Primary Ovarian Insufficiency (POI)

Adele – Hello Parody (Hella Cravings)
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• Physiology of Ovarian Follicles
• Definitions
  • Menopause
  • Polycystic Ovarian Syndrome (PCOS)
  • Primary Ovarian Insufficiency (POI)
  • Diminished Ovarian Reserve (DOR)
• Diagnostic Criteria of POI
• Prevalence
• Causes
• Management of Sequelae
• Post-Test

OBJECTIVES
By the end of this presentation, the audience will be able to:
• Identify patients with POI
• Understand the difference between POI and DOR
• Know the diagnostic tests to order to confirm the diagnosis
• Counsel patients about prognosis & morbidities involving POI
• Offer appropriate treatment
Women with primary ovarian insufficiency (POI) may intermittently produce estrogen and ovulate.

- POI occurs only in women under the age of 40.
- Women with POI do NOT need contraception because they are infertile.
- All women with diminished ovarian reserve (DOR) also have POI.
- All women with POI also have DOR.
- The cause of POI is unknown in the vast majority of cases.
- Women with POI are at risk of osteopenia and cardiovascular disease.
- The first line treatment for women with POI is combination BCP.
- Women with POI who take HRT are at risk for breast cancer.
- Women with POI and low bone density should take bisphosphonate (Fosamax) to prevent fracture.

**Physiology of Ovarian Follicles**

- 2,000,000 follicles
- 1,000,000 follicles
- 100,000 follicles
- 100 follicles

**Egg Development**

- A female will NOT produce any new eggs in her lifetime.
- Only 400-500 eggs will be released in her lifetime.
- The rests undergo apoptosis (or programmed cell death).

**Etiologies of Oligomenorrhea & Secondary Amenorrhea**

- 40% Ovarian Disease
- 15% Hypothalamic Dysfunction
- 13% Pituitary Disease
- 5% Uterine Disease
- 1% Other

ETIOLOGIES OF OLIGOMENORRHEA & SECONDARY AMENORRHEA

- Menopause
- PCOS
- POI

OVARIAN DISORDERS

- Menopause:
  - Permanent cessation of menstruation for 12 consecutive months
  - Median age: 51.4 years
  - Reflection of complete ovarian follicular depletion

- Polycystic Ovarian Syndrome (PCOS):
  - Most common hormonal disorder among women of reproductive age
  - Characterized by hyperandrogenism, ovulatory dysfunction and, polycystic ovarian morphology

- Primary Ovarian Insufficiency (POI):
  - Development of hypergonadotropic hypogonadism before the age of 40
  - A spectrum disorder - a continuum of impaired ovarian function
  - Previously and erroneously known as:
    - Premature menopause
    - Premature ovarian failure

DIAGNOSTIC CRITERIA OF POI

- Age < 40 years
- Abnormal Menstruation > 4 mos
  - Secondary Amenorrhea
- Oligomenorrhea
- FSH in the menopausal range on 2 occasions at least 1 month apart
PHYSIOLOGY OF POI

PREVALENCE of POI

- Affects 1% of the general population
- 1:1000 at age 20; 1:100 at age 40
- Ethnicity may affect prevalence
- Higher incidence among:
  - African American
  - Hispanic
- > 50% of young women with spontaneous POI have reported seeing 3 or more clinicians before laboratory testing was finally done.

CLINICAL PRESENTATION of POI

- Menstrual changes (oligomenorrhea or amenorrhea)
  - Intermittent ovarian function occurs in 50-75% of women with spontaneous POI
- Infertility
  - 5-10% conceive & have a normal pregnancy
- Estrogen deficiency symptoms:
  - Hot flashes
  - Night sweats
  - Vaginal dryness
- Decreased libido

**DIMINISHED OVARIAN RESERVE (DOR)**

- NOT synonymous with POI
- A term used in the context of female infertility evaluation and treatment
- Decrease in the number and quality of the remaining eggs in the ovaries
- 10% of women have lower ovarian reserve than what is expected for their age
- Women with DOR have regular menstruation
- Women with DOR can be of varying age
- FSH is in the premenopausal range
- Infertility is the sole clinical presentation
- IVF with donor egg provides the most optimal fertility therapy

**DIAGNOSIS**

<table>
<thead>
<tr>
<th>Clinical State</th>
<th>Serum FSH</th>
<th>AMH</th>
<th>Fertility</th>
<th>Menses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Regular</td>
</tr>
<tr>
<td>PCOS</td>
<td>Normal</td>
<td>Normal to High</td>
<td>Reduced</td>
<td>Irregular</td>
</tr>
<tr>
<td>DOR</td>
<td>Normal</td>
<td>Low</td>
<td>Reduced</td>
<td>Regular</td>
</tr>
<tr>
<td>POI</td>
<td>Elevated</td>
<td>Low</td>
<td>Reduced to Absent</td>
<td>Irreg or absent</td>
</tr>
<tr>
<td>Menopause</td>
<td>Elevated</td>
<td>Low</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

