Primary Ovarian Insufficiency (POI)

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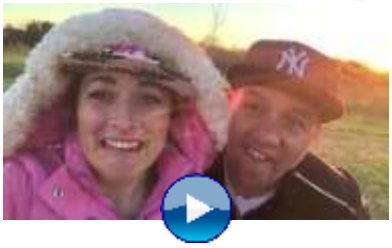
Adele – Hello Parody (Hella Cravings)



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DISCLOSURES

CONTENTS:

- Objectives
- Pre-Test
- 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

Pre-Test QUIZ

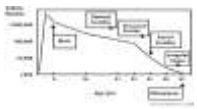
- Women with primary ovarian insufficiency (POI) may intermittently produce estrogen and ovulate
- POI occurs only in women under the age of 40
- Women with POI do NOT need contraception because they are infertile
- All women with diminished ovarian reserve (DOR) also have POI
- All women with POI also 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

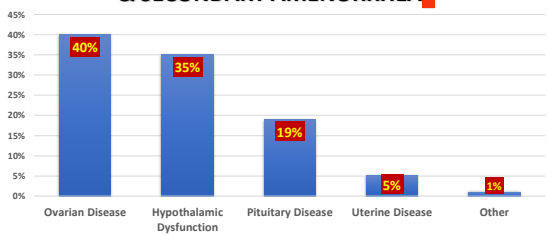
Egg Development:

- 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)



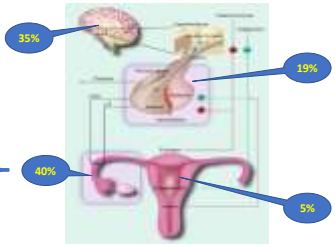
http://health.howstuffworks.com/human-reproduction4.htm

ETIOLOGIES OF OLIGOMENORRHEA & SECONDARY AMENORRHEA*



*Practice Committee of the American Society for Reproductive Medicine. (2008). Current evaluation of amenorrhea. Fertility and Sterility, 90, S219–S225.

ETIOLOGIES OF OLIGOMENORRHEA & SECONDARY AMENORRHEA



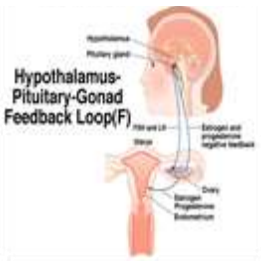
- Menopause
- PCOS
- POI

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]
  - A spectrum disorder - a continuum of impaired ovarian function
  - Previously and erroneously known as:
    - Premature menopause
    - Premature ovarian failure

[a]Nelson LM et al. *Clinical Practice. Primary ovarian insufficiency. NEJM. 2009; 360 (6): 606.*

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*

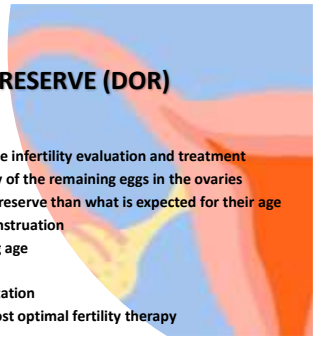
*Coulam CB, et al. Incidence of premature ovarian failure. Obstetric Gynecology. 1986; 67 (4): 604.
*Luborsky JL et al. Premature menopause in a multi-ethnic population study. Hum Reprod. 2003 Jan;18(1):199-206.
*Alzubaidi NH. Meeting the needs of young women with secondary amenorrhea and spontaneous POI. Ob Gyn. 2002; 99(5 Pt 1): 720.

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

*Nubayter ZR et al. A prospective evaluation of antral follicle function in women with 46 XX spontaneous primary ovarian insufficiency. Fertility Sterility. 2010; 94(5): 1769.
*Van Kasteren YM et al. Premature ovarian failure: systematic review on interventions to restore ovarian function and achieve pregnancy. Hum Reprod Update. 1999; 5(5): 483.

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

Clinical State	Serum FSH	AMH	Fertility	Menses
Normal	Normal	Normal	Normal	Regular
PCOS	Normal	Normal to High	Reduced	Irregular
DOR	Normal	Low	Reduced	Regular
POI	Elevated	Low	Reduced to Absent	Irreg or absent
Menopause	Elevated	Low	Absent	Absent

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*

	Etiology	Frequency (%)
	Idiopathic	329 (88.2%)
Chromosomal Abnormalities (9%)	X-Chromosome Abnormalities	25 (6.7%)
	• Turner Syndrome	6 (1.6%)
	• FMR-1 Premutation Carrier (Xq27.3)	8 (2.1%)
	• Bone morphogenetic protein	3 (0.8%)
	• Other X chromosome abnormalities (deletions, translocations)	8 (2.1%)
	46XY Gonadal Dysgenesis	2 (0.5%)
	Autosomal Causes	6 (1.6%)
	• FSH receptor / Estrogen receptor beta gene mutation	3 (0.8%)
	• Blepharophimosis ptosis epicanthus inversus syndrome (BPES)	3 (0.8%)
	Iatrogenic Causes	8 (2.1%)
	• Chemotherapy / Radiotherapy / Surgery / Infection / Toxin	
	Autoimmune Causes	3 (0.8%)

*D. Goswami and G. S. Conway. Premature ovarian failure. Human Reproduction Update, vol. 11, no. 4, pp. 391–410, 2005.

