Premature Ovarian Insufficiency

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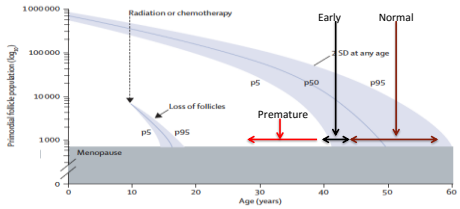
Disclaimers

- Advisory Board: Pfizer, Abbott
- Lecturer: Pfizer, Abbott, Besins
- Researcher: Funds for research from Merck, Bayer, Organon, Novartis, Wyeth, Pfizer

The decline in Ovarian reserve with age



Exponential decline in ovarian follicles with age and the accelerated decline seen following chemotherapy. p5 == 5th centile, p95 = 95th centile

From: DeVos M et al Primary Ovarian Insufficiency Lancet 2010;376:911.21

Primary (Premature) Ovarian Insufficiency (POI)

Term	Frequency cited
Gonadal dysgenesis	2675
Premature Ovarian Failure	1461
Premature Menopause	799
Early menopause	468
Hypergonadotropic Hypogonadism	268
Ovarian Dysgenesis	181
Primary Ovarian Failure	130
Hypergonadotropic Amenorrhoea	44
Primary Ovarian Insufficiency	33
Climacterium praecox	5

Cooper A et al. Fertil Steril 2013;95:1890-1897

Primary Ovarian Insufficiency

- A disorder arising in the ovary irrespective of cause
- Is defined as the presence of menopausal level serum gonadotropins in association with irregular menses in women younger than 40.
- It may be iatrogenic or it may arise spontaneously either alone or as part of a number of ultra-rare syndromes
- It may be sporadic or familial and is due to either a decreased number of follicles during development or an accelerated rate of follicular loss
- Untreated POI is associated with increased incidence osteoporosis, heart disease, cognitive impairment and premature death

POI: More common than we think?

Idiopathic POI is thought to affect 1% of women under age 40

A review of a 1958 birth cohort of 4968 British women[1] found

- 7.4% suffered Idiopathic or Iatrogenic POI
- Incidence was 3 x higher in lower socioeconomic classes
- Poor QoL was twice as common with negative perceptions persisting even after 10 years

Incidence in China has been reported[2] as high as 10%

1.Islam and Cartwright. Imperial College London 2011 (ESHRE abstract)
2.Mueck and Ruan, personal communication.

Early menarche and nulliparity increase risk of early menopause

- Data from the InterLACE study
- 51,450 post menopausal women from 9 observational studies.
- 2% suffered premature menopause and 7.6% early menopause
- Women with menarche <11 had increased risk of POI (RR1.80, 1.53-2.12)
- Nulliparous women had increased risk of POI (RR2.26, 1.84-2.77)
- *Nulliparous women with early menarche had 5 fold increased risk of POI* (RR 5.64, 4.04-7.87) and an increased risk of early menopause (RR 2.16, 1.48-3.15) compared with women menarche >12 and 2 children.

Mishra G et al, Human Reproduction 2017;pp1-8 early on line

Causes of POI

Genetic	Immunological	Infections	Metabolic	Iatrogenic
X monosomy	Hypothyroid	Mumps	17 hydroxylase deficiency	Ovarian surgery
X Trisomy	Addisons	TB	Galactosemia	Chemotherapy
FMR 1 mutation	Diabetes	Malaria		Radiotherapy
Deletions	Coeliac	Shigella		
Translocations	APS 1 and 2	Varicella		
FOXL 2	ITP, Candidiasis	CMV		
FSH, LH	SLE, RA, Sjogrens	HSV		
GALT, Inhibin	Chronic Hepatitis			

- The majority are idiopathic or iatrogenic

Fragile X Syndrome

- A genetic condition causing intellectual disabilities, learning difficulties and various physical characteristics. It is the commonest known cause of autism.
- 1:150 women are carriers of a faulty FMR 1 gene (a pre-mutation or an increase in the number of CGG repeats from 1-50 up to 58-200)
- Of these 25% will be affected by POI
- As with idiopathic POI, female FX carriers may spontaneously conceive.
- A family history of POI or family members with intellectual disabilities may point to FMR 1
- Genetic screening is important to identify these women as, should they conceive, they are at risk of bearing a child with FXS.
- Male carriers of a faulty FMR1 gene are generally more severely affected than females.

