

Skin, Bones, Hearts & Private Parts, 2020

**PCOS:
The Tip of the
Endocrine Iceberg**

Barb Dehn NP FAANP, NCMP

NurseBarb.com

@NurseBarbDehn

Disclosures

- Vendor: Cord Blood Registry
- Speaker's Bureau / Advisory Board: AMAG, TherapeuticsMD, Hologic, El Camino Hospital

Objectives

- Describe the evaluation of women with PCOS.
- Describe the androgen excess and insulin resistance common in PCOS.
- Specify pharmacologic treatment options for the manifestations of PCOS.
- Discuss serious risks and fertility concerns associated with PCOS, prevention and pharmacologic treatment strategies.

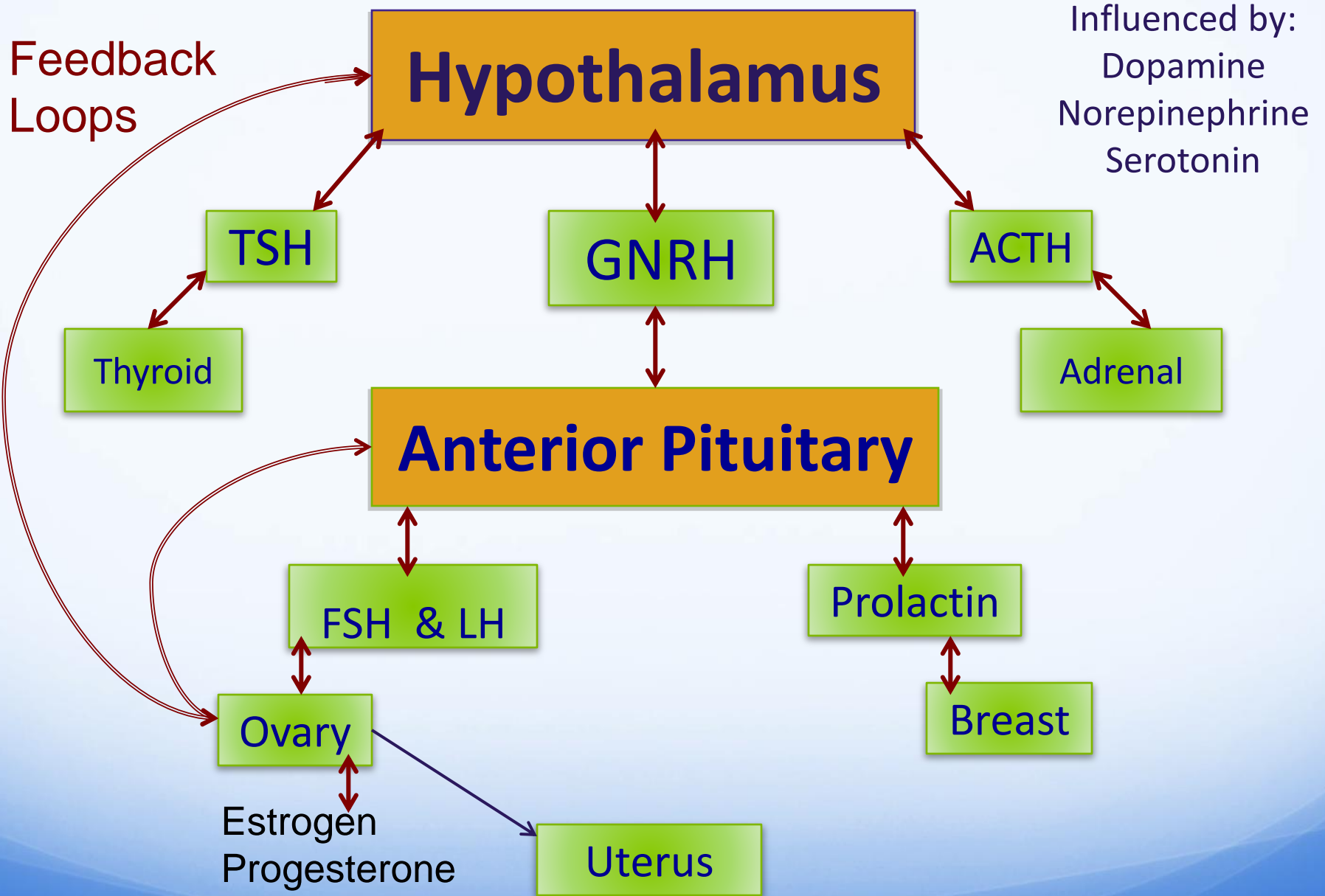
What You See is Just the



Review of Menstrual Cycle

- Hypothalamus/Pituitary
- Ovary
- Uterus & Endometrium

