Worcestershire Acute Hospitals NHS Trust

Premature Ovarian Insufficiency (POI)

This guidance does not override the individual responsibility of health professionals to make appropriate decision according to the circumstances of the individual patient in consultation with the patient and /or carer. Health care professionals must be prepared to justify any deviation from this guidance.

Introduction

This guideline offers the best practice advice regarding:

1) Assessment, diagnosis, and management of POI
2) The care of women with premature ovarian insufficiency, both primary and secondary.

This guideline is for use by the following staff groups:
Medical staff

Lead Clinician(s)

Kiritea Brown — Obstetrics and Gynaecology Consultant
Reham Marie — Obstetrics and Gynaecology Registrar

Approved by Gynaecology Governance on: 11th November 2022

Approved by Medicines Safety Committee on: 1st May 2023
Where medicines included in guideline

Review Date: 1st May 2026
This is the most current document and should be used until a revised version is in place

Key amendments to this guideline

Date	Amendment	Approved by:
May 2023	Document approved	Medicines Safety Committee

Definition

- Premature ovarian insufficiency (or hypergonadotrophic hypogonadism) is a clinical syndrome defined by the loss of ovarian activity before the age of 40 years.
- Now termed 'insufficiency' (rather than failure) to better describe the fluctuating nature of the condition.
- It is characterised by menstrual disturbance (amenorrhea or oligomenorrhea) with raised gonadotropins (FSH and LH) and low oestradiol.
- It affects about 1% of the population <40 years- 0.1% <30 years and 0.01% <20 years.

Aetiology

1) Unexplained or Idiopathic (70-90%)
    - Family history present in 20-30% of cases
2) Autoimmune processes (30%): ?causal or just associated
    - ie Hashimoto's thyroiditis, Type 1 diabetes, adrenal insufficiency, coeliac disease
3) Chromosomal and genetic defects (10-20%): mostly X-linked
    - ie Turner syndrome or Fragile X
    - more frequent in primary than secondary amenorrhoea
4) Iatrogenic (surgery: bilateral salpingooophorectomy BSO)/chemotherapy/radiation)
    i) 40% in cases treated with alkylating agents, but can be restoration 6m following some chemotherapy regimens
    ii) Radiation: pending dose and age
5) Infections (POI reported after various infections mumps, HIV, herpes zoster, cytomegalovirus, tuberculosis, malaria, varicella, and shigella).
    i) No confirmed association: so not tested for
6) Toxic: cigarette smoking
7) Metabolic: galactosaemia

Symptoms

Symptoms are typical of the menopause:

- May be intermittent due to the fluctuations in ovarian activity
- 12-14% of women experience no symptoms
    - more likely in young women with primary amenorrhea.
- Menstrual cycle changes (oligo or amenorrhea)
    - Where primary amenorrhoea – 21% will have a karyotype abnormality
- Vasomotor: hot flushes, night sweats
- Psychosocial: mood changes, poor concentration, lack of energy, sleep disturbance
- Genitourinary: Vaginal symptoms, dyspareunia, dryness, urinary symptoms
- Sexual dysfunction: low libido.
- Asymptomatic: more likely in young women with primary amenorrhea.

Clinicians should always enquire about symptoms of oestrogen deficiency in women presenting with oligomenorrhea or amenorrhea.

Predictors of POI

1. Genetic abnormalities
2. Family history of POI
3. Multiple pregnancy
4. Early menarche
5. Nulliparity/low parity
6. Cigarette smoking
7. Underweight

Diagnosis

The diagnosis of POI is based on the presence of menstrual disturbance and biochemical confirmation in women <40 years.
ESHRE recommended diagnostic criteria is:

1) **Oligo/amenorrhea for at least 4 months, AND**
2) **An elevated FSH level > 25 iu/l on two occasions 4 weeks apart.**

- *FSH can be checked whilst on progesterone only contraception or using a Mirena@, but needs to be checked at least 4-6weeks after stopping the COCP or high dose progesterone.*
- *Do not routinely use anti-mullerian hormone, oestradiol or antral follicle count for diagnosis.*
    - AMH can be undetectable for up to 5 years before periods cease.

