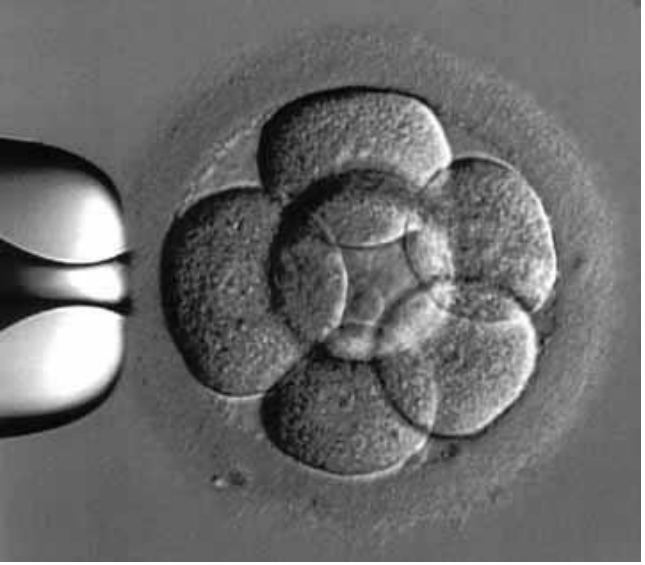

EASTERN WASHINGTON WOMEN'S HEALTH CONFERENCE OCTOBER 11, 2019

Diagnosis & Management of Ovulatory Disorders

Christopher Herndon, M.D.
Reproductive Endocrinology & Infertility

UW Medicine

DISCLOSURES

None

OBJECTIVES

At the conclusion of this presentation, attendees should be able to:

1. Describe the differential, diagnostic evaluation and clinical management of irregular cycles

2. Identify the reproductive and general health implications associated with ovulatory disorders

3. Review evidence-based strategies for optimized clinical management including treatment for fertility

INITIAL EVALUATION OF AMENORRHEA / IRREGULAR CYCLES

- Primary or secondary
- Hormonal vs. structural
- hCG, TSH, prolactin

- Both hypo- and hyperthyroidism are associated with menstrual irregularities
- Hyperprolactinemia - broad differential but most common: **medication-induced** (e.g. antipsychotic dopamine blockade agents) or a **secreting pituitary adenoma**.

EVALUATION OF ANOVULATION

World Health Organization Classification:

- **Class I** (low FSH/LH, low estradiol)
- **Class II** (~normal FSH/LH/estradiol)
- **Class III** (high FSH/LH, low estradiol)

EVALUATION OF ANOVULATION

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CLASS I
HYPOTHALAMIC-PITUITARY DISORDERS

- Congenital (Kallman's Syndrome) associated with anosmia, idiopathic IHH), acquired (tumor, infiltrative disease, iatrogenic, Sheehan's syndrome.
- Typically FSH > LH usually less than 5 mIU/mL; E2 < 50 pg/mL
- MRI of pituitary
  If acquired, must consider other HP axes (e.g. corticotrophic, thyrotropic)
- Functional hypothalamic amenorrhea / female athletic triad - 1) menstrual dysfunction, 2) negative energy balance, and 3) decreased bone-mineral density
- Screen for eating disorders
- DEXA (use Z score in younger women)
- HRT, Calcium, Vitamin D, exercise

EVALUATION OF ANOVULATION

World Health Organization Classification:

- **Class I** (low FSH/LH, low estradiol)
- **Class II** (~normal FSH/LH/estradiol)
- **Class III (high FSH/LH, low estradiol)**

CLASS III
PREMATURE OVARIAN INSUFFICIENCY

- Onset menopause before age 40
- FSH / LH / Estradiol & AMH
- Most common idiopathic
- Mosaic Turner Syndrome (check karyotype)
- Fragile X pre-mutation (6% check # CGG repeats FMR1 on X chromosome)
- Autoimmune 5-9% (anti-adrenal / anti-21 hydroxylase antibodies, TSH)

- HRT (increased cardiovascular risk, bone density depletion)
- Donor ovum recipient IVF if amenorrrheic

EVALUATION OF ANOVULATION

World Health Organization Classification:

