Learning Objectives

- Discuss the steps in the evaluation and management of amenorrhea and oligomenorrhea
- Describe the consequences of untreated amenorrhea and oligomenorrhea
- Prerequisites:
  - NONE
- See also – for closely related topics
  - FLAME LECTURE 208: Diagnosis of PCOS
  - FLAME LECTURE 207: Oligomenorrhea
  - FLAME LECTURE 210: Presentation of Androgen Excess
  - FLAME LECTURE 211: Treatment of Androgen Excess
CLINICAL FEATURES
COMPLEX INTERRELATION OF PATHOPHYSIOLOGY & CLINICAL SIGNS

HYPER-ANDROGENISM & HIRSUTISM

POLYCYSTIC OVARIIES

INSULIN-RESISTANCE

OLIGO-OVULATION

Treatment is aimed at:
-- bothersome symptoms
-- reducing risks of associated health consequences
PCOS COMPLICATIONS

While PCOS can effect fertility, there are also a number of pregnancy-related complications:

- 20-40% higher SAB rate above baseline\(^2\)
- Increased risk of gestational DM (OR 3.4)\(^3\)
- Increased risk of gestational HTN (OR 3.4)\(^3\)
- Increased risk of pre-eclampsia (OR 2.2)\(^3\)
- Increased risk of preterm birth (OR 1.9)\(^3\)
- Increased risk of NICU admission (OR 2.3)\(^3\)
PCOS COMPLICATIONS

- Hyperandrogenemia (70-80% of pts)
- Menstrual abnormalities (75-85% of pts)
- Insulin resistance (40% of pts)
- Type II DM (4-10% of pts)
- Obesity (50% of pts)
- Dyslipidemia (70% of pts)
- Metabolic syndrome (35-50% of pts)
- HTN & Cardiovascular disease
- Endometrial hyperplasia/cancer
GENERAL GOALS

- Amelioration of hyperandrogenic symptoms or abnormal uterine bleeding
- Help treat obesity and metabolic complications that lead to DM and heart disease
- Normalize menses to help manage contraception, ovulation, or abnormal uterine bleeding
- Prevent endometrial hyperplasia and cancer
PATHOPHYSIOLOGY REMINDER

THE SIMPLE VERSION

Image adapted from upToDate.com
TREATMENT STRATEGIES FOR VIRILIZATION & HIRSUTISM

HYPERANDROGENISM (70-80% of pts)
- ↑ Total Testosterone
- Frontal balding
- Acne & Seborrhea
- Deepening of voice
- ↑ muscle mass
- Clitoromegaly

HIRSUITISM (5-15%)
- Male pattern hair growth

OVARIAN SUPPRESSION
- OCPs
- GnRH agonists (Lupron)

ANDROGEN ANTAGONISTS
- Spironolactone
- Flutamide
- Finasteride

COSMETIC
- Shaving, bleaching
- Laser, Electrocautery
- Eflornithine (topical)
SO HOW DO OCPs WORK?

- FIRST LINE TREATMENT
- OCPs decrease LH $\rightarrow$ decrease Testosterone production $\rightarrow$ decrease free Testosterone levels available to have an affect
- OCPs also increase sex-hormone binding globulin (SHBG) $\rightarrow$ increase testosterone-binding capacity $\rightarrow$ decrease free Testosterone levels available to have an affect
HOW DO ANDROGEN ANTAGONISTS WORK?

- Antiandrogens should only be considered after >6 months of OCPs + cosmetic therapy have failed to improve symptoms
  - Must be taken with contraception given teratogenicity risks (male under-virilisation)

- Spirinolactone:
  - Inhibits the action of Dihydrotestosterone (DHT) by occupying the androgen receptor in the hair follicle
    - DHT is a more potent form of free Testosterone
  - Directly inhibits 5-alpha-reductase activity (aka blocks conversion of T to DHT)
  - Inhibits ovarian and adrenal production of androgens by inhibiting cytochrome p450c17
HOW DO ANDROGEN ANTAGONISTS WORK?

► Finasterine:
  ► Selective 5-alpha-reductase inhibitor (blocks conversion of T to DHT)

► Flutamide:
  ► Potent non-steroidal selective androgen receptor antagonist
TREATMENT STRATEGIES FOR GLUCOSE INTOLERANCE & OBESITY

**WEIGHT LOSS**
- Women who lose even 5-10% of their total body weight through diet and exercise can reduce central fat up to 40%, improve insulin sensitivity, and restore ovulation.