[Other societies use different cut offs for FSH:

- *BMS recommends >40 and NICE >30 iu/l*
- *Goldenberg 1973 et al found no follicles at ovarian biopsy with FSH >33*
- *ESHRE found: Women with an autoimmune cause have lower FSH levels]*

Investigations

1) Chromosomal analysis:
    a. To rule out Turner syndrome, Y-chromosome material
        i. Cases with gonadal dysgenesis associated with the presence of Y-chromosome have a high risk of gonadal dysplasia in 1/3rd of cases
2) Fragile-X permutation (FMR1):
    a. The implications should be discussed before the test is performed (see leaflet)
    b. Relatives of women with Fragile-X permutation should be offered genetic counselling and testing
    c. Present in 0.8-7.5% of sporadic cases, and 13% where family history of POI
3) Antibody screen: If unknown cause or if an immune disorder is suspected.
    a. 21 hydroxylase antibody (21OH-Ab) or alternatively adrenocortical antibodies:
    b. thyroid (TPO-Ab) antibodies: 24% (vs 12-15% in general population)
    c. Consider ovarian antibodies – less useful as high rate of false (+)ve
4) Consider: coeliac disease (TTG screen), Vitamin B12, folate and HbA1c

Test	Implications	
	Positive	Negative
Genetic / Chromosomal		
Karyotyping (for diagnosis of Turner syndrome)	Refer to endocrinologist, cardiologist and geneticist	a second analysis of the karyotype in epithelial cells (in case of high clinical suspicion)
Y-chromosomal material	Discuss gonadectomy with the patient	
Fragile-X	Refer to geneticist	
Autosomal genetic testing – not indicated at present	Unless other evidence suggesting specific mutation (ie BPES)	
Antibodies		
Adrenocortical antibodies or 21OH antibodies	Refer to endocrinologist for testing of adrenal function and to rule out Addison's disease.	Re-test in later life only if clinical signs or symptoms develop
TPO-Ab	Test TSH every year	

Taken from ESHRE Guideline[1]

Risks to health with early menopause

1) Reduced life expectancy – by ~2 years if POI <40years
    a. largely due to the increased risk cardiovascular disease.
2) Cardiovascular disease – 2x increased risk of ischaemic heart disease
3) Reduced bone mineral density
    a. Increased risk of osteoporosis (8-14%) and fractures in later life.
    b. Bisphosphonates should not be used as first line in POI
4) Psychosocial and psychosexual health
    a. Significant negative impact on psychological wellbeing and quality of life with increased incidence of depression
    b. Should have access to specialist counsellors
5) Detrimental effect on cognition and potentially early dementia, Parkinson's
    a. Should be discussed when planning oophorectomy for women under 50 years
    b. Most studies show protection if HRT used until the age of 50 years
6) Increased central obesity
7) Type 2 diabetes and hypercholesterolemia
8) Loss of fertility and decreased sexual functioning:
    a. Small chance of pregnancy (<5% natural conception), contraception should be used if they wish to avoid pregnancy.
        i. Resumption most likely: secondary amenorrhoea, follicles on USS, family history of POI, higher oestradiol levels
    b. Spontaneous pregnancies after idiopathic POI or most forms of chemotherapy do not show any higher obstetric or neonatal risk than in the general population.

c. No interventions that have been reliably shown to increase ovarian activity and natural conception rates
d. Oocyte donation is an established option for fertility
e. No predictive test and no established preventative measures. If risk factors for POI; fertility preservation (oocyte/embryo cryopreservation) is a promising option, although studies are lacking.
f. In women with established POI, the opportunity for fertility preservation is missed.
g. HRT may help improve fertility; taking HRT is safe if conceive whilst taking it

Management: To be initiated in either primary or secondary care pending medical professionals experience. Care can be then continued in primary care, with advice from the Gynaecology team whenever necessary.

