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# Hormone replacement options for women with POI after cancer treatments

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# Declarations

Ferring Pharmaceuticals

- travel & hospitality to attend ESHRE Annual Meeting 2018

# Hormone replacement options for women with POI after cancer treatments

Learning points:

- what is POI
- who gets it after cancer treatment
- why does it need treatment
- what are the treatment options
- special considerations
  - after risk-reducing surgery
  - after VTE
  - after estrogen-dependent cancer

# Premature Ovarian Insufficiency: definition

→ clinical syndrome defined by loss of ovarian activity before the age of 40 y

→ characterised by **menstrual disturbance** (amenorrhea or oligomenorrhea >4 months) with **raised gonadotropins** and low estradiol

• transient resumption of menstrual cycles may occur

ESHRE Guideline on Management of POI 2015

# Premature Ovarian Insufficiency: definition

**raised gonadotrophins**

- diagnostic accuracy of FSH unproven
- Goldenberg et al 1973
  - no follicles in primary amenorrhoea if FSH >33mIU/ml
  - no follicles in secondary amenorrhea if FSH was >40 mIU/ml
- La Marca et al 2009
  - autoimmune POI FSH range 26-64 mIU/ml, median 37 mIU/ml
  - idiopathic POI range 61-166 mIU/ml, median 99 mIU/ml

⟶ FSH level > 25 IU/l on two occasions > 4 weeks apart

# Effects of oncology treatments on ovarian function

- pelvic surgery
  - oophorectomy
  - hysterectomy } ovarian function +/- preserved
  - pelvic dissection }
- radiotherapy to pelvis
  - ovarian transposition: ovarian reserve often compromised
  - uterine & endometrial function compromised
- chemotherapy
  - variable reduction in primordial follicle number: “ovarian reserve”
  - no effect on egg quality

# Consequences of deficient estrogen in young women

→ Vasomotor

hot flushes, night sweats

→ Genito-urinary

vaginal dryness, dyspareunia, sexual dysfunction, urinary Sx

→ Neurological

cognitive impairment

→ General

aching joints, psychological wellbeing

→ Cardiovascular disease

→ Osteoporosis

- Untreated POI is associated with reduced life expectancy, largely due to cardiovascular disease

# Life Expectancy

Evidence mainly from surgical POI

- BSO before 45 y vs no surgery – increased mortality

  HR 1.67; 95% CI 1.16-2.40, p=0.006 Rocca *et al* 2006

- main causes of premature death were cardiovascular disease, osteoporosis and fractures

Similar mortality outcomes in epidemiological studies of all-cause POI from different ethnic populations

# Life Expectancy

- obesity may increase mortality risk
- no data on influence of other potential factors

  eg smoking, lipids etc

- no data on effect of HRT on mortality

→ Women with POI should be advised on how to reduce cardiovascular risk factors by not smoking, taking regular exercise, and maintaining a healthy weight

# Summary of indications for HRT

| Sequelae of POI | HRT indicated? | Supporting recommendation/conclusions |
|---|---|---|
| Vasomotor symptoms | Yes | HRT indicated for treatment of symptoms |
| Genito-urinary symptoms | Yes | Both systemic & local estrogens are effective |
| Life expectancy | ? | HRT may be of indirect benefit |
| Bone health | Yes | Estrogen replacement recommended to maintain bone health & prevent osteoporosis; plausible will reduce fracture risk |
| Cardiovascular health | Yes | Lack of longitudinal data but strongly recommended |
| Quality of life | ? | HRT may be of indirect benefit |
| Sexual function | Yes | Adequate E2 starting point for normalising sexual function. Local E2 may be required for dyspareunia |
| Neurological function | ? | Estrogen replacement may reduce risk of possible cognitive impairment |

# Hormone Replacement Therapy: estrogen

- 17 B-estradiol = “natural”, “bioidentical”, main ovarian estrogen E2
- estradiol valerate EV
- ethinyl estradiol EE
- conjugated equine estrogens CEE
- tibolone