**METFORMIN:** a Biguanide insulin-sensitizer
- Should be added to regimen when OCPs and lifestyle changes don’t achieve desired goals (OR in all PCOS pts with BMI $\geq 25$).
- Reduces hepatic glucose production and intestinal absorption, and increases peripheral glucose uptake.
  - Increases SHBG which will binds free T.
- Side effects: GI (nausea/vomiting/diarrhea), LACTIC ACIDOSIS (RARE).
- Contraindications: use with caution in pts that have liver or renal disease and avoid in patients receiving IV contrast for imaging.
- Dosing: 500mg QD; can titrate up to 1000mg BID.
TREATMENT STRATEGIES FOR OLIGO-OVULATION

CYCLE REGULATION & ABNORMAL UTERINE BLEEDING

- Anovulatory cycles can lead to endometrial hyperplasia and even carry a risk for endometrial cancer
  - Thus with abnormal uterine bleeding, first consider an endometrial biopsy
- Cyclic progesterone, OCPs, GnRH agonists, and Metformin all may contribute to helping regulate the menstrual cycle in PCOS patients
## TREATMENT OF INFERTILITY

- **Diet & Exercise**
  - **BMI < 30**
    - Aromatase Inhibitor (Letrozole)
  - **BMI ≥ 30**
    - Anti-estrogens (Clomid) +/- Metformin
    - Gonadotropins (rFSH)
      - rFSH + IUI or IVF

- Laparoscopic ovarian drilling (diathermy) can also be 2nd line therapy in PCOS pts who are clomiphene citrate resistant w/ anovulatory infertility and no other infertility risk factors
TREATMENT OF INFERTILITY

Before starting any of the following methods, one can consider “re-setting” the cycle.

Many of these patients haven’t had menses for 1-6 months, and who knows when they will ovulate next???

The most common way to cause a withdrawal bleed is to give a 10-day course of progesterone.
TREATMENT OF INFERTILITY

- **Letrozole**
  - Aromatase inhibitor (blocks conversion of androgens to estrogens)
  - **Side effects:** hot flushes, mood swings, bloating, headaches, nausea, fatigue, dizziness

- Legro et al, NEJM, 2014: randomized PCOS pts to Letrozole vs. Clomiphene for 5 treatment cycles
  - **Live-birth rate:** Letrozole (27.5%), Clomiphene (19.1%)
  - **Congenital anomaly rate:** Letrozole (3.9%), Clomiphene (1.5%)
  - Bone and cardiac anomalies also reported in Biljan et al 2005, thus despite numerous studies failing to substantiate findings, a black box warning has been given and it is not commonly used in some places
Clomiphene citrate

- Selective estrogen receptor modulator (SERM) which competitively binds to ER in the hypothalamus → blocks negative feedback of E2 → increased GnRH → increased FSH → increased follicular development
- 80-90% of women will ovulate, 20-25% chance of pregnancy per cycle, 5-10% risk of multiple pregnancy
- Side effects: hot flushes, mood swings, breast tenderness, bloating, headaches, visual changes (will stop treatment for this given concern for permanent changes), ovarian hyper-stimulation syndrome (see next slide)
- Preferable choice in patients with BMI <30

Legro et al, NEJM, 2007: randomized PCOS pts to Metformin alone vs. Clomiphene alone vs. Clomiphene + Metformin for six months
- Live-birth rate: Metformin (7.2%), Clomiphene (22.5%), Both (26.8%, but not sig)
What is Ovarian Hyperstimulation Syndrome (OHSS)?

- A transient, but potentially dangerous, exaggerated response to ovulation induction resulting in an increase in capillary permeability. This third spacing is thought to be caused by:
  - Increased secretion of protein-rich fluid from enlarged ovaries
  - Increased follicular fluid levels of pre-renin and renin
  - Angiotensin-mediated changes in capillary permeability
- **Mild symptoms**: abdominal pain and distention, nausea, vomiting, diarrhea
- **Severe symptoms**: rapid weight gain, tense ascites, hemodynamic instability, respiratory difficulty, oliguria
- **Treatment**: expectant management, fluid restriction, electrolyte correction, consideration of diuretics, IV albumin, paracentesis
Recombinant FSH
- It is reasonable to attempt ~3-5 cycles with metformin, clomiphene, or letrozole, however if these fail to result in a pregnancy, one can consider using recombinant gonadotropins to guide follicle growth followed by an exogenous HCG trigger

Risks:
- Symptoms: headache, N/V, bloating, mood changes
- Ovarian Hyperstimulation Syndrome
- Cycle cancellation from too few or too many follicles (i.e. >2)
  - There is up to a 25% of multiple birth using gonadotropins

Laparoscopic Ovarian Drilling
- There is insufficient evidence to show that drilling w/ laser or diathermy is better than gonadotropins as 2nd line therapy
IMPORTANT REFERENCES / LINKS

- PRACTICE BULLITEN 108 – PCOS
- Uptodate: Clinical manifestations of polycystic ovary syndrome in adults
- Uptodate: Treatment of polycystic ovary syndrome in adults

1. Teede et al, Hum Reprod 2018
4. ASRM Practice Committee Bulletin, 2008