- **Reduce risk of sequelae by optimising health**
  - Take regular weight-bearing exercise, and maintain a healthy weight
  - A balanced Mediterranean diet, and supplements of calcium and vitamin D. The recommended nutritional intake (RNI) for calcium is 1000mg/day, and for vitamin D 800iu/day.
  - Stop smoking: linked to early menopause, but no causative relation to POI.
  - Avoid excessive alcohol intake

- Hormonal replacement: with the aim to achieve physiological levels of oestrogen, until the age of the natural menopause.
  - There is limited evidence assessing the optimal regimen, dose and route of administration of HRT with POI

- **Oestrogen**: role in primary prevention of diseases of the cardiovascular system and for bone protection, and potentially other long-term health problems including cognitive decline.
  - 17β-oestradiol is preferred to ethinylestradiol or conjugated equine oestrogens for oestrogen replacement
  - Transdermal preparations recommended to reduce the risk of thromboembolism associated with oral oestrogen preparations
  - Start at a low dose and increase for symptom control
    - ie: 25/50microgram patch increasing to 75-100microgram or 2mg equivalent gel or oral oestradiol

- **Progestogen** should be given in combination with oestrogen therapy to protect the endometrium in women with an intact uterus.
  - Give continuously as better endometrial protection
  - Whilst there may be advantages to micronized natural progesterone, the strongest evidence of endometrial protection is for oral cyclical combined treatment.
  - The Mirena@ is licenced for endometrial protection and contraception
  - Utrogestan@ 100mg orally at night on an empty stomach (continuous regimen)

- Sedative side effect, food increases rate of absorption
- If wishing to maintain fertility can be given as a sequential preparation for 12-14 days of the cycle at 200mg

  - Progesterone can also be given as a combined patch with oestrogen.

- **Testosterone** replacement may also be required by some women
  - Ensure first adequately oestrogenised
  - Adequate counselling as 'off-label' and lack long-term data
  - Most beneficial for patients following surgical menopause after a BSO with hypoactive sexual desire disorder
  - *See testosterone replacement guideline WHAT-TP-027 and patient information leaflet WHAT-PI-1105.*

➢ ***Hormones can be replaced as either HRT or COCP – discuss with the women their preferences of type and route of administration. There is very limited data assessing the optimal regimen***

Advantages	HRT	COCP
Acceptability	Perceived increased stigma	More accepted – like peers
Cost	Prescription cost	Free
Contraception	Need additional unless using Mirena@	Is contraception
Pill free week	Depending regimen	May have symptoms, can run packs together
Oestrogen type	Natural - 17β-oestradiol	Synthetic - ethinylestradiol
Cardiovascular	More protection, lowers BP	Less effect
Bone mineral density	More favourable	Less favourable
Cognition	May reduce cognitive decline	No evidence

- **Local oestrogen** may be required to treat dyspareunia and genito-urinary symptoms (in addition to HRT)
  - Lubricants (eg. SYLK) or moisturisers (eg. Replens) are useful for treatment of vaginal discomfort and dyspareunia for women alongside or instead of HRT. These or similar alternatives can be purchased over-the-counter.

- Psychological and lifestyle interventions should be accessible to women with POI.
- Alternative and complementary treatments – evidence on efficacy is limited and data on safety are lacking.

- **DEXA scan**: consider at the time of diagnosis to measure bone mineral density (BMD)
  - If BMD is normal and adequate systemic oestrogen replacement is commenced, the value of repeated DEXA scan is low.
  - If a diagnosis of osteoporosis is made and oestrogen replacement or other therapy initiated, BMD measurement should be repeated within 2-5 years.