Making the Diagnosis: Be suspicious

- The diagnosis is often missed.
- Investigate any young woman with over 3 months of irregular or absent menstrual cycles
- Vasomotor Symptoms in 75%
- Remember the other common causes of 2^0 Amenorrhoea
- - Hyperprolactinaemia,
- - Hypothalamic amenorrhoea,
- - Polycystic Ovarian Syndrome
- - Pregnancy

Assessing the patient

- A thorough history is critical.
- Family history particularly endocrine or autoimmune disease, surgery, cancers, mental illness.
- FSH, Prolactin, TSH, BhCG.

- If FSH raised, repeat in 6 weeks plus AMH, Thyroid and Adrenal Abs, Karyotype, FMR 1 gene mutation -under age 30, or FH of POF,

- Bone Density assessment
- Pelvic ultrasound to exclude multicystic ovaries (eg autoimmune oophoritis)
- Metabolic health assessment

Rafique, Sterling and Nelson. Obstet Gynecol Clin Nth Am 2012;39:567-86

Secondary amenorrhoea 1.01

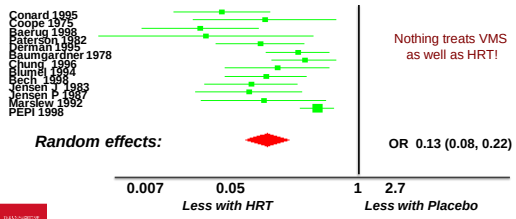
Condition	test
Menopause	**HIGH FSH**, HIGH LH, **LOW Estradiol**
Hypothalamic amenorrhoea	**LOW FSH**, LOW LH. **LOW Estr**adiol
Pregnancy	BHcG positive
Hyperprolactinaemia	**High prolactin**, Often galactorrhoea, visual disturbances
Polycystic Ovarian Syndrome	**Ultrasound diagnosis** " string of pearls" Androgens often raised, SHBG low Hyperlipidaemia, Insulin Resistance LH:FSH ratio > 2 (old fashioned)

Consequences of POI

- Vasomotor symptoms (75-90%)
- Reduced (loss) of fertility
- Negative psychological impact
- Declining bone density
- Increased risk of minimal trauma fracture
- Increased risk of cardiovascular disease
- Cognitive impairment
- Concurrent autoimmune diseases

THE CORNERSTONE OF TREATMENT OF POI FOR MOST WOMEN WILL BE HORMONE THERAPY

Up to 90% of women with POI will experience vasomotor symptoms

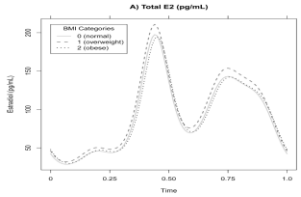


Nothing treats VMS as well as HRT!

OR 0.13 (0.08, 0.22)

MacLennan A H et al. Cochrane database of systematic reviews 2004; CD 002978

Using MHT in women with POI



- The mean estradiol level in a normal menstrual cycle is:
  - 100 pg / ml
  - 367 pmol / ml
- Women with POI may require higher doses of estrogen than women in their 50s
- WHI data is not applicable to these women

Yeung E et al Int. J Obes. 2013;37:237-43

Mishell D.R. Am J O&G 1971;111:60-65

Fertility and ovarian dysfunction

- Up to 50% of women diagnosed with POI may resume menses
- 5-10% may unexpectedly become pregnant.
- Counselling around this sensitive issue is critical.
- For women wishing to conceive, options include expectant Mx, oocyte or embryo donation, pre chemo collection of oocytes or harvesting of ovarian tissue, adoption and fostering.
- Women not wishing to conceive need contraceptive advice

Nelson L. N Eng J Med. 2009;360:606-14
Kjaer T et al Human Reprod 2011;26:2401-7

Psychological illness is increased in POI

Anxiety, Depression, Loss of self esteem, shyness, Diminished well being and sexual dysfunction are increased in patients with POI and are affected by;

- Delays in diagnosis
- The underlying pathophysiology (surgical menopause, cancer)
- The age of the woman, her family and relationship status
- Fertility status
- The individual support network

Mann E et al Climacteric 2012;15:481-9

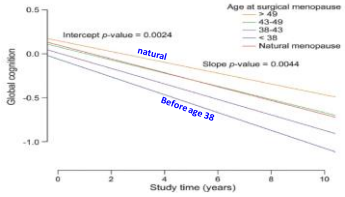
The effect of surgical menopause on cognition

Early Surgical menopause is associated with:

- a faster decline in cognition
  -RR 1.46 (1.13-1.90)
- Increased Alzheimers pathology
  notably neuritic plaques

HRT for at least 10 years will lessen the cognitive decline

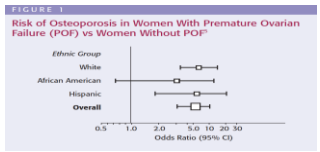
- Age at natural menopause has no impact on cognition