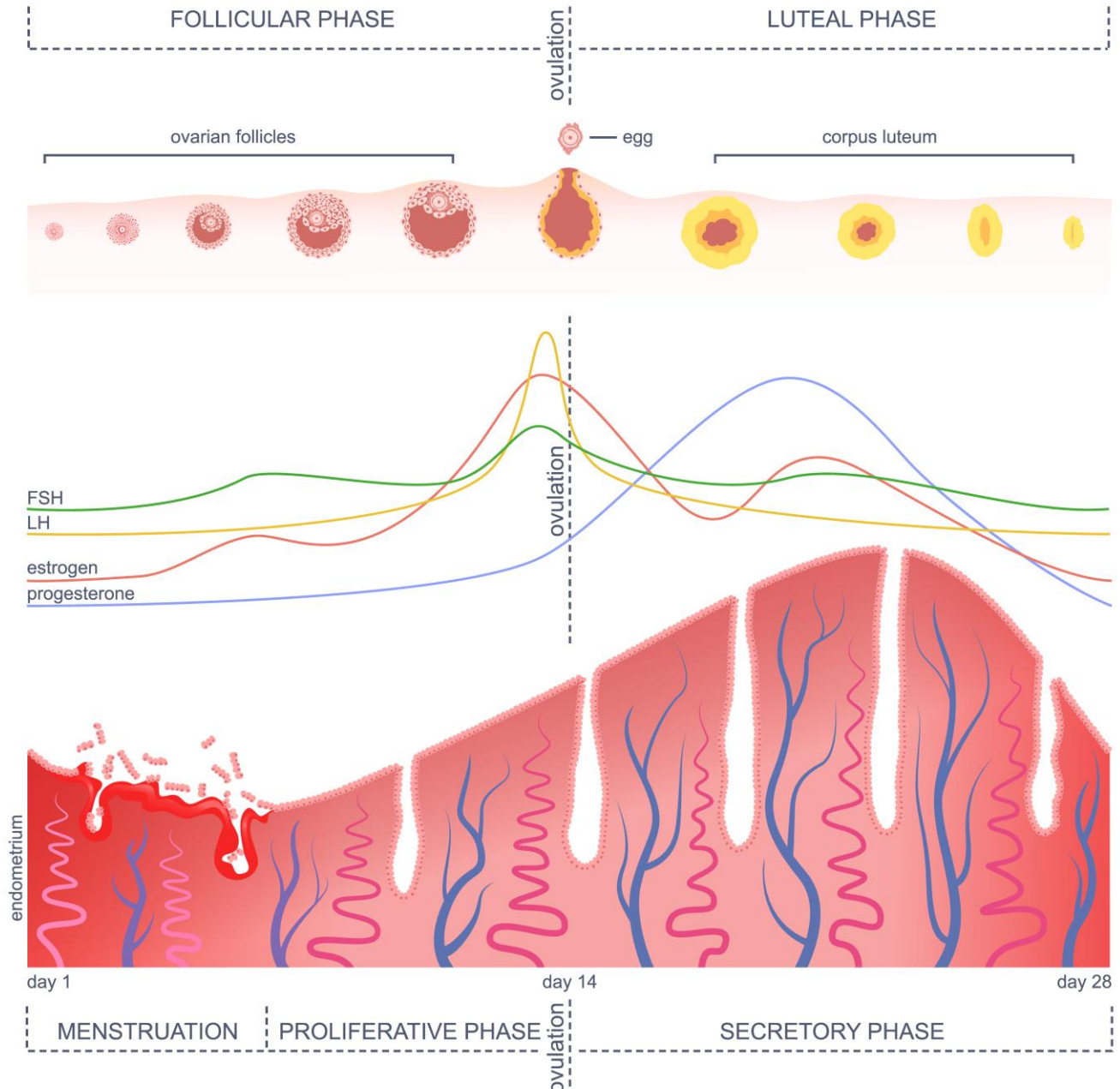
- Follicular Phase
- Ovulation
- Luteal Phase
- Menses



The Menstrual Cycle

- **3 feedback loops & 4 Stages**
- **Long** - target gland hormones
 - Estrogen, Progesterone
- **Short** - pituitary hormones on hypothalamus
- **Ultrashort** - inhibition of releasing hormone on itself
- **4 stages:** Proliferation, Ovulation, Luteal, Menstrual

MENSTRUAL CYCLE



The Ovarian Cycle

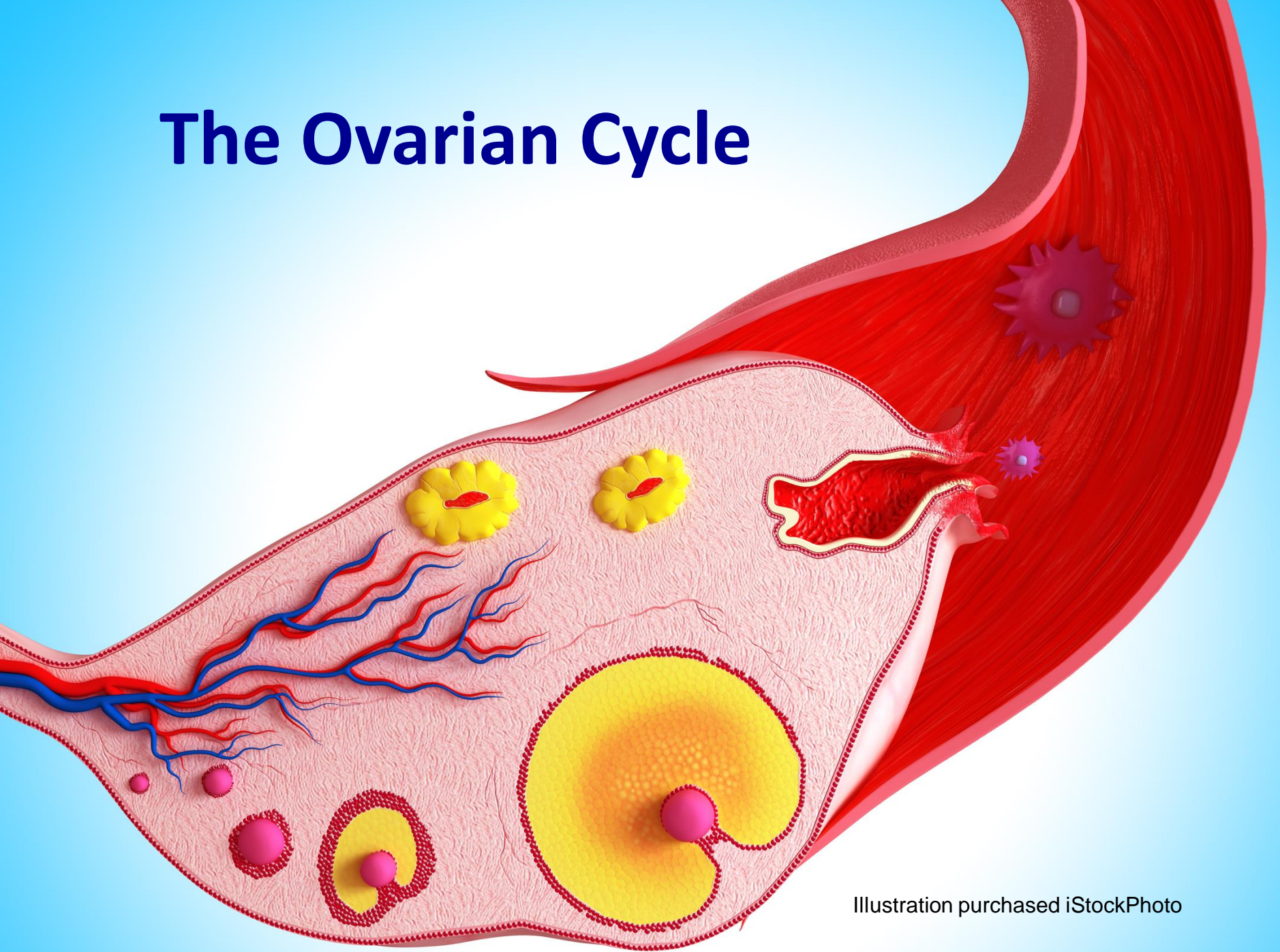


Illustration purchased iStockPhoto

Follicle growth depends on:

- Granulosa Cells responding to ↓ LH and ↑ FSH
- Conversion of androgens - estrogens
- One follicle becomes dominant, producing the greatest amt of E_2
- This higher level E_2 feeds back to the pituitary to ↓ FSH.