- A decrease in BMD should prompt review of oestrogen replacement therapy and of other potential factors. Review by a specialist in osteoporosis may be appropriate.
  - GP to commence Adcal 1500mg chewable tablets BD

Additional Management of POI with special issues

- Turner Syndrome:
  - Offered HRT throughout the normal reproductive lifespan
  - Refer to a cardiologist with a specialist interest in adult congenital heart disease and should have a general medical and endocrine examination.
  - At diagnosis and annually: BP, smoking, weight, lipid profile, fasting plasma glucose, HbA1c

- BRCA gene mutation or after breast cancer:
  - HRT is generally contra-indicated in breast cancer survivors
  - HRT can be used in carriers of BRCA1/2 mutation with no personal history of breast cancer after prophylactic bilateral salpingo-oophorectomy (BSO).

- Endometriosis:
  - HRT following BSO, can be effective for managing vasomotor symptoms.
  - Progesterone for at least the first year can reduce the risk of disease reactivation if they have also had a hysterectomy

- History of VTE – refer to haematologist prior to commencing HRT. Transdermal (TD) route is preferred as this has a lower risk of VTE compared to oral oestrogen.

- Migraine with aura, Hypertension, Obesity and fibroids – are not contra-indications for HRT. Transdermal route is advised as it has a lower risk of VTE compared to oral preparations.

➢ *For primary ovarian failure – refer to Paediatric Gynaecology team for investigation and further management for puberty induction with 17B-oestradiol.*

The potential benefits of Oestrogen replacement

- Maintain bone health and prevent osteoporosis; with a reduced rate in the risk of fracture.
- Possibly reduce the risk of cognitive impairment
- HRT has not been found to increase the risk of breast cancer before the age of natural menopause. Women with POI may in fact have a lower risk of breast cancer due to the lower hormone levels associated with the condition.
- Increased life expectancy as decreases cardiovascular risk

The potential risks of HRT with POI

- Short term:
  - breast tenderness, bloating and break through bleeding
- Long term:
  - VTE – normally related to obesity, transdermal preparations have significantly better profile than oral
  - General risks on older women do not seem to apply to younger women with POI ie stroke
  - No increased risk of breast cancer in POI up until 51 years

Management in pregnancy

- Oocyte donation pregnancies are high risk and should be managed in an appropriate obstetric unit. Women and their partners should be encouraged to disclose the origin of their pregnancy with their obstetric team
  - Oocyte donation appears to be independently associated with higher risk of obstetric complications: PIH, PET and lower fetal birth weight
- Antenatal aneuploidy screening should be based on the age of the oocyte donor
- Women presenting for oocyte donation who are suspected of having POI should be fully investigated prior to oocyte donation, including thyroid and adrenal function as well as karyotype
- Pregnancies in women who have received radiation to the uterus are at high risk of obstetric complications and should be managed in an appropriate obstetric unit
- Pregnancies in women with Turner Syndrome are at very high risk of obstetric and non-obstetric complications and should be managed in an appropriate obstetric unit with cardiologist involvement
- A cardiologist should be involved in care of pregnant women who have received anthracyclines and/or cardiac irradiation.
- Women previously exposed to anthracyclines, high dose cyclophosphamide or mediastinal irradiation should have an echocardiogram prior to pregnancy, and referral to a cardiologist if indicated.
- Women with POI should have their blood pressure, renal function, and thyroid function assessed prior to pregnancy
- Pregnancy in some women can be of such high risk that clinicians may consider oocyte donation to be life threatening and therefore inappropriate.

Long-term Monitoring

- HRT should be continued until at least the age of natural menopause.
- Annually review to check compliance and any side effects or new symptoms
- Monitor cardiovascular risk: BP, weight, smoking status
  - If Turner syndrome; also assess lipid profile, fasting plasma glucose and HbA1c annually

- Check TSH yearly if positive TPO-Ab.
- No routine monitoring tests are required but may be prompted by specific symptoms or concerns
- Increase oestrogen dose as necessary to control symptoms
  - Check levels if concerned not absorbing, and try a different delivery route
- Long-term – take until at least the age of 51 years, many women may choose to continue longer; their relative risks will change as will the dose they need

Patient support

http://www.daisynetwork.or.uk/
ESHRE Patient information leaflet on POI (and iatrogenic)
Fragile X Syndrome: Birmingham Women's Information Leaflet for patients and families

Research

Worcester Hospital is hoping to be part of the upcoming POISE Trial. Investigating the optimum management for POI; HRT verses COCP.

http://poiregistry.net – an anonymous global register set up by investigators at Imperial College London, UK

Monitoring

Page/ Section of Key Document	Key control:	Checks to be carried out to confirm compliance with the Policy:	How often the check will be carried out:	Responsible for carrying out the check:	Results of check reported to: *(Responsible for also ensuring actions are developed to address any areas of non-compliance)*	Frequency of reporting:
	WHAT?	**HOW?**	**WHEN?**	**WHO?**	**WHERE?**	**WHEN?**
	These are the 'key' parts of the process that we are relying on to manage risk. We may not be able to monitor every part of the process, but we MUST monitor the key elements, otherwise we won't know whether we are keeping patients, visitors and/or staff safe.	What are we going to do to make sure the key parts of the process we have identified are being followed? (Some techniques to consider are; audits, spot-checks, analysis of incident trends, monitoring of attendance at training.)	Be realistic. Set achievable frequencies. Use terms such as '10 times a year' instead of 'monthly'.	Who is responsible for the check? Is it listed in the 'duties' section of the Policy? Is it in the job description?	Who will receive the monitoring results? Where this is a committee the committee's specific responsibility for monitoring the process must be described within its terms of reference.	Use terms such as '10 times a year' instead of 'monthly'.

References

References and Resources

1) ESHRE: Management of Women with Premature Ovarian Insufficiency. December 2015
2) ESHRE: Diagnostic work-up in suspected POI patients
3) ESHRE: patient information leaflet
4) NICE: Menopause diagnosis and management NG23
5) POI White Paper, Nick Panay
6) IMS – International Menopause Society Recommendations on Women's Midlife Health 2016
7) BMS: POI Summary Consensus Statement. April 2020

Contribution List

Contribution List

This key document has been circulated to the following individuals for consultation;

Designation
All members of the Gynaecology Governance Team
Gynaecology Consultants: Jon Hughes, Angus Thompson, Mamta Pathak, Laura Veal, Alex Blackwell, Manon Van Seters, Rina Panchal, Jonathan Chester, Prabath Suraweera, Paul Moran, Harnek Rai
Matrons and Specialist Nurses

This key document has been circulated to the chair(s) of the following committee's / groups for comments;

Committee
Gynae Governance Meeting

Supporting Document 1 - Equality Impact Assessment Tool

To be completed by the key document author and included as an appendix to key document when submitted to the appropriate committee for consideration and approval.

Please complete assessment form on next page;

Herefordshire & Worcestershire STP - Equality Impact Assessment (EIA) Form
Please read EIA guidelines when completing this form

Section 1 - Name of Organisation (please tick)

Herefordshire & Worcestershire STP		Herefordshire Council		Herefordshire CCG	
Worcestershire Acute Hospitals NHS Trust	x	Worcestershire County Council		Worcestershire CCGs	
Worcestershire Health and Care NHS Trust		Wye Valley NHS Trust		Other (please state)	

Name of Lead for Activity	**Kiritea Brown**

Details of individuals completing this assessment	**Name**	**Job title**	**e-mail contact**
	Kiritea Brown	**O&G Consultant**	**Kiritea.brown@nhs.net**
Date assessment completed	**26.11.2022**		

Section 2

Activity being assessed (e.g. policy/procedure, document, service redesign, policy, strategy etc.)	**Title: Policy / Clinical Guideline**			
What is the aim, purpose and/or intended outcomes of this Activity?	To ensure correct management of patients diagnosed with Premature Ovarian Insufficiency			
Who will be affected by the development & implementation of this activity?	❑ x ❑ ❑	Service User Patient Carers Visitors	x ❑ ❑ ❑	Staff Communities Other _____
Is this:	❑ Review of an existing activity x New activity ❑ Planning to withdraw or reduce a service, activity or presence?			

What information and evidence have you reviewed to help inform this assessment? (Please name sources, eg demographic information for patients / services / staff groups affected, complaints etc.	General observation of patients coming through the Fertility and menopause clinics. No previous local hospital guideline on how these patients should best be managed.
Summary of engagement or consultation undertaken (e.g. who and how have you engaged with, or why do you believe this is not required)	Involved the Gynae Governance team
Summary of relevant findings	

Section 3

Please consider the potential impact of this activity (during development & implementation) on each of the equality groups outlined below. **Please tick one or more impact box below for each Equality Group and explain your rationale**. Please note it is possible for the potential impact to be both positive and negative within the same equality group and this should be recorded. Remember to consider the impact on e.g. staff, public, patients, carers etc. in these equality groups.

Equality Group	Potential positive impact	Potential neutral impact	Potential negative impact	Please explain your reasons for any potential positive, neutral or negative impact identified
Age	x			For women <40yrs it should help improve their care
Disability		x		
Gender Reassignment		x		
Marriage & Civil Partnerships		x		
Pregnancy & Maternity		x		
Race including Traveling Communities		x		
Religion & Belief		x		
Sex		x		
Sexual Orientation		x		
Other Vulnerable and Disadvantaged Groups (e.g. carers; care leavers; homeless; Social/Economic		x		

Equality Group	Potential positive impact	Potential neutral impact	Potential negative impact	Please explain your reasons for any potential positive, neutral or negative impact identified
deprivation, travelling communities etc.)				
Health Inequalities (any preventable, unfair & unjust differences in health status between groups, populations or individuals that arise from the unequal distribution of social, environmental & economic conditions within societies)		X		

Section 4

What actions will you take to mitigate any potential negative impacts?	Risk identified	Actions required to reduce / eliminate negative impact	Who will lead on the action?	Timeframe
	x	.		
How will you monitor these actions?				
When will you review this EIA? (e.g in a service redesign, this EIA should be revisited regularly throughout the design & implementation)	**In 3 years time to check for any National guideline updates**			

Section 5 - Please read and agree to the following Equality Statement

1. Equality Statement

1.1. All public bodies have a statutory duty under the Equality Act 2010 to set out arrangements to assess and consult on how their policies and functions impact on the 9 protected characteristics: Age; Disability; Gender Reassignment; Marriage & Civil Partnership; Pregnancy & Maternity; Race; Religion & Belief; Sex; Sexual Orientation

1.2. Our Organisations will challenge discrimination, promote equality, respect human rights, and aims to design and implement services, policies and measures that meet the diverse needs of our service, and population, ensuring that none are placed at a disadvantage over others.

1.3. All staff are expected to deliver services and provide services and care in a manner which respects the individuality of service users, patients, carer's etc, and as such treat them and members of the workforce respectfully, paying due regard to the 9 protected characteristics.

Signature of person completing EIA	 Kiritea Brown
Date signed	26.11.2022
Comments:	
Signature of person the Leader Person for this activity	 Kiritea Brown
Date signed	26.11.22
Comments:	

Supporting Document 2 – Financial Impact Assessment

To be completed by the key document author and attached to key document when submitted to the appropriate committee for consideration and approval.

	Title of document:	Yes/No
1.	Does the implementation of this document require any additional Capital resources	No
2.	Does the implementation of this document require additional revenue	No
3.	Does the implementation of this document require additional manpower	No
4.	Does the implementation of this document release any manpower costs through a change in practice	No
5.	Are there additional staff training costs associated with implementing this document which cannot be delivered through current training programmes or allocated training times for staff	No
	Other comments:	

If the response to any of the above is yes, please complete a business case and which is signed by your Finance Manager and Directorate Manager for consideration by the Accountable Director before progressing to the relevant committee for approval.