Schoemaker, 1999)
- Only proven therapy for obtaining a pregnancy is via use of donor oocyte

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Management: Diet and Lifestyle

- Modification of dietary and lifestyle factors assists
 - menopausal symptom control
 - improve psychological symptoms
 - cardiovascular disease and osteoporosis risk reduction

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Management: Diet and Lifestyle

- Cooler environment
 - fans including hand fans
 - air conditioning
 - water facial spray
 - cool drinks
- Clothing
 - dress in layers
- Reduce hot flushes
 - regular exercise (including aerobic exercise, resistance training and walking)
 - avoid smoking
 - reduce weight

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Management: Diet and Lifestyle

- Diet
 - avoid spicy foods
 - balanced healthy diet
 - add dietary phytoestrogens (not supplements as safety unknown)
 - reduce intake of caffeine and alcohol
- Relaxation
 - paced respiration
 - biofeedback
 - behavioural therapy

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Management: Symptom Control

- ET/ EPT
 - initiate early
 - higher doses E required for symptom control and maintenance of BMD (equivalent to 1.25mg CEE)
 - no consensus regarding the best form of HRT in woman with PM
 - oral, transdermal
 - implants (if TAH+BSO)
 - role of newer agents
 - Tibolone (in women with oophorectomy)
 - intranasal E

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Management: Symptom Control

- ET/ EPT
 - proposed advantages of cyclical P
 - monthly withdrawal bleeding psychologically important to some women
 - development of amenorrhoea may indicate pregnancy
 - ? Safety of long term continuous P in young women
 - Vaginal E for treatment of urogenital symptoms
 - If pregnancy not desired
 - Low dose OCP

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Management: Symptom Control

- Androgens
 - diagnosis of female androgen deficiency
 - symptoms including diminished wellbeing, decreased sexual function, dysphoric mood and fatigue
 - low serum testosterone concentration
 - positive effects on wellbeing, vasomotor symptoms, sexual function and BMD demonstrated in clinical studies in older postmenopausal or younger oophorectomised women
 - adaptation of testosterone preparations designed for men (or tibolone)
 - role of DHEA?

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Management: Symptom Control

- Non-hormonal therapies
 - used in women with contra-indications to oestrogen therapy
 - management of urogenital symptoms
 - vaginal lubricants
 - Replens, Syk, KY jelly

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Management: Symptom Control

- Non-hormonal therapies
 - management of vasomotor symptoms
 - recent meta-analysis (Nelson HD et al., JAMA, 2006) reported significant reduction in hot flushes with:
 - Venlafaxine (37.5-75mg/day)
 - Paroxetine (10-25 mg/day)
 - Clonidine (0.05-0.1mg/day)
 - Gabapentin (300mg-900mg/day)
 - magnitude of effect small
 - no long term efficacy or safety data

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Other therapies

- Bioidentical hormones
 - no safety & efficacy data
 - form of HRT
 - marketing misleading
 - money making
- Soy / phytoestrogen supplements
 - no safety data in cancer
- Herbal therapies
 - Black Cohosh
 - Dong Quai

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Management: Long Term Sequelae

- Related to specific aetiologies
 - Screening for associated autoimmune dysfunction
 - POF may precede the onset of Addison's disease by 8-14 years
 - natural history of other associated autoimmune disorders ill-defined
 - yearly TFTs and fasting glucose (Anasti et al., 1998)
 - Complications of Turner's syndrome
 - cardiac, hearing loss, hypothyroidism
 - Cancer survivors

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Management: Long Term Sequelae

- Cardiovascular Disease

Age at menopause (years)	Women-years of follow-up	Number of events	Annual hazard of cardiovascular mortality (95% CI) at biological age:		
			65 years	70 years	75 years
≤39	7650	43	4.9 (2.5-7.3)	6.6 (3.5-9.7)	13.1 (6.9-19.2)
40-44	22 559	99	3.4 (2.2-4.5)	5.7 (4.1-7.4)	8.2 (5.6-10.8)
45-49	62 163	238	3.2 (2.6-3.9)	4.4 (3.5-5.2)	7.1 (5.6-8.6)
50-54	96 482	391	2.6 (2.1-3.1)	4.7 (4.0-5.4)	8.8 (7.5-10.1)
≥55	13 863	53	2.7 (1.4-4.1)	4.3 (2.6-6.0)	7.0 (4.2-9.9)

Van der Schouw et al., 1996

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Management: Long Term Sequelae

- Cardiovascular disease
 - treat modifiable risk factors
 - diet and lifestyle
 - lipid lowering drugs
 - treat hypertension
 - ?effect of HRT on risk

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Management: Long Term Sequelae

- Osteopaenia/ Osteoporosis
 - BMD is reduced in women with PM
 - 66% women with POF FN BMD <1SD
 - 34% women with POF LS BMD <1SD (Anasti et al., 1998)
 - degree of BMD loss varies between different cohorts of women
 - POF> oophorectomy >chemotherapy+radiotherapy> chemotherapy
 - therapy
 - diet and lifestyle
 - calcium and vitamin D supplements where required
 - ET (high dose) + ?androgens
 - ?Bisphosphonates/ SERM/ Tibolone

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Management: Long Term Sequelae