**CASE STUDY**

- 38 y.o. G1P1 presents with infertility and recent onset oligomenorrhea since stopping her OCP 1 year ago. She is wondering whether being on long-term OCP is responsible for her irregular menses and infertility.
- PMHx: Healthy
- PSHx: s/p cesarean delivery
- Meds: PNV daily
- FMHx: father is healthy; mother has hypertension
- Physical Exam:
  - 5’2”; Weight = 145 lbs; BMI = 26.5 kg/m2; LMP = 9/23/2018
  - Normal pelvic exam
- Assessment:
  - New onset oligomenorrhea
  - Secondary infertility
### BASIC PRELIMINARY TESTS

- HCG
- FSH
- Estradiol
- TSH
- Prolactin
- Testosterone
- DHEA-S
- 17-OH Progesterone
- AMH

*Order this test only if patient also presents with infertility concerns.*

### CASE STUDY

**Test Results:**
- HCG $<$ 1
- FSH = 36
- Estradiol $<$ 10
- TSH = 1.55
- Prolactin = 18
- Testosterone = 27
- DHEA-S = 100
- 17-OH Progesterone = 38
- AMH = 0.03

**To Confirm POI Dx:**
- Repeat FSH & E2 after at least 1 month later
- If FSH & E2 remain in menopausal range, dx of POI is confirmed

### CAUSES OF POI

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>329 (88.2%)</td>
</tr>
<tr>
<td>X-Chromosome Abnormalities</td>
<td>25 (6.7%)</td>
</tr>
<tr>
<td>Turner Syndrome</td>
<td>6 (1.6%)</td>
</tr>
<tr>
<td>FMR1/Hermansel Center (Tas8)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Bar syndrome</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Other idiopathic abnormalities</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>46,XY Gonadal Dysgenesis</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Autosomal Causes</td>
<td>6 (1.6%)</td>
</tr>
<tr>
<td>FMR1 mutation / FMR1 methylation</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Methyladenosine triphosphate synthase (MATS)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Introgenic Causes</td>
<td>6 (1.6%)</td>
</tr>
<tr>
<td>Chromosomal Abnormalities (%)</td>
<td></td>
</tr>
<tr>
<td>Autoimmune Causes</td>
<td>3 (0.8%)</td>
</tr>
</tbody>
</table>

SMOKING

Does smoking increase my risk of POI?

Answer: Yes. Cigarette smoking has been shown to increase the risk of DOR and POI.

POI PREVENTION

Are there preventive measures I can take to prevent POI?

Answer: There are currently no known preventive measures to decrease your risk of POI. Nevertheless, it’s important to maintain a healthy lifestyle.

HEREDITARY

Is POI hereditary?

Answer: Most cases of POI occur sporadically. However, 10%-15% of cases have an affected first-degree relative.
ADDITIONAL TESTS

- Chromosome Analysis
  - Turner’s Syndrome
  - 46 XY Gonadal Dysgenesis
- FMR-1 (Fragile X premutation carrier testing)
- Antibody Testing:
  - Thyroperoxidase Ab (TPO)
  - Adrenal Antibody Screen
  - Serum Calcium

Turner’s Syndrome

- 45 X0 or 46 XX mosaic - gonadal dysgenesis
- Amenorrhea due to accelerated apoptosis
- Clinical features:

46 XY Gonadal Dysgenesis

- Sex development disorder associated with anomalies in gonadal development
- Mixed gonadal dysgenesis typically results in the presence of female external and internal genitalia despite the 46,XY karyotype
- Y chromosome-containing cells have a high likelihood of developing gonadoblastoma, thus requiring gonadal removal
Fragile-X (FMR-1) Premutation Carrier

- Fragile X Syndrome (FXS) is the most common inherited form of mental retardation
- FMR1 is an X-linked gene that codes for an RNA binding protein
- 1% prevalence of FMR1 premutation carrier state in the general population
- 16% of FMR1 premutation carriers develop POI
- 14% of familial POI will have a premutation in the FMR1 gene
- Carrier should have genetic counseling regarding risk of having a child with FXS

Autoimmunity

Antibody Testing

- Thyroperoxidase Ab (TPO) > if +, check TSH, FT4, T3 annually
- Hypothyroidism
- Adrenal Antibody Screen > if +, check am cortisol & ACTH annually
- Addison's Disease
- Ovarian Antibody Screen > lacks specificity; therefore, this test is NOT warranted
- Serum Calcium (there's currently no Parathyroid Antibody or Anti-Calcium Sensing Receptor Antibody test available in HC)

Management of Idiopathic POI

- IMPORTANCE OF EARLY DIAGNOSIS
  - Avoidance of diagnosis delay (5 yr delay in 25% of women)
  - Rule out other causes:
    - Pregnancy
    - Hypoprothrombinemia
    - Hyper or hypothyroidism
    - PCs
    - Adrenal insufficiency
    - Parathyroid hormone insufficiency
    - Chromosomal abnormalities
  - Osteoporosis Prevention
  - Cardiovascular Prevention
Management of Idiopathic POI