Dominant Follicle

- Identified by cycle day 5
- It survives and grows faster because of:
 - Greater numbers of FSH receptors
 - Increased Estrogen production in the granulosa cells
- Estrogen must rise, only then can LH surge

Ovulation

- Occurs 24 - 36 hrs after peak Estradiol levels attained - leads to LH surge
- Occurs 10 -12 hours after LH peak
- LH *must* be maintained for at least 14 hours for the full maturation of the follicle to occur

Luteal Phase

- Granulosa cells increase in size, accumulate a yellow pigment (lutein)
- Produces Progesterone which in turn inhibits FSH and new follicular growth
- Progesterone further acts on the endometrium making it thicker and more glandular

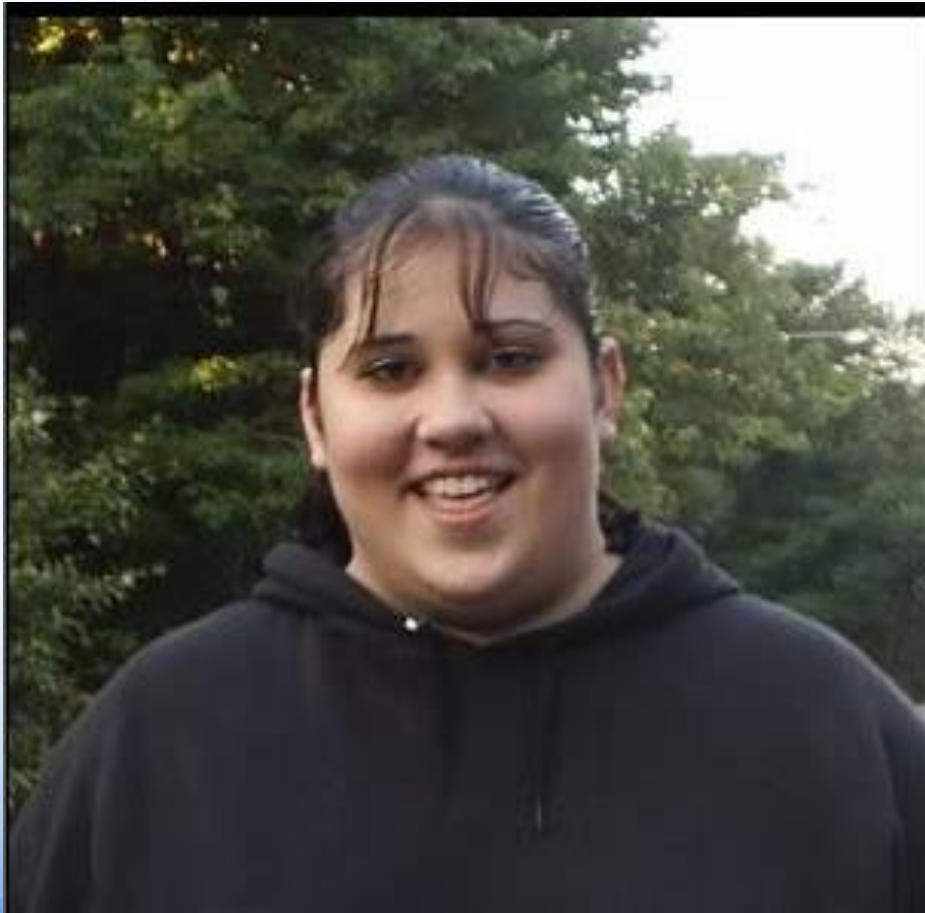
Normal Cycling

- Normal Interval: 21-35 days
- 15% of women have 28 day cycles
- Duration of flow 2 to 8 days, average is 4-6
- Normal volume is 30 ml
- Range: 20 - 80 ml