SMOKING

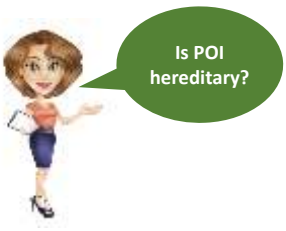
Answer:
Yes. Cigarette smoking has been shown to increase the risk of DOR and POI[*].

[*] *Chang SH et al. Premopausal factors influencing premature ovarian failure and early menopause. Maturitas. 2007;58(1):19–30*

POI PREVENTION

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

HEREDITARY



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

[*] *Dvan Kastere YM, et al. Familial idiopathic premature ovarian failure. Human Reproduction. 1999; 14:2455-9.*

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

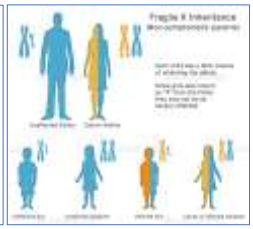
- 45 X0 or 46 XX mosaic - gonadal dysgenesis
- Amenorrhea due to accelerated apoptosis
- Clinical features:

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

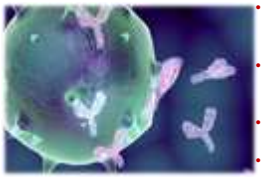
Fragile-X (FMR-1) Premutation Carrier

- 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 FMR-1 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



*Hagerman RJ et al. The fragile X permutation: into the phenotypic fold. Curr Opin Genet Dev. 2002;12(3):278–283.
*Sherman SL. Premature ovarian failure in the fragile X syndrome. Am J Med Genet. 2009;97(3):189.

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 Para-thyroid Antibody or Anti-Calcium Sensing Receptor Antibody test available in HC)**

*Bakalov VK et al. Adrenal abs detect asymptomatic auto-immune adrenal insufficiency in young women with POI. Human Reproduction. 2002; 17(8): 2096.

Management of Idiopathic POI

- **IMPORTANCE OF EARLY DIAGNOSIS**
  - **Avoidance of diagnosis delay (5 yr delay in 25% of women*)**
  - **Rule out other causes:**
    - ✓ **Pregnancy**
    - ✓ **Hyperprolactinemia**
    - ✓ **Hypo or hyperthyroidism**
    - ✓ **PCOS**
    - ✓ **Adrenal insufficiency**
    - ✓ **Parathyroid hormone insufficiency**
    - ✓ **Chromosomal abnormalities**
  - **Osteoporosis Prevention**
  - **Cardiovascular Prevention**

*Alzubaidi NH. Meeting the needs of young women with secondary amenorrhea and spontaneous POI. Ob Gyn. 2002; 99(5 Pt 1): 720.

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*

*Popat VB et al. Bone mineral density in estrogen deficient young women. J Clin Endoc Metab. 2009; 94(7):2277.
*Ryan J et al. Impact of a premature menopause on cognitive fxn in later life. BJOG. 2014; 121(13): 1729.
*Davis M et al. The psychosocial transition associated with spontaneous 46 XX POI. Fertility Sterility. 2010;93(7): 2321.

Management of Idiopathic POI

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

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

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)
- Prometrium 100 mg daily (oral)

OR

Sequential Progestogen
- Provera 10 mg daily for 12 days
- Prometrium 200 mg daily for 12 days

*Alzubaidi NH. Meeting the needs of young women with secondary amenorrhea and spontaneous POI. Ob Gyn. 2002; 99(5 Pt 1): 720.

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

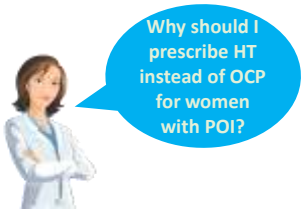
*ACOG Committee Opinion. Hormone Therapy in Primary Ovarian Insufficiency. Number 698, May 2017

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

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

HT vs OCP



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.

CONTRACEPTIVE OPTIONS

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

HORMONE THERAPY

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

CONTRACEPTIVE OPTIONS

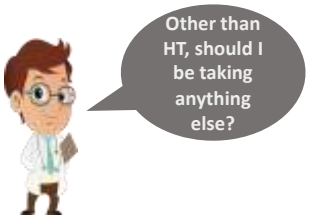
Answer:
5%-10% may spontaneously conceive. However, you if want to actively pursue pregnancy, your best chance to conceive would be via IVF with donor egg. Another option is adoption.

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.

Webber L et al. *HRT for women with premature ovarian insufficiency: a comprehensive review. Human Reproduction. Vol. 2017; Issue 2; 7-2017.*

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**

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

German Coastguard Sinking

DISCUSSION?

QUESTIONS?

To Do Better, Be Better ……

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

— Vince Lombardi