- **Class I** (low FSH/LH, low estradiol)
- **Class II (~normal FSH/LH/estradiol)**
- **Class III** (high FSH/LH, low estradiol)

POLYCYSTIC OVARY SYNDROME

- 5-10% of adult female population
- Common syndrome with **a wide spectrum of presentations**
- Prevalence relatively stable across ethnic and racial populations; but may present differently
- Metabolic phenotype may be milder in African American women and worse in Hispanic women (Engmann et al. Am J Ob/Gyn 2017)

PCOS HAS MANY DIFFERENT PRESENTATIONS

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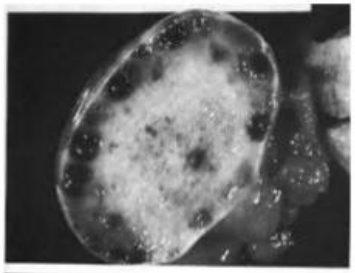
POLYCYSTIC OVARY SYNDROME

- Although PCOS is associated with hyperandrogenism and infertility early in life, it is a harbinger of a lifelong condition that can lead to serious sequelae such as **diabetes mellitus, hyperlipidemia, endometrial hyperplasia/carcinoma, central obesity, and sleep apnea**

STEIN-LEVENTHAL SYNDROME

- Case series of 7 women: “Amenorrhea associated with polycystic ovaries” in Am J Ob/Gyn 1935



Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol 1935; 29:181-191.

- Pathology: endometrial hyperplasia, multiple follicle cysts, absent corpus luteum
- Usually associated with bleeding (due to dysfunctional uterine bleeding or hyperplasia)
- Reported pregnancies after wedge resection

NIH (1990) CRITERIA

Evidence of

- Oligo and/or anovulation

AND

- Clinical and/or biochemical signs of hyperandogenism

6% of population

(Bozdag et al. 2016)

*assumes other disorders are excluded

ROTTERDAM (2003) CRITERIA

2 out of 3 of the following*:

- Oligo and/or anovulation
- Clinical and/or biochemical signs of hyperandogenism

  - Clinical (acne, hirsutism, alopecia) and/or biochemical signs (elevated total/free testosterone or DHEAS) of hyperandrogenism

- Sonographic evidence of polycystic ovaries

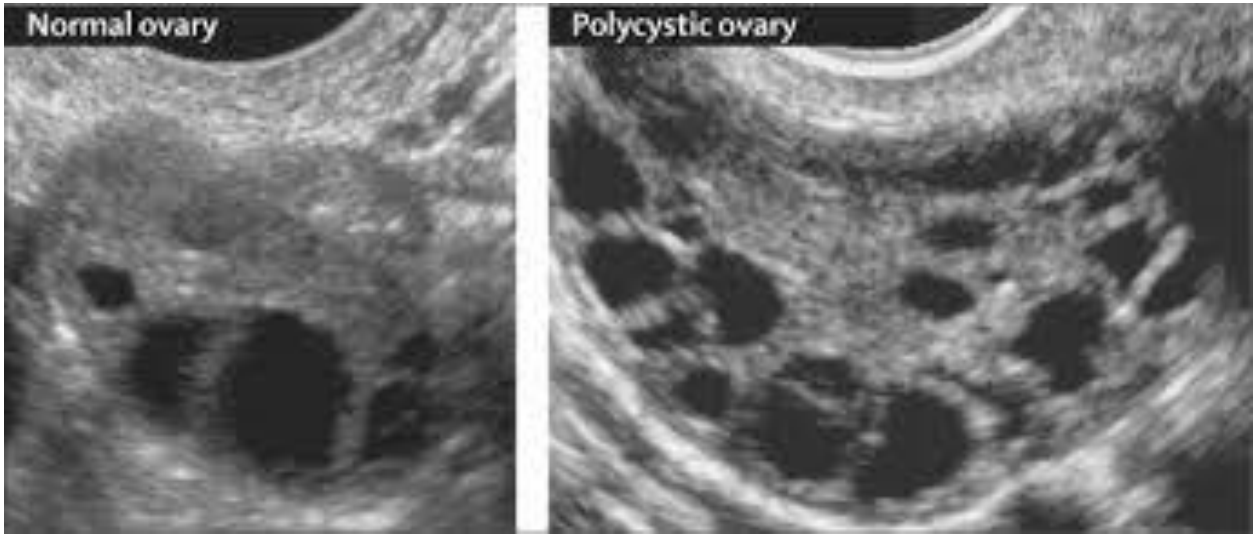
  - ≥12 follicles [2-9 mm diameter] in one ovary and/or increased ovarian volume >10 mL. Follicle distribution, increase in stromal echogenicity/volume not directly considered.

10% of population

(Bozdag et al. 2016)

*assumes other disorders are excluded

“POLYCYSTIC” OVARIES ON ULTRASOUND



Defined as ≥ 12 follicles per ovary or ovarian volume ≥ 10 ml on either ovary

Note: PCO Morphology (peripheral array) is not directly considered in diagnostic criteria. Increase in ovarian stroma only partially consider through volume

FOUR GROUPED PHENOTYPES

1. **Classic PCOS** (Hyperandrogenism/oligoamenorrhea/PCOM)

2. **Hyperandrogenic anovulation** (Hyperandrogenism/oligoamenorrhea)

3. **Ovulatory PCOS** (Hyperandrogenism/PCOM but no ovulatory dysfunction)

4. **Non-hyperandrogenic PCOS** (Oligomenorrhea/PCOM)

Christ Repro Biomed Online 2017; 35: 480-483

PHENOTYPES

- **Hyperandrogenism** correlates best with **metabolic syndrome**
- **PCOM** correlates best with **responsiveness to ovarian stimulation** but is also correlated to **metabolic syndrome**

- ***Insulin resistance and dyslipidemia are critical long term health issues for women with PCOS***, but are not identified by any of these criteria
- Diagnostic criteria overlap with normal states: many women with isolated PCOS morphology lead normal reproductive lives

Goverde Hum Reprod 2009 Christ, Repro Biomed Online 2017; 35: 480-483; Cela, Gyn Endo 2017;

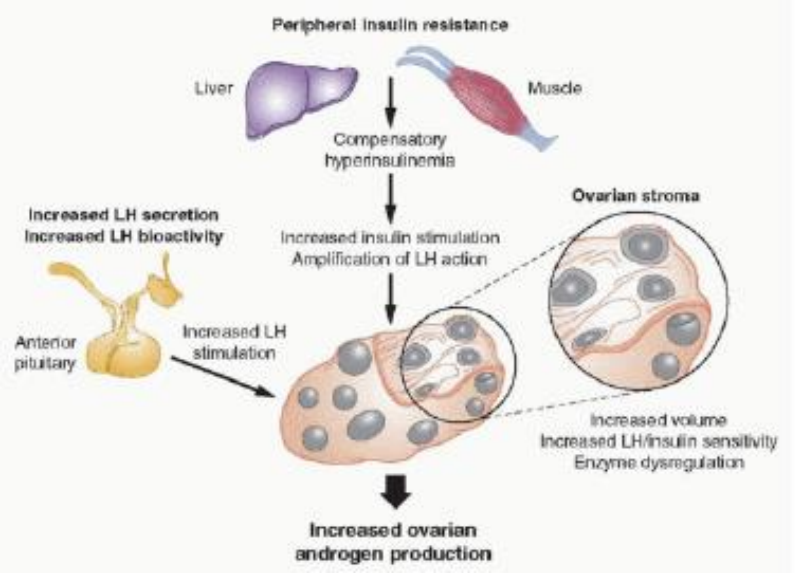
PCOS – ETIOLOGIES

- **Multifactorial; heterogenous; complex genetic trait that interacts with other environment factors**

- ov40 - 85% of women with PCOS age-matched are erweight

- **Insulin resistance**
  - **30% of lean PCOS**
  - **70% of obese PCOS**

- Insulin resistance is **independent of obesity but significantly amplified** in its presence



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GENETICS OF PCOS

- **No single gene identified but a strong genetic component**
- Genes examined involved in gonadotropin secretion, ovarian folliculogenesis, insulin secretion, androgen biosynthesis and action
- **71% monozygotic; 38% dizygotic correlation** in twin study (Vink et al. 2006)
- **20% prevalence of PCOS in mothers; 40% in sisters** (Legro et al. PNAS 1998, Kahdar-Miller et al. Fertil Steril 2001)
- In families with PCOS, males can present with balding before the age of 30
- Challenges in study (genetic complexity, heterogeneity, small sample size) although population wide studies promising

PATHOPHYSIOLOGY OF PCOS

- Increased LH and insulin stimulation drive aberrant androgen production in theca cells of ovarian follicles
- Androgen and insulin inhibit hepatic sex hormone binding globulin (SHBG)
- Leads to increased free androgen

HYPERANDROGENISM

- **50-90% of patients with PCOS have clinically measurable hyperandrogenism** (DeVane 1975)

- Androgens (Testosterone, androstenedione, DHEAS)
- Total vs. free testosterone - Free testosterone most sensitive but clinical assays unreliable (requires equilibrium dialysis)

- Differential
  - Non-Classic Congenital Adrenal Hyperplasia (CAH) - check 17 OH progesterone
  - Cushing Syndrome

- Mild hyperandrogenism vs. virilization
- Total T less than 150 ng/dL generally excludes ovarian / adrenal tumors
- Adrenal / ovarian imaging; selective ovarian vein sampling in rare cases

ACNE

Acne is seen in approximately one-third or more of PCOS patients (Task Force of the AES in 2006— **15% to 25%**)

Androgen excess has also been associated with more severe acne

ANDROGENIC ALOPECIA

Progressive, **non-scarring**, patterned loss of scalp terminal hairs.

Commonly underdiagnosed-

Incidence is 8%, an underestimation

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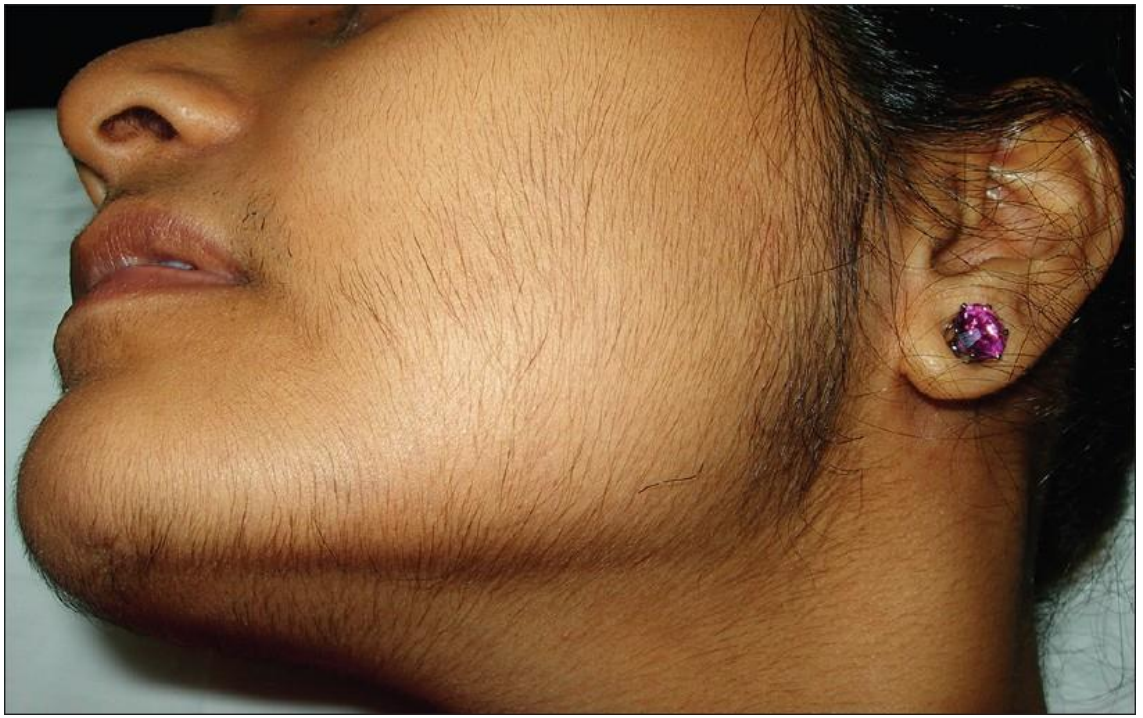