Oppose with progesterone unless absent uterus

# Hormone Replacement Therapy: regimens

- continuous combined: E+P continuously
- cyclical combined: E continuously + P for 12-14 days/28 (month)
- long cyclical combined: E continuously + P for 12 days every 3 months

# Hormone Replacement Therapy: regimens

- continuous combined: E+P continuously

  *lowest risk endometrial hyperplasia*

  *irregular bleeding esp in young*

- cyclical combined: E continuously + P for 12-14 days/28 (month)

  *?higher breast cancer risk in postmenopausal women*

  *relevance to POI?*

- long cyclical combined: E continuously + P for 12 days every 3 months

  *highest risk endometrial hyperplasia*

# Hormone Replacement Therapy: route

## estrogen

- oral
- transdermal
  - gel: pump/sachet
  - patch: twice/week or weekly
- vaginal: cream/pessary
- [implant
- intramuscular]

# Hormone Replacement Therapy: route

## estrogen

- oral
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## progestogen

- oral
- transdermal
  - but only combined with E
- vaginal: pessary/gel
- rectal: suppository
- intrauterine (Mirena)

# Which regimen/route?

- Patient choice
- Transdermal estrogen more physiological
- Micronised progesterone natural
- Contraceptive needs/fertility desires

- Role of COCP – only if contraception required/compliance

# Risks of HRT

None for healthy women with POI

*Estrogen is not an optional extra for most women with POI*

# Risks of HRT

- no increased risk of breast cancer up to 49 yo
- endometrial cancer and hyperplasia
  - data from postmenopausal women
  - continuous combined may reduce risk
  - COCP reduces risk in normal women
- VTE: no significant difference to placebo
  - non-procedure related may be lowest in those with menopause  age 40-49y, higher <39yo & >56 yo

  sub-analysis of WHI study

# HRT: special considerations

- BRCA gene mutation carriers
- venous thromboembolism
- estrogen-dependent cancers

# HRT & BRCA gene mutation carriers

After risk-reducing BSO, no personal history of breast cancer

- Rebbeck *et al* 2005: breast cancer risk reduction
  - 462 mutation carriers – unchanged by HRT use
  - follow up 3.6 years

- Armstrong *et al* 2004: life expectancy
  - unchanged by HRT use up to age 50 y
  - continuing HRT resulted in reduced life expectance
    -0.79 to -1.09 years

# HRT & BRCA gene mutation carriers

→ HRT is a treatment option for women carrying BRCA1/2 mutations but without personal history of breast cancer after prophylactic bilateral salpingo-oophorectomy (BSO)

# HRT & venous thromboembolism

- No studies for HRT use in POI after VTE

- Several studies show evidence of increased risk in post-menopausal women using HRT

  Canonico *et al* 2008 ; Rossouw *et al* 2002;

  Hoibraaten *et al* 2000; Cushman *et al* 2004

# HRT & venous thromboembolism

Type of estrogen may be relevant

- tibolone

Route of delivery may be important

- transdermal estrogen may not increase risk of VTE

Type of progestogen may be relevant

- risk may be lower with progesterone or pregnane derivatives (e.g. dydrogesterone, medroxyprogesterone acetate, cyproterone acetate) than with norpregnane derivatives

