Advances in Premature Ovarian Insufficiency (POI)
RCOG World Congress: Cape Town 2017

Nick Panay
Patron: Daisy Network
Hon Director of Conferences: RCOG
Board member: International & British Menopause Societies
Definition - POI

- Accelerated loss of ovarian follicles and therefore ovarian reserve before the age of 40 years

**Menstrual disturbance**
- Elevated gonadotrophins
- Estrogen deficiency

- Climacteric symptoms
- Cardiovascular disease
- Bone density
- Fertility implications

- Controversy over nomenclature, aetiology and prevalence
  - ‘premature ovarian failure’ & ‘primary ovarian insufficiency still in use!
  - Genetic, autoimmune, infective causes but “idiopathic” still main category!
  - Observational data suggest a 7% incidence and in some countries a 20% incidence is quoted e.g. China /India (Verbal communication)!
Review
Premature menopause or early menopause: Long-term health consequences


Fig. 1. The effects of bilateral oophorectomy increased with younger age at the time of oophorectomy for several outcomes investigated by the Mayo Clinic Cohort Study of Oophorectomy and Aging [2,28,29]. Risk was expressed using hazard ratios and 95% confidence intervals. The age strata on the x-axis are slightly different for overall mortality and cardiovascular mortality versus cognitive impairment or dementia and parkinsonism.
Effect of primary ovarian insufficiency and early natural menopause on mortality: a meta-analysis

X-Y. Tao\textsuperscript{a,b}, A-Z. Zuo\textsuperscript{a}, J-Q. Wang\textsuperscript{b} and F-B. Tao\textsuperscript{a,b}

POI
- Gallagher LG 2011: 1.10 (0.52, 2.34)
- Cooper GS 1998: 1.50 (0.67, 3.36)
- Jacobsen BK 1999: 1.70 (1.00, 2.80)
- Subtotal (I-squared = 0.0\%, p = 0.645): 1.48 (1.02, 2.16)

ENM
- Cooper GS 1998: 0.60 (0.26, 1.44)
- Mondul AM 2005: 1.09 (1.00, 1.18)
- Jacobsen BK 1999: 1.10 (0.60, 1.90)
- Gallagher LG 2011: 1.12 (0.70, 1.77)
- Subtotal (I-squared = 0.0\%, p = 0.599): 1.09 (1.00, 1.18)

NOTE: Weights are from random effects analysis

Figure 4. Forest plot of ischemic heart disease mortality comparison: early age at natural menopause vs. normal age at natural menopause. POI, primary ovarian insufficiency; ENM, early natural menopause; RR, relative risk.
POI: New Guidelines

• Specific POI guidelines now developed by ESHRE & NICE

• but .... without definitive research we are left to advise women with POI using
  – limited RCT data
  – inappropriate guidelines extrapolated from different patient populations (natural menopause)
  – do data from oophorectomised POI population apply to spontaneous POI?
New POI Guidelines

NICE

Menopause: diagnosis and management

NICE guideline
Published: 12 November 2015
nice.org.uk/guidance/ng23
BMS Recommendations
Call for a database/registry
www.thebms.org.uk

“We recommend to the Department of Health that a Premature Menopause Register should be established as a priority”

“All those women who have undergone premature menopause and are at greater risk of osteoporosis, cardiovascular disease and cognitive decline should be on this register”
Premature ovarian insufficiency (POI) remains poorly understood and under-researched. Controversy persists over nomenclature, with terms such as 'premature ovarian failure' and 'primary ovarian insufficiency' still in usage. Women with POI require integrated care to address physical, psychosocial, and reproductive health as well as preventative strategies to maintain long-term health. However, there is an absence of evidence-based guidelines for diagnosis and management.

In the absence of prospective, randomized, controlled trial (RCT) data, there is a need for high-quality observational data. There have been calls for a database registry to provide this information. Individual centers generally do not have sufficient exposure to women with POI to gather sufficient observational or RCT data to give meaningful results on disease characterization and long-term outcomes. Cooper and colleagues make the point that fragmented research leads to fragmented patient care. We are in total agreement with Cooper and colleagues that, without definitive research, we are left to advise women with POI using inappropriate or premenopausal practice guidelines that are based on a different patient population.

The collaborative effort of the effort of the various investigators who will contribute to the database will be important in helping to refine and characterize the various presentations of POI along the lines of the STRAW (1) and the POI registry (2).