- Cancer
 - observational studies indicate an increased risk of cancer mortality in women with early menopause (Cooper and Sandler, 1998)
 - recurrent malignancy where PM secondary to cancer therapy

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Management: Long Term Sequelae

- Reduced risk of breast cancer
 - Effect of HRT unknown

(Collaborative Group on Hormonal Factors in Breast Cancer, 1997)

a: By menopausal status and age at menopause			
	Cases/Controls	RR (95% CI)	RR and 99% FCI*
Premenopausal	20165/41561	1.00 (0.026)	
Perimenopausal	1171/1728	0.77 (0.045)	
Postmenopausal			
By age at natural menopause (years)			
<35	64/168	0.46 (0.108)	
35-39	230/544	0.51 (0.062)	
40-44	1125/2655	0.62 (0.032)	
45-49	3697/7552	0.70 (0.020)	
50-54	5263/9135	0.81 (0.021)	
≥55	1294/1541	0.89 (0.044)	
By age at bilateral oophorectomy (years)			
<35	86/268	0.48 (0.091)	
35-39	122/295	0.65 (0.096)	
40-44	225/494	0.66 (0.072)	
45-49	303/570	0.72 (0.066)	
≥50	256/376	0.90 (0.089)	

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Management: Long Term Sequelae

- Cognitive function?
 - Short term RCTs show beneficial effects of ET in women (mean age 45 years) post TAH + BSO versus placebo (Sherwin, 1988; Phillips and Sherwin, 1992)
 - cognitive dysfunction may occur after adjuvant chemotherapy for breast cancer (Shapiro and Recht, 2001)
 - altered risk of Alzheimer's disease?
 - benefit/ risk of long term HRT unknown

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Management: Psychological Issues

- "I feel like an alien"
 - feelings expressed at premature menopause support group (Farrell et al., 2002)
 - confusion, anger, grief, sadness, depression, loss, loneliness, isolation, resentment, feeling "old before their time"
 - issues regarding loss of control, loss of fertility, altered body image, relationships, sexuality

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Management: Psychological Issues

- Questionnaire study of 64 women with POF (Liao et al., 2000)
 - increased depression and stress
 - highest levels of depression associated with
 - younger age at diagnosis
 - diagnosis of POF within the last 2 years
 - prior psychological treatment
 - low levels of self esteem and life satisfaction
 - higher life satisfaction in women with children
 - lower sexual esteem and satisfaction
 - *“provision of psychological care should be an integral part of clinical management”*

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Management: Psychological Issues

- Issues related to:
 - premature menopause
 - cancer
 - fertility
 - relationships
 - pre-existing psychopathology
- Provide women with an opportunity to express their emotions
- Involve the woman's partner
- Consider referral to psychologist/ psychiatrist
- Encourage the development of support networks

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Management: Education & Information

- Increased patient satisfaction (Alzubaidi et al., 2002)
 - >5 minutes spent discussing diagnosis
 - referred to other sources of information
- Compliance with long term HRT dependent on patients understanding of long term sequelae
- Counselling
- Websites:
 - www.jeanhailes.org.au
 - www.earlymenopause.org.au
 - www.menopause.org.au
 - www.psychology.org.au
 - www.endocrineonline.org.uk

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Management: Summary

- Prompt and accurate diagnosis
- Inform in a sensitive and supportive manner
- Counselling
- Identify and address psychological issues
- Institute HRT or appropriate alternative
- Assess and monitor for the presence of long term sequelae and institute appropriate treatment

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Case Study

- 35 year old woman
- Presenting with:
 - 4/12 amenorrhoea
 - nocturnal hot flushes
 - sleep disturbance
 - emotional lability
- Post chemotherapy & radiotherapy following surgery for left breast cancer 12 months previously

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Case Study cont...

- Past history:
 - Para 2 G2 – NVD
 - COCP 19-25yrs, then husband had vasectomy
 - elite athlete in teens with secondary amenorrhoea
- Family history:
 - maternal aunt & 1st cousin – breast cancer
 - father (59) – angina & recent stent
 - Maternal grandmother (85) with osteoporosis with fractures, ↑ BP and diabetes
- Examination:
 - no abnormal findings apart from recent surgery for breast cancer

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Case Study cont...

What investigations would you order?

- FSH, LH, oestradiol, TFT, prolactin, pregnancy test, FBE, ESR
- Vaginal ultrasound
- Investigations indicate early menopause repeat FSH & oestradiol after at least one month

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Case Study cont...

How would you manage this woman?

- Counselling - ? whether had pre-counselling before chemo
- Lifestyle modifications – diet, exercise
- Treatment of symptoms:
 - non-hormonal treatment
 - HRT
- Investigation of further long-term complications
 - DEXA, calcium intake
 - CV work-up, left breast radiology, ↑ risk CVD

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Question 1

What are your recommendations for the duration of hormone replacement therapy particularly for a woman with Turner's Syndrome?

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Question 2

Could you please talk about bio-identical hormones and explain some examples?

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Question 3

What is the Gold Standard for diagnosis of premature menopause?

Is there any place for anti-Mullerian hormone?

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Question 4

What about using testosterone therapy and what are the associated risks?

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Question 5

What are your thoughts on POF and abnormal liver function?

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Question 6

What would be the approach to fertility preservation prior to chemotherapy for breast cancer?

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