With PCOS

It's All Different

I have PCOS



PCOS can look like this



This is what PCOS can look like



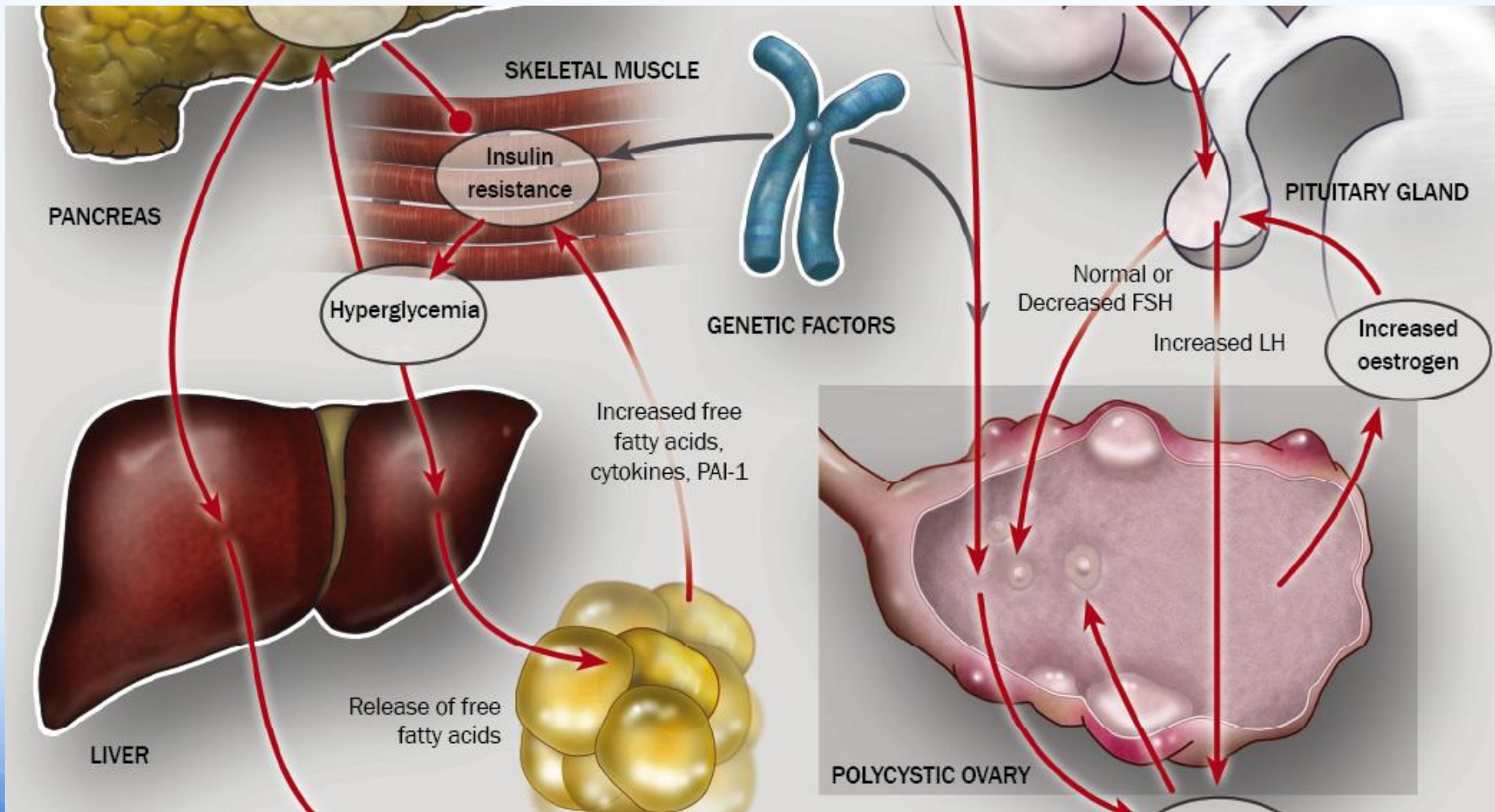
Common Endocrine Disorder

- 4- 12% of reproductive age women in US
- 4 - 9% in European women
- Ethnic variations in presentation
- Recognition by clinicians may be delayed by
 - Lack of concern by pts for menstrual irregularity
 - Use of Oral Contraceptives: mask symptoms
 - Leaner women may not exhibit signs until they begin to gain weight

Clinical features of PCOS

- Hirsutism 60-90%
- Oligomen 50-90%
- Infertility 55-75%
- Cysts U/S 50-75%
- Obesity 40-60%
- Amenorrhea 26-51%
- Acne 24-27%
- DUB 29%
- Normal cycle 22%
- Alopecia 20-25%

PCOS



Etiology: Overview

- Multiple & complex issues all interacting
- Ovarian dysfunction - Anovulation
 - Too much androgen production
 - Ovaries don't aromatize androgens to estrogen
 - Apoptosis dysfunction – GH and ILGF-1
- Obesity & Insulin Resistance
- Excess androgens produced outside the ovary

With PCOS

- Mild hyperestrogenic state in periphery, *not in the ovary* leads to:
 - Low FSH, constant high LH
 - No LH spike, no Estrogen spike
 - No ovulation = No luteal phase
 - Low Progesterone

High LH leads to:

- Stimulation of ovarian theca cells:
- Increases production of androgens:
testosterone androstenedione
- Low FSH relative to LH - ovarian granulosa cells *cannot* aromatize the androgens to estrogens

PCOS = Anovulation

- No peak estrogen = no dominant follicle = anovulation.
- The follicles do not ovulate, become atretic, and thus the evidence of multiple small follicles emerges on U/S



Mild Hyperestrogenism

- Bones protected
- Constant proliferative stimulation to endometrium
 - Breakthrough bleeding to AUB
 - Endometrial hyperplasia
 - **At risk for endometrial carcinoma**
- *Clinical pearl: Should have withdrawal bleed with progesterone*

Androgens increased

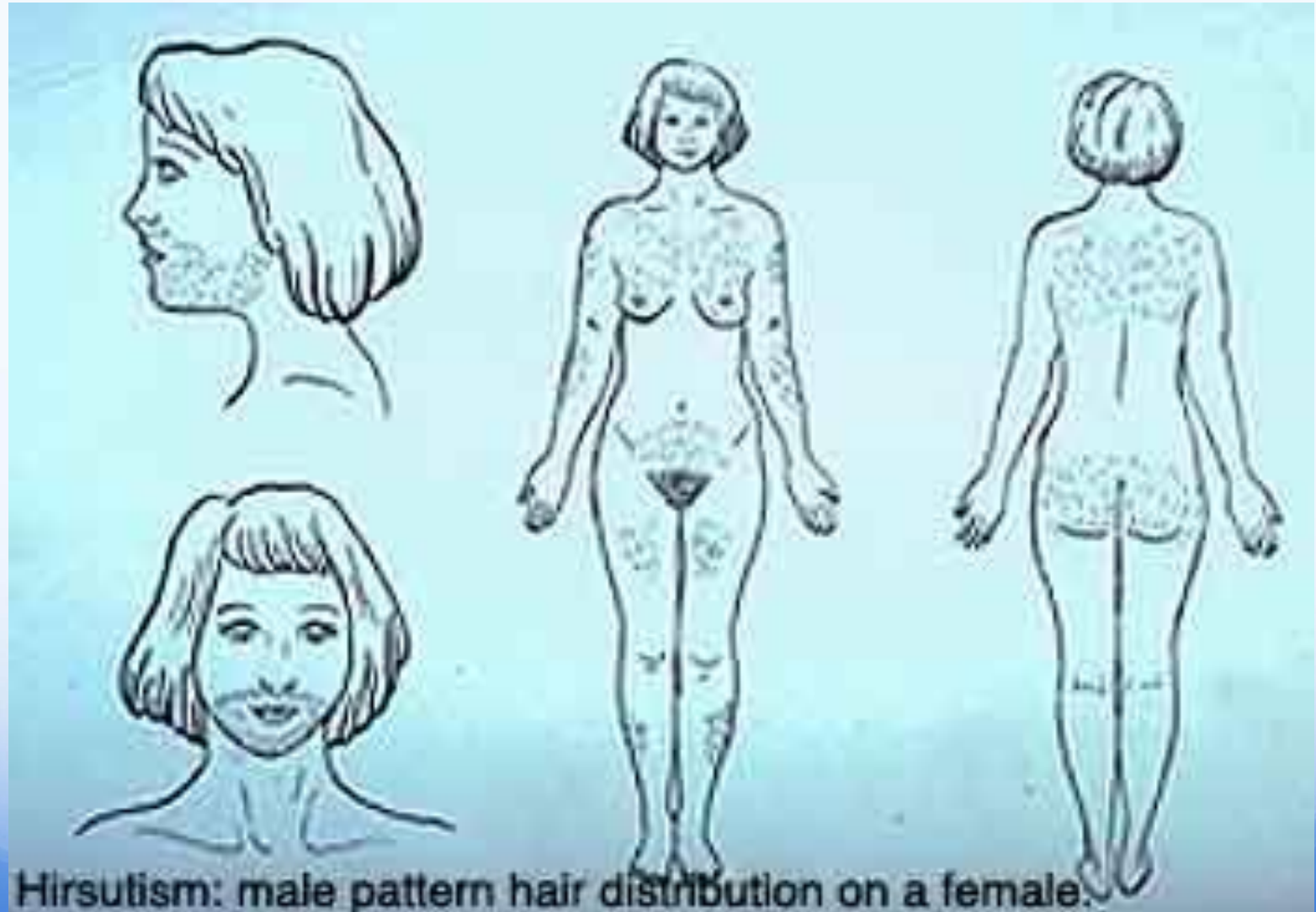
- Increased Testosterone (T) leads to:
- Lower SHBG → more ↑'d free T
- Ovary = T ↓s aromatase activity
- Adrenal gland ↑s androgens (40 to 70%)
- And even more ↑'d peripheral conversion of androgen precursors
- Pituitary responds with ↑'d LH

Ultrasound of PCOS Ovaries

- Surface area may be doubled
- Volume may be increased 3 fold
- Thickened tunica (capsule)
- Presence of “string of pearls”



Hirsutism



Hirsutism: male pattern hair distribution on a female.

Acanthosis Nigricans



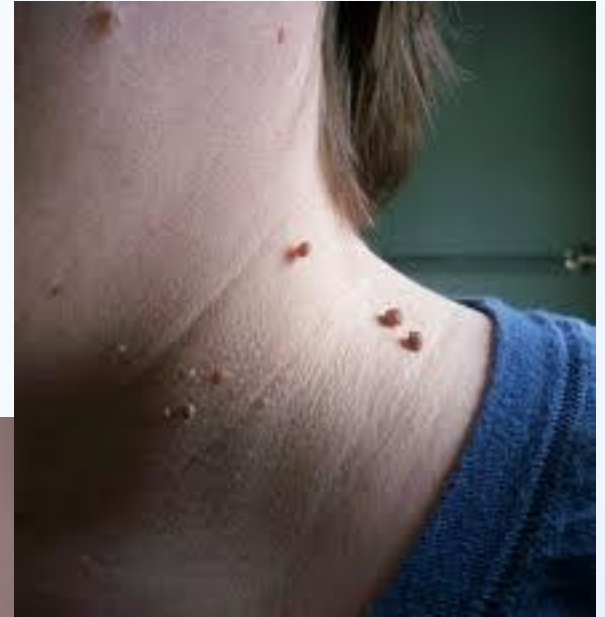
Acanthosis

- Pathogenesis poorly understood
- Likely related to an interplay of
 - Increased circulating insulin
 - Activation of Insulin Like Growth Factor (ILGF) receptors on keratinocytes
 - At high concentrations insulin may also displace IGF-1 from IGF Binding Protein (IGFBP)
 - Increased circulating IGF may lead to keratinocyte and dermal fibroblast proliferation

Androgenic Alopecia



Acne & Skin Tags



Diagnosis: AE Society

1. Hyperandrogenism:

- Hirsutism and/or hyperandrogenemia

+

2. Ovarian Dysfunction: Oligo-anovulation and/or Polycystic ovaries on Ultrasound

+

3. Exclusion of other androgen excess

- Non-classic Congenital Adrenal Hyperplasia (CAH)
- Androgen secreting tumors
- Cushing's syndrome

Diagnosis of Exclusion

Rapid Virilization - NOT PCOS

- Increased muscle mass
- Deepening of voice
- Clitormegaly
- Rapid progression of hirsutism
- Loss of female body contour
- Must be investigated to rule out ovarian tumor producing Testosterone

Exclude other causes of Excessive Androgens

Condition

Lab findings

Hyperprolactinemia

↑ Prolactin

Adrenal tumors

↑ DHEA/DHEAS

Ovarian tumors

↑ Testosterone

Non-classic CAH

↑ 17 - OHP

Cushings

Abnormal dexamethasone
suppression test

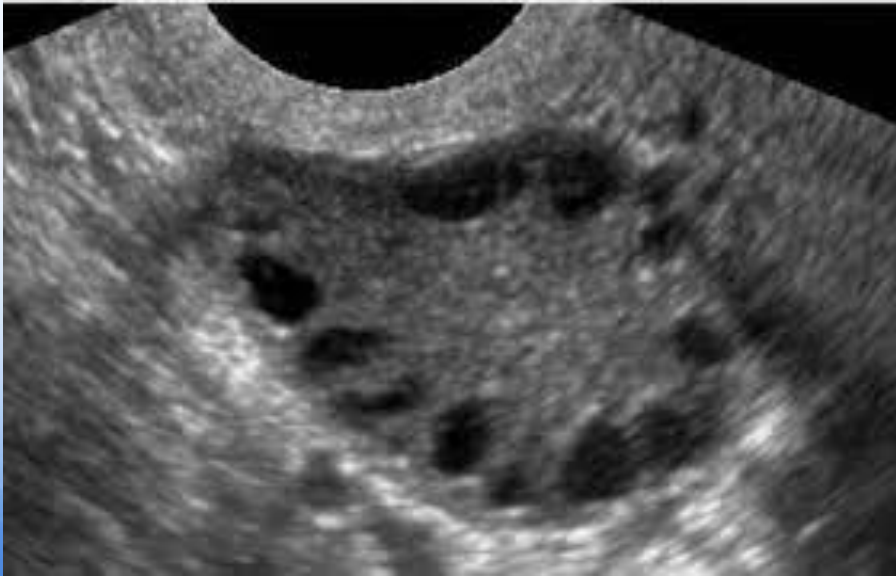
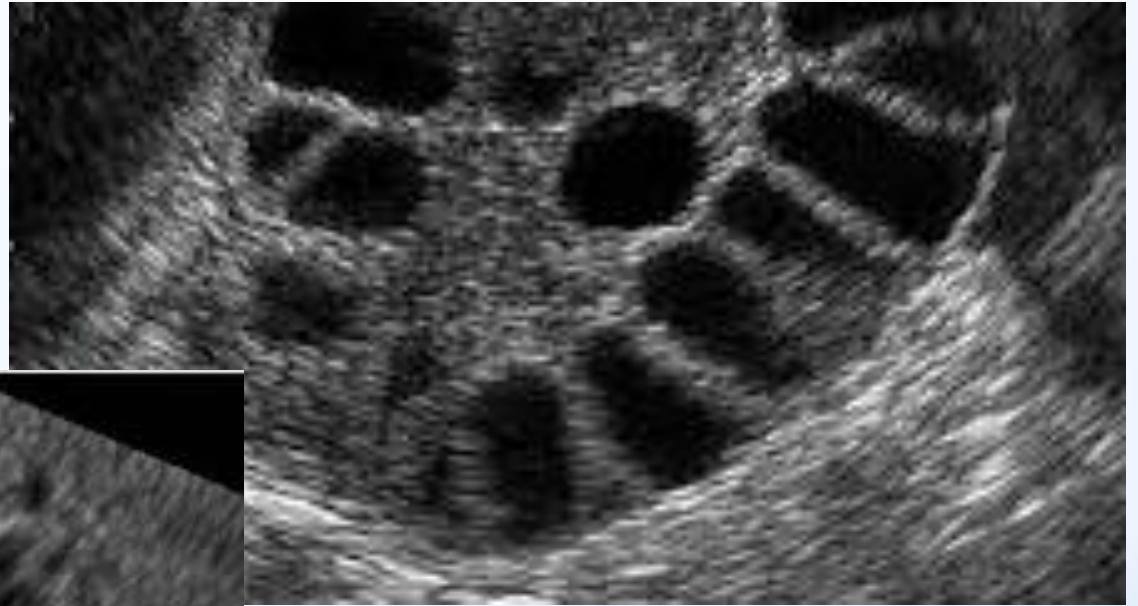
Androgen workup

- Testosterone
 - Total < 0.90 ng/mL
 - Free < 2.2 pg/mL
- DHEAS - < 430 ug/dL
- 17 - OHP - < 1.7 ng/mL
 - get early (< 8 am) draw during follicular phase

Ultrasound evaluation

- Ultrasound days 3 - 5
- Presence of 12 or > follicles in each ovary
- Follicles should be 2 - 9 mm in diameter
- Only one ovary with this description is sufficient for Dx

PCOS Ultrasound Images



Your Work UP

- HgB A1 C
- Comprehensive Metabolic panel
 - Creatinine needs to be in the normal range to initiate Metformin
 - Fasting glucose
- Lipid profile
 - Triglycerides are a surrogate marker for IR

Work up Endometrial suspicions

- Endometrial biopsy: based on
 - Patient's age
 - Length of time with Abnormal bleeding
- Women with AUB (> 1 year)
- > 35 with AUB > 6 months
- Consider for any women with an endometrial stripe that is > 12 - 13 mm

Work up starts therapeutic process

- Validate woman's concerns
- Opportunity for education on what and why
- Need for recurrent education on IR, Lipids, endometrial protection, fertility concerns
- Once manifestations start to resolve, many women feel better psychologically

Treatments for PCOS

Protect endometrium

- Combined OC' s, Ring or Patch
 - Look for low androgenic progestins
- Progestins for 10 days each month
- Medroxyprogesterone Acetate (Provera[®]) 10 mg or Micronized Progesterone (Prometrium[®]) 100 - 200 mg at hs
- Progestin containing Intra Uterine System
- Ablation for women past childbearing

Progestins

- Pregnancy test negative? Then, induce withdrawal bleed with 10 days progesterone
 - 10 mg Medroxyprogesterone Acetate (Provera[®])
 - 100 mg Micronized Progesterone (Prometrium[®])
- Then use the *least* androgenic progestin in OCs
 - Norgestimate
 - Norethindrone
 - Desogestrel
 - Drospirenone
- *Avoid* levonorgestrel and norgestrel

COCs First Line Treatment

- Combined oral contraceptives – Estrogen + Progestin
- Increases Sex Hormone Binding Globulin (SHBG)
 - Binds to all androgens
 - Reduces free Testosterone
 - Slows hair growth in 60-100% of women with hyperandrogenism
 - Reduces Acne

Why COCs? Here's more

- Suppresses LH = Fewer circulating androgens
- By providing a balance of progestogen to E₂
- Mimics a proliferative and secretory cycle
- Reduces proliferation from unopposed estrogen
- Cycling the endometrium = less risk Endometrial CA

COCs Contraindications

- Migraine with Aura
- Smokers over 35
- HTN
- Hx of clots
- Use with caution in women who's BMI is > 35 as they have a higher risk of clots

Oral Contraceptives

- Use Monophasic pills – avoid bi or triphasic
- Start with 30 or 35 mcg E₂
- 20 mcg may cause irregular bleeding
 - Avoid Lo LoEstrin - 10 mcg of Estradiol
- Use OCPs with fewer hormone free days
 - 24 Active with hormone and 4 hormone free
- Anticipatory guidance what to expect in the first 3 months of any new contraceptive

35 mcg Estradiol Choices

- With Norethindrone 0.40 mg
 - Briellyn, Femcon FE, Ovcon 35, Zenchant, Zeosa
- With Norethindrone 0.5 mg
 - Brevicon, NeCon, Nortrel
- Norgestimate 0.25 mg
 - Estarylla, MonoNessa, OrthoCyclen, Sprintec

30 mcg Estradiol Choices

- With Desogestrel 0.15mg
 - Desogen, Ortho-Cept
- With Drospirenone 3 mg
 - Yasmin, Safyral, Syeda, Yaela
- With Norethindrone Acetate 1.5 mg +/- FE
 - Gildess, Junel, Larin, LoEstrin, Microgestin

25 mcg Estradiol Choices

- With Norethindrone 0.40 mg
- All of these are 24 day***
- All are chewable
- Four hormone free pills have Ferrous Fumarate 75 mg
- Generess FE, Kaitlib FE, Layolis FE