# HRT & venous thromboembolism

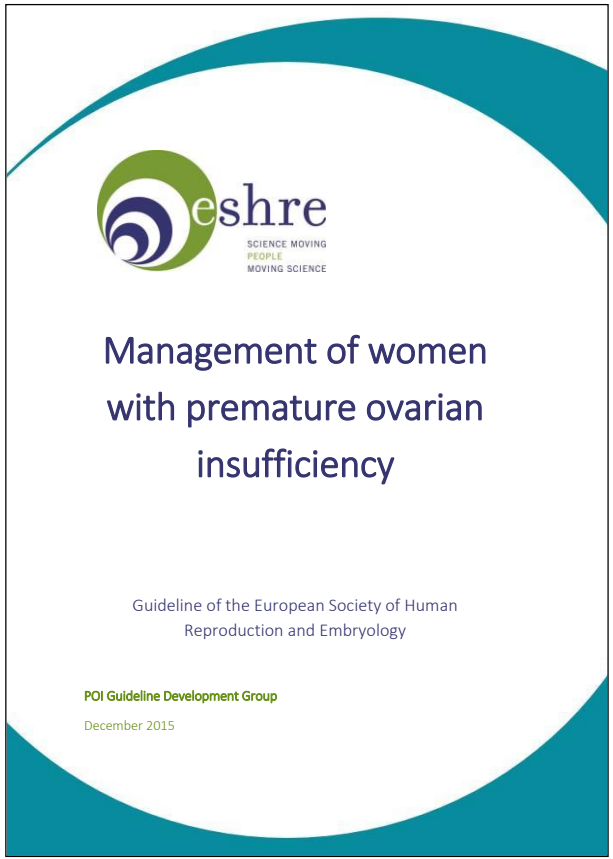
→ Women with POI and a history of prior venous thromboembolism (VTE) or thrombophilic disorder should be referred to a haematologist prior to commencing HRT

→ Transdermal estradiol is the preferred route of delivery for women with POI at increased risk of VTE

# Options after estrogen-dependent cancer

- vaginal moisturisers, lubricants, ?estrogen
- bisphosphonates for osteoporosis
- exercise for vasomotor Sx after breast cancer (Duijts et al, 2012)
- SSRIs, SNRIs, clonidine, gabapentin – reduce frequency & severity hot flushes (Rada et al, 2010)
- soy isoflavones* better than placebo for UG Sx but no benefit for vasomotor Sx (Mittal et al, 2011)
- black cohosh* - short-term use only (hepatotoxicity)?

**no safety data*


eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE
Management of women with premature ovarian insufficiency
Guideline of the European Society of Human Reproduction and Embryology
POI Guideline Development Group
December 2015

# ESHRE Guideline on the management of POI

**Chair of the GDG**

| | |
|---|---|
| Lisa Webber | UK |
| Melanie Davies | UK |
| (co-chair until December 2014) | |

**GDG members**

| | |
|---|---|
| Richard Anderson | UK |
| Didi Braat | Netherlands |
| Beth Cartwright | UK |
| Renata Cifkova | Czech Republic |
| Sabine de Muinck Keizer-Schrama | Netherlands |
| Eef Hogervorst | UK |
| Femi Janse | Netherlands |
| Lih-Mei Liao | UK |
| Veljko Vlaisavljevic | Slovenia |
| Carola Zillikens | Netherlands |

**Invited experts**

| | |
|---|---|
| Frank Broekmans | Netherlands |
| Gerard Conway | UK |
| Alberto Falorni | Italy |
| Angela Maas | Netherlands |
| Anette Tonnes Pedersen | Denmark |

**Patient representative**

| | |
|---|---|
| Jane Bartlett | UK |

**Methodology expert**

| | |
|---|---|
| Nathalie Vermeulen | Netherlands |

# ESHRE Guideline on the management of POI

**PART A: Introduction to POI**

- Nomenclature
- Definition
- Prevalence

**PART B: Diagnosis of POI**

- Symptoms
- Diagnosis and Initial assessment
- Assessment of causation
  - chromosomal and genetic defects
  - autoimmune ovarian damage
  - infectious causes
  - iatrogenic causes
  - environmental causes
  - idiopathic POI
- Implications for relatives

**PART C: Sequelae of POI**

- Life expectancy
- Fertility and pregnancy
- Bone health
- Consequences for the cardiovascular system
- Quality of life in women with POI
- Sexual and genito-urinary function
- Neurological function
- Hormone replacement therapy
- Puberty induction
- Complementary treatments in POI

- Take a holistic approach to care of women with POI
    - consider how POI may affect all aspects of her life
    - consider how her health may affect the sequelae of POI
- Emphasize importance of healthy lifestyle
    - weight/BMI, exercise, smoking, control of known cardiovascular risk factors