The STRAW + 10 collaborators, including many specialists and special groups such as POI, will be paying attention for staging of reproductive health through the use of a biomarker to further refine the definition of POI, with a view to developing a hormone to precisely define POI and early ovarian insufficiency.

There is a database need for the remaining one to respond to interventions, such as controlled release hormone therapy and those not receiving hormone therapy. This is particularly important for women with rare causes and hormone-sensitive cancers where RCTs are unlikely ever to be performed.

Regarding treatment questions which urgently need to be addressed include whether the type of hormone replacement therapy (HRT) matters, whether the replacement of estradiol (HRT) and versus transdermal estradiol in patients with estrogen deficiency, whether versus replacement of follicle-stimulating hormone (FSH), estrogen, and FSH at the same time, and whether the effects of these regimens on quality of life and hormone status are significant.

The database would also be useful to identify patterns of spontaneous cases with no pathogenic mechanism can be identified.

Objective: To articulate the need for a new approach to primary ovarian insufficiency. The condition, also known as premature menopause or premature ovarian failure, is defined by the presence of menopausal-level serum gonadotropins in association with irregular menstrual periods in adolescent girls or women younger than 40 years. It can be instigating, such as delayed menarche or menopause, as a result of spontaneous, or as part of a host of ulterior etiological factors. In a large percentage of spontaneous cases no pathogenic mechanism can be identified.

Design: Literature review and consensus building at a multidisciplinary scientific workshop.

Conclusions: There are major gaps in knowledge regarding the etiologic mechanisms, psychosocial effects, natural history, and medical and psychosocial management of primary ovarian insufficiency. An international research consortium and database registry formed under the guidance of an umbrella organization would provide a pathway to comprehensively increase basic and clinical knowledge about the condition. Such a consortium and patient registry would also provide clinical samples and clinical data with a goal toward defining the specific pathogenic mechanisms. An international collaborative approach that combines the structure of a patient registry with the principles of integrative care and community-based participatory research is needed to advance the field of primary ovarian insufficiency (Ferti Sterili 2010; 94:1-13. © 2010 by American Society for Reproductive Medicine).

Key Words: Premature ovarian insufficiency (POI), premature ovarian failure (POF), premature menopause, diminished ovarian reserve, sex steroid deficiency, infertility, menstrual cycle, patient registry, research consortia, participatory research, integrative medicine.
Database Opportunities - Summary

- Characterise various presentations of ROI STRAW + 10 Guidelines

- Can we use AMH / AFC / other markers to precisely predict the course / timing of ovarian insufficiency?

- Create global bio bank for genetic studies...

Genomics England
Collaborative UK study

Early Onset Familial Premature Ovarian Insufficiency (EOFPOI)

Targeted gene sequencing has enabled identification of likely causative mutations in a modest proportion of POI families e.g. Fragile X

Large scale whole genome sequencing could enable identification of novel causative genomic factors.

- Collaboration with other centres globally e.g. Utrecht / Belgrade / Beijing possible
Database Opportunities - Summary (2)

• Determine long term response to interventions e.g. COC v HRT v No treatment
  – Particularly important in women with rare causes / hormone sensitive cancers where RCTs are unlikely to be performed

• Does the type of HRT matter?
  – Oral v Transdermal E2
  – E2 / SERM
  – E2 dose
  – Progesterone / retroprogesterone v androgenic progestins

• Quantify precise risks e.g. psychological / osteoporosis /breast / cardiovascular disease / cognitive dysfunction
POI Database

- All patients with POI entered into database for audit purposes, >10 years of recruitment
- Dedicated POI clinics / MDT approach / collaboration with other units commenced
- Funding from NIHR Imperial BRC used to commission Semantic Web Company Factmint
## POI History / Investigations

<table>
<thead>
<tr>
<th>Detailed history</th>
<th>Especially for family history of early menopause</th>
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<tbody>
<tr>
<td><strong>Hormone Profile</strong></td>
<td>FSH &gt;25 on 2 occasions 4-6 weeks apart, Estradiol, Thyroid function, FAI and prolactin; …insulin resistance / lipids / bone markers long term monitoring</td>
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<tr>
<td><strong>Autoimmune screen</strong></td>
<td>Anti thyroid &amp; anti adrenal antibodies</td>
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<tr>
<td><strong>Karyotyping and genetic analysis</strong></td>
<td>Especially in &lt;30 years or family history (Turner’s / Fragile X)</td>
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<tr>
<td><strong>Pelvic USS</strong></td>
<td>To assess antral follicle count</td>
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<tr>
<td><strong>DEXA</strong></td>
<td>Baseline bone mineral density</td>
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<tr>
<td><strong>Anti–mullerian hormone</strong></td>
<td>To assess ovarian reserve</td>
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Secure Web-based application