Shuster L et al Maturitas 2010; 65:161-66 Bove R et al Neurology 2014;82:222-229

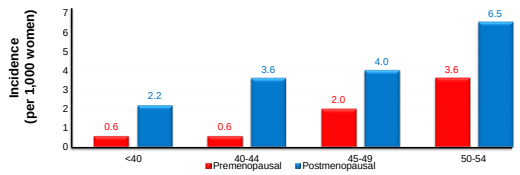
The effect of POI on bone health

- ★POI increases the risk of Osteoporosis.
- ★Surgical menopause appears to increase the rate of bone loss compared to natural menopause.
- ★HRT will improve BMD and reduce fracture risk
- ★COCP may not be as effective



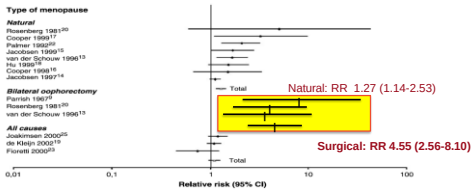
Luborski et al. Human Reproduction 2003;18: 199-206

Incidence of Cardiovascular Disease: Relation to Menopause Status



Kannel W, et al. *Ann Intern Med.* 1976;85:447-52.

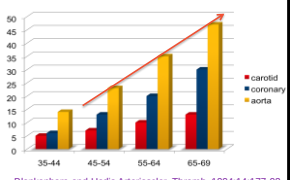
The effect of early menopause on cardiovascular disease



Atsma F et al Menopause 2006;13:265-279

Effects of menopause on CVD parameters

- **Estrogens offer cardio protection in pre menopausal women**
- Estrogens administered to recently PM women:
- Increases exercise tolerance (via a calcium antagonistic effect)
- Improves coronary artery reactivity
- Reduces acetylcholine induced arterial constriction in women (not men)
- Slows progression of atheromatous plaque



Blankenhorn and Hodis Arterioscler. Thromb. 1994;14:177-92

Rosano et al. Climacteric 2017 (in press)
Kannel et al Ann Intern Med 1976;85:447-452, Matthews K et al NEJM 1990;322:641-6,
Do KA et al Am J Epidemiol.2000;151:584-93, Lobo Menopause 2007;14:562-566
Joakimsen et al J Clin Epidemiol.2000;53:525-30

POI and Related Diseases

Premature Ovarian Insufficiency is associated with:

- Autoimmune Thyroid disease (15-20%),
- Diabetes (3%), Addisons disease (3%),
- Polyglandular syndromes (3%)
- Ocular surface diseases . Dry eye in up to 20%
- SLE, Rheumatoid arthritis, Galactosemia, Myasthenia gravis

- Early menopause secondary to other diseases will also be associated with the consequences of the initiating cause

POI and hormone therapy

- **Results from WHI do not apply to young women with POI**
- The main goal of hormone therapy in POI is to alleviate symptoms and to maintain bone and cardiovascular health.
- The critical hormone is estradiol.
- The dose required may be higher than used in older women.
- Progesterone is required only for endometrial protection
- Testosterone may be required
- Treatment should be continued at least until the average age of the menopause

De Villiers T et al Global Consensus on MHT Climacteric 2013;16:203-4
Rafique, Sterling and Nelson. Obstet Gynecol Clin Nth Am 2012;39:567-86

MHT: Treatment Options

Oral Contraceptives
may not be as beneficial for bones)

MHT

- Non oral therapy for long term use (some women will prefer oral.)
- Estrogen only for women post hysterectomy
- Continuous Combined MHT
- Sequential MHT
- TSEC – Estrogens plus SERM
- Testosterone may be necessary

Managing POI without Estrogen

For women who cannot, or prefer not to, use MHT:

- Healthy Lifestyle interventions
- Management of adverse metabolic changes and BP
- Bone sparing Agents (bisphosphonates, denosumab)
- FOR VMS:
  - Pharmacological treatment of vasomotor symptoms
  - Stellate Ganglion block
  - Cognitive Behavioural therapy
  - Neurokinin B receptor blockers ?

Summary:

- POI is more common than you think; remain vigilant and investigate thoroughly.
- HRT is the cornerstone of treatment and should be continued until at least age 50 .
- Dose and type of therapy may need modification over time
- Remain watchful for signs of return of spontaneous ovulation including unexpected pregnancy
- Regular monitoring of general well being, psychological health, possible autoimmune endocrinopathies, cardiovascular and bone health.
- A multi discipline approach is preferred