20 mcg Estradiol Choices

- With Drospirenone 3 mg
 - Gianvi, Loryna, Nikki, Yaz
 - With 24 day cycle: BeYaz**
- With Desogestrel – all are biphasic – avoid if possible
- With Norethindrone Acetate 1.0 mg +/- FE
 - Gildess, Larin, LoEstrin, Microgestin, Minastrin,

NuvaRing

- Ring contains 11.7mg of Etonogestrel and 2.7 mg Ethinyl Estradiol, releases:
- 0.12 mg/day of etonogestrel
- 15 mcg of EE
- Package insert: leave in place for 3 weeks, remove for 1 week for menses

Mirena - IUD

Levonorgestrel

- office procedure
- 5 years
- Provides contraception
- May have 3-6 months of prolonged unscheduled bleeding
- 40% of women have amenorrhea
- If Mirena is used for a Polyp or Fibroid – about 30% of women go on to other procedures

Treat Hirsutism

- It takes 3 months of *any* hormonal Rx for coarse (terminal) hair change to velus hair
- Combined hormonal treatment prevents new hair growth, does not remove old hair
- After 3-6 months, consider initiating spironolactone 200 mg 1/day
- Electrolysis or laser is best, initiate after 3 months of treatment

Spironalactone

- Helps reduce hair diameter
- K⁺ sparing diuretic – check lytes, BP
- Can cause feminizing effects on a fetus
- Not first line, use with or after OCs
- Consider using as a “reducing agent” to prep for permanent hair removal

Other Meds for Hirsutism

- Finasteride – Propecia
 - 5 alpha reductase inhibitor
 - Blocks conversion of Testosterone to more active metabolite: dihydrotestosterone
 - Used for male pattern baldness and BPH
 - Teratogen

Vaniqa

- Eflornithine (Vaniqa[®])
 - Doesn't remove hair, slows the growth
 - See effects within 4 weeks
 - Hair returns 8 weeks after d/c

Minoxidil 2%

- Prolongation of growth or anagen phase and increase in follicle hair size
- 20% of women will see moderate hair growth
- More will see hair loss slow or stop
- May see more hair fall out in first 4 weeks as new hair pushes out old hair

PCOS and Type II DM

- For women 14 - 44:
 - 31 % have undiagnosed glucose intolerance
 - 7.5% have diabetes
- For women aged 40-50:
 - 15% have type 2 diabetes

Metformin

- Check Creatinine levels prior to initiation
- 500 mg BID to TID dosing
- Consider extended release: Glumetza
- Low cost and works immediately
- Combine with low carb diet, TLC, exercise

Metformin

- Reduces hepatic glucose production and intestinal absorption
- Increases peripheral glucose uptake
- Increases SHBG = decreased androgens
- Avoid with:
 - Creatinine < 1.4 , Elevated transaminase
 - Stop 1 day prior to any IV contrast dye study or surgery

Lipids

- Follow NCEP guidelines
- Weight loss will decrease Cardiovascular risk factors
- Treating IR and DM with Metformin will decrease Triglycerides and LDL
- Consider adding Omega -3 fatty acids to decrease liver fat content (not proven to affect CV events)

Infertility

- Pretreat with Metformin for 4 weeks or longer to induce weight loss
- Clomiphene is first line
- Then add metformin if necessary
- Referral to Reproductive Endocrinologist
- Clomiphene resistant? Ovarian drilling

Clomiphene Citrate: Clomid

- Structurally similar to Estradiol
- Binds to Estrogen receptors in the brain, so circulating Estrogen levels seem too low : It Blocks Estrogen receptors
- Hypothalamus responds by increasing GnRH: Pituitary responds by increasing FSH and LH
- Taken for 5 days in first few days of cycle
 - Typically days 3 - 7

Clomiphene Citrate (Clomid®)

- Starting dose 50 mg, may increase to 100 mg
- Highest pregnancy rates: 1st 3 months of use
- Do not continue past 6 months
- Likelihood of pregnancy then is remote

Clomiphene Side Effects

- Hot Flashes, Mood Swings, Emotional side effects
- Abdominal discomfort, Nausea
- Visual disturbances
- Ovarian cyst formation
- Thinning of the uterine endometrial lining
- Reduced production of cervical mucous

Aromatase Inhibitors : Ai

- Class of drug used to treat breast cancer and as chemoprevention in high risk women
- Aromatase is the enzyme that synthesizes estrogen.
- Estrogen receptor positive breast and ovarian cancers require Estrogen to grow
- Ais block the production of estrogen or block the action of estrogen on the receptors

Letrozole: Adverse Reactions

- Seen in greater than 20%:
- Hot flashes, night sweats, headache, dizziness
- Arthralgia, edema, bone pain

Letrozole in PCOS only

- Suppresses ovarian Estrogen production
- Leads to increased FSH production
- Dose: 2.5 mg/day on days 5-9
- May increase to 5 mg or 7.5 mg per day
- Often used with IUI
- **May increase risk of birth defects**

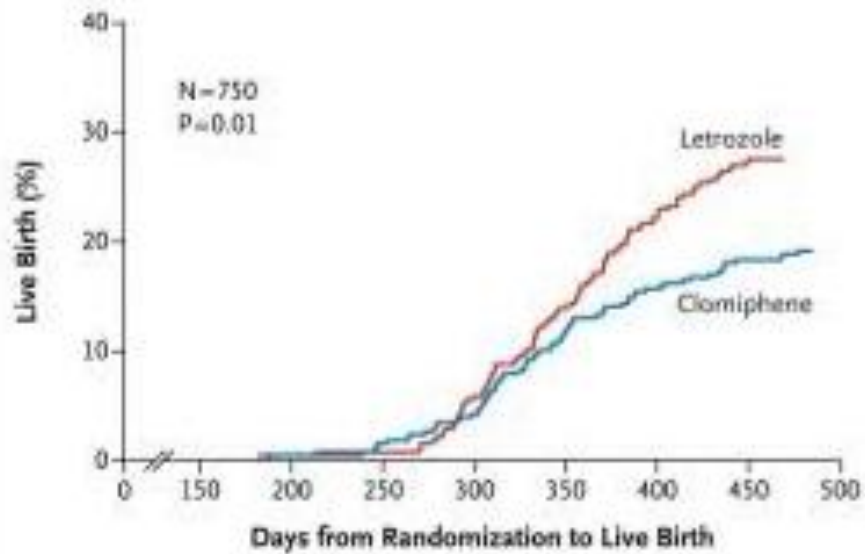
Letrozole vs Clomiphene: PCOS

- PCCOS II Study Randomized (n = 750)
- **Letrozole (L) vs Clomiphene (C)**
- Increased ovulation
 - L: 834/1352 cycles vs C: 688/1425 cycles
- Increased Live Birth Rate
 - L: 103/374 women vs C : 72/376 women