WELCOME

Log In To The Registry

For Health workers and patients needed to register us in London and internationally

About The Registry

The International Premature Ovarian Insufficiency Registry is based in the UK

Contact The Registry

West London Menopause Service Queen Charlotte's and Chelsea and Westminster Hospitals

A diagnosis of Premature Ovarian Insufficiency (POI) impacts on many aspects of a young woman's health. We are a group of doctors led by Mr Nick Panty, Consultant Gynaecologist from Imperial College London, Queen Charlotte's & Chelsea and Chelsea and Westminster Hospitals. We aim to bring together clinicians, scientists, patients, academia, industry and government under one umbrella to produce a national and international database to support the research and understanding of POI.

WHY IS THERE A NEED FOR A DATABASE?

Rare diseases limit the experience of any one centre of care, which leads to fragmented research and patient care. By producing and managing this database we can work towards increased understanding of the natural history of the disease, targeted treatment regimens and improving overall patient care.

CALL FOR COLLABORATION

By working as a collective we have an opportunity to collect valuable data and make considerable progress in understanding and treating POI.
1) Registration of Interest – 43 registrations globally, >800 POI patients

2) Entry of legacy data complete - 484 patients

3) Prospective data entry of data – 343 patients (many thanks to Laura Cucinella, Geetika Shah, Lynne Robinson and Marie Gerval!)

4) Further collaboration needed - Please register your interest now!
International Collaboration on POI
Sample of Registered Institutions

UK
- Imperial College London
- Northwick Park London
- Liverpool Women’s Health Foundation
- Birmingham Women’s Hospital
- Kings College London
- Poole General Hospital
- Norfolk & Norwich University
- Salisbury Hospital
- RGH, Cardiff
- University of Aberdeen
- Southport & Ormskirk NHS
- Market Cross Surgery, Mildenhall

International
- University of Cape Town, South Africa
  …..thanks to Zephne van de Spuy!
- Red de Salud UC Christus, Chile
- Scientific Centre of Family Health & Human Reprod Irkutsk, Russia ..thanks to Inna Kovalenko & Larisa Suturina
- Research Center for Obstetrics, Gynaecology & Perinatology Moscow, Russia…thanks to Galina Chernuka and Vera Smetnik
- Beijing Capital University, O & G hospital, China…thanks to Li Yanglu, Ruan Xyangyan
- Ottowa Hospital, Canada
- University of Melbourne, Australia
- University of Pavia, Italy
- Vilnius University Hospital, Lithuania
- Hospital de Sant Pau Barcelona, Spain

Any contributions verbally, post, e mail and offers to collaborate gratefully received!
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POI Registry Dashboard

- Updated automatically every 24 hours from the data in the POI registry

  Fully editable, so new visualizations and dashboards can be created

  Filterable - click on bar in one chart, other data update to focus on that cohort
Aetiology of POI @ West London Menopause Centre

- Idiopathic (56.9%)
- Cancer (26.6%)
- Benign (14.1%)
- Genetic (2.4%)

Symptoms at presentation of POI

- VMS, tiredness and vaginal dryness commonest symptoms
- Mood, libido and cognitive issues also common problems
Symptoms by Aetiology

Maclaren & Panay 2017
Timely diagnosis is vital...

• Often significant delay in diagnosis quoted
  ○ >50% see ≥ 3 clinicians before diagnosis made
  ○ 25% diagnosis > 5 years

• Delay and subsequent period of estrogen deficiency cited as contributor to low bone density

• Guideline implementation important!

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**Diagnosing premature ovarian insufficiency**

1.6.1 Take into account the woman’s clinical history (for example, previous medical or surgical treatment) and family history when diagnosing premature ovarian insufficiency.

1.6.2 Diagnose premature ovarian insufficiency in women aged under 40 years based on:
  - menstrual symptoms, including no or infrequent periods (taking into account whether the woman has a uterus) and
  - elevated PSH levels on 2 blood samples taken 4–6 weeks apart.