CONSEQUENCES OF ESTROGEN DEFICIENCY

- Hot Flashes
- Insomnia
- Vaginal Dryness
- Bone Loss (2 to 3% lower bone density compared with control women)
- Cardiovascular morbidity & mortality
- Emotional Health — higher scores on depression, anxiety, and negative affect scales
- Physical Well-Being: impaired cognition, diminished libido

RECOMMENDED THERAPY:

First-line approach - HT (either orally or transdermally) that achieves replacement levels of estrogen is recommended

Estrogen

Estrace 1 – 2 mg daily (oral)
Climara 0.1 mg/day (transdermal)
Premarin 0.625 – 1.25 mg daily (oral)

Continuous Progestogen

Provera 2.5-5 mg daily (oral)
Premometrum 100 mg daily (oral)

Sequential Progestogen

Provera 10 mg daily for 12 days
Prometrium 200 mg daily for 12 days

Sequelae of POI

Vasomotor symptoms
GU symptoms
Bone Health
CV Health
Sexual Function
Quality of Life

BONE HEALTH

- 9.4% vs 3.3% - Incidence of hip fracture in women starting menopause at age 40 compared with those starting menopause at age 48
- 2.5X greater - vertebral fracture in women who experienced menopause before age of 45 compared with those who experienced menopause after age of 50

Risk factors for low bone mass:
- Delay in POI diagnosis of 1 year or more
- Vitamin D insufficiency
- Lack of calcium supplementation
- Nonadherence to prescribed HT
- Sedentary lifestyle

HT, not bisphosphonates (i.e., Fosamax), is the drug of choice for osteopenia or osteoporosis in women with POI

ACOG Committee Opinion. Hormone Therapy in Primary Ovarian Insufficiency. Number 698, May 2017
CARDIOVASCULAR HEALTH

- 2% decreased in cardiovascular mortality for every year that menopause was delayed after the age of 39
- 50% greater risk of ischemic heart disease-related death – for patients who became menopause between the ages of 35 - 40 years compared with those who experienced menopause between the ages of 49 - 51
- Significantly diminished brachial artery endothelial dysfunction in women with POI compared with age & body mass index-matched control
- Brachial artery diameters of women with POI were comparable with those of the control group after HT
- HT has been shown to:
  - Improve endothelial dysfunction
  - Reduce intima media thickness
  - Reduce blood pressure, plasma angiotensin, & creatinine

HT vs OCP

Why should I prescribe HT instead of OCP for women with POI?

Answer:
OCP provides higher steroid hormone than is necessary for physiologic replacement; thus, it is not recommended as first-line management.

CONTRACEPTIVE OPTIONS

Answer:
She has several options. She can opt to use BCP, Nuvaring, Xulane, Nexplanon, Mirena, or Paragard. If she chooses Nexplanon or Mirena, she needs to continue taking her daily estrogen. If she chooses Paragard, she should continue taking her HT.

What if the patient wants effective contraception?
CONTRACEPTIVE OPTIONS

You did not mention Depo-Provera. Is this an option?

Answer: Women with POI are already at risk of osteopenia. It’s best not to use Depo-Provera if there are other contraceptive alternatives.

CONTRACEPTIVE OPTIONS

I have POI. Can I still have a baby?

Answer: 5%-10% may spontaneously conceive. However, you if want to actively pursue pregnancy, your best chance to conceive would be via IVF with donor egg. Another option is adoption.

HORMONE THERAPY

Answer: Physiologic estrogen & progestin replacement should be continued until patient reaches the age when menopause usually occurs (around 51 years of age).

How long should I keep my patient with POI on HT?

Answer: 5%-10% may spontaneously conceive. However, you if want to actively pursue pregnancy, your best chance to conceive would be via IVF with donor egg. Another option is adoption.
HORMONE THERAPY

Answer: There is currently NO evidence that HT increases the risk of breast cancer in women with POI who are taking HT earlier in their lives. The results from the WHI’s trials linking menopause HRT to breast cancer are not applicable to young women with POI whose exposure to physiologic estrogen has been withdrawn prematurely.

Should I be concerned about breast cancer with intake of HT?

OTHER RECOMMENDATIONS

Answer: YES.
- Calcium 1,200 mg daily
- Vit D3 1,000 units daily
- Treatment of associated conditions
- Regular physical activity
- Healthy body weight
- Emotional support

Other than HT, should I be taking anything else?

Post-Test Quiz

T: Women with primary ovarian insufficiency (POI) may intermittently produce estrogen and ovulate
T: POI occurs only in women under the age of 40
F: Women with POI do NOT need contraception because they are infertile
F: All women with diminished ovarian reserve (DOR) also have POI
T: All women with POI also have DOR
T: The cause of POI is unknown in the vast majority of cases
T: Women with POI are at risk of osteopenia and cardiovascular disease
F: The first line treatment for women with POI is combination BCP
F: Women with POI who take HRT are at risk for breast cancer
F: Women with POI and low bone density should take bisphosphonate (Fosamax) to prevent fracture
To Do Better, Be Better ......

"Perfection is not attainable, but if we chase perfection, we can catch Excellence."

— Vince Lombardi