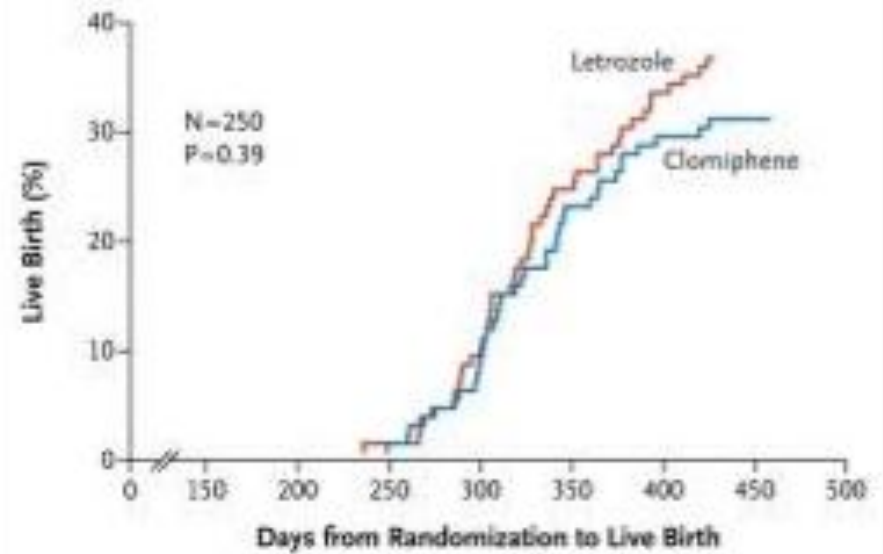
Letrozole vs Clomiphene

- No statistically significant differences in pregnancy loss L: 49/154 vs C: 30/103
- No statistically significant rates of congenital anomalies, though L group had 4 major, C had 1
- Letrozol: increased fatigue and dizziness
- Clomiphene: increased hot flushes

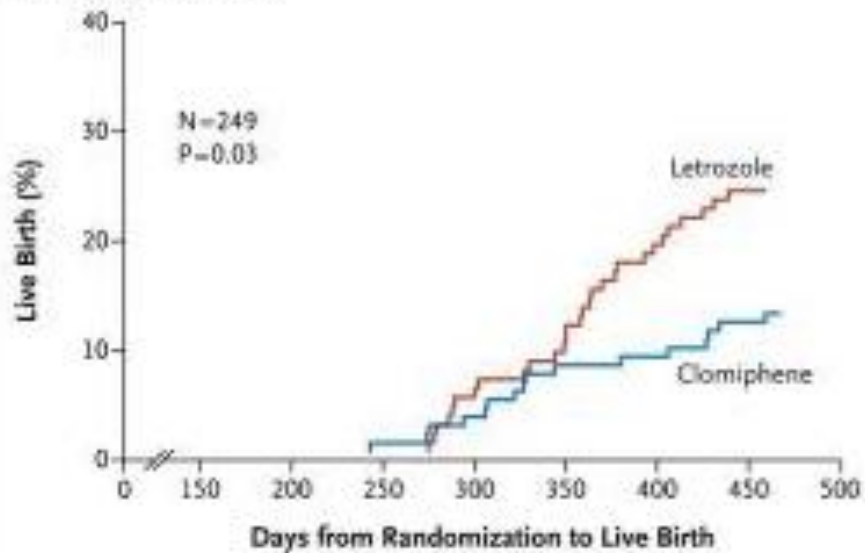
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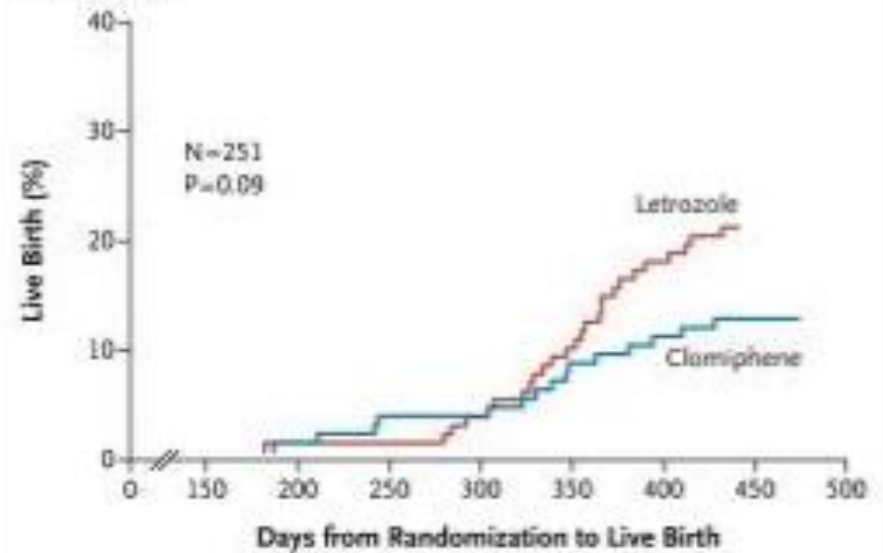
B BMI, ≤ 30.3



C BMI, >30.3 to ≤ 39.4



D BMI, >39.4



Pregnancy with Hx of PCOS

- Much higher risk for Gestational Diabetes
- Pre-eclampsia
- C-section & Increased risk for LGA
- Preterm and Post-term
- Not at increased risk for stillbirth or neonatal demise

Key Points



- PCOS is the tip of the iceberg
- Red flag for multiple underlying risks of IR, Diabetes, CVD, Infertility, Depression, Endometrial Cancer
- Physical (phenotypic) manifestations often negatively impact self-esteem
- This is NOT IN THEIR CONTROL
- We can mitigate the consequences

Implications for Practice

- Increase your “index of suspicion”
- Validate their experience
- What are their concerns and motivations
- Help them achieve their goals
- Intervene early with OCs
- Encourage wt loss with low carb diet, metformin, and regular exercise

Questions

Thank You

Barb Dehn

NP FAANP NCMF

NurseBarb.com

[@NurseBarbDehn](https://www.instagram.com/NurseBarbDehn)

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