1.6.3 Do not diagnose premature ovarian insufficiency on the basis of a single blood test.
Time to delayed diagnosis and its impact on Bone Mineral Density Measured by Spine T score

For every unit increase in time (month) BMD as measured by spine T score decrease by 0.026, \( p=0.001 \) (1 way anova)

Principles of Hormone Replacement in POI

Estrogen replacement (E2 / EE) is first line treatment in POI at least until average age of menopause
Committee on Safety of Medicines www.mhra.gov.uk

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

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
Survey of EMAS members: 2015
Pill v HRT in POI

APRIL - POLL RESULTS

What would be your first choice in a twenty year old with premature ovarian insufficiency?

- The combined oral...
- Menopausal hormone therapy

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Role of the COC in POI

• COC often seen as simpler and more peer-friendly
  – “Driven by practicalities rather than science”
    • Prof G Conway
  – Delivers synthetic ethinyl estradiol
  – Symptom resurgence during pill-free week

• 3 small RCTs of HRT vs COC thus far..
  – COC most suppressed FSH$^1$
  – HRT less hyperinsulinaemia$^1$, increased bone
    formation markers$^2$ and improved LS BMD$^3$

3 Cartwright, et al. JCEM, 2016
Lumbar spine BMD

2 Yr Study of COCP V HRT V No Treatment N=36

HRT vs COCP at 24 months
p=0.040
(12 months p=0.021)

GROUP
- no treatment
- HRT
- COCP

Cartwright B, Robinson J, Seed P, Fogelman I, Rymer J JCEM 2016
Hormone Therapy in POI

- POI require higher doses of estrogen than older women
  - 75-100 μg 17β-E2 patch, 3-4 doses of E2 gel, 2-4mg pO
  - Utrogestan cc100mg/sc200mg, Mirena or Femoston (PO)

- Optimal E2 levels for prevention of long-term sequelae?
  - Aim for 300 – 500pmol/l - mid follicular E2 levels

- Androgen replacement should also be considered esp after iatrogenic POI e.g. testim gel 0.5-1.0ml / day
NICE POI Future Research Recommendations

• THE DEFINITIVE PROSPECTIVE RCT – COC V HRT

• APPLICATION SUBMITTED TO INSTITUTE OF HEALTH RESEARCH UK

• Good quality data should be available within 5 years of a large RCT of COC versus HRT. Outcomes: quality of life, cardiovascular and osteoporosis risk markers.

• Longer term observational data important to assess major outcomes e.g. CVD, fractures and cognition
KEY TAKE HOME MESSAGE

• COC FOR POI – 1^{ST} FEW YEARS (\(\leq 5\)Y) PROB OK

• AVOID / SHORTEN HFI IF USING COC!

• \textit{?ROLE FOR ESTRADIOL (E2) PILLS}
  • ZOELEY / QLAIRA TBC
Patient concerns – POI Survey

Singer et al, Climacteric 2011
Fertility options

• IVF with donor oocytes confers the highest chance of pregnancy ≈ 50-60% per cycle

• Adoption, surrogacy, child free living

• 50% would not consider OD even though 90% nulliparous at time of diagnosis in our unit!

• Role of DHEA in POI: Limited data, controversial

• Oogonial stem cells?..

Premature ovarian insufficiency: how to improve reproductive outcome?

Ben-Nagi J, Panay N.
Advances in Fertility Options in POI

• Stem cells in adult ovaries (Oogonial stem cells)

• Unclear why they stop transforming into oocytes – possible genotoxic effects

• Cells could be stimulated to produce oocytes thus reversing menopause – only in mouse model thus far

• US, Chinese and Edinburgh groups working on this

Women with POI need support from peers and professionals

The Daisy Network

A large support group for women suffering with Premature Ovarian Insufficiency (POI).

www.daisynetwork.org.uk
Please join us in Vancouver 6-9th June 2018 for the IMS World Congress
Thanks to the team and to you for listening!

West London Menopause and PMS Team:
   Claire Bellone, Claudine Domoney, Marie Gerval, Heidi Grech, Annie Hawkins, Etienne Horner, Naomi Low-Beer, Kate Maclaran*

*POI Database: Best Free Communication @ ISGE Florence March 2012

The Royal Brompton Team:
   John Stevenson & Peter Collins

Factmint Team:
   Alex Parkes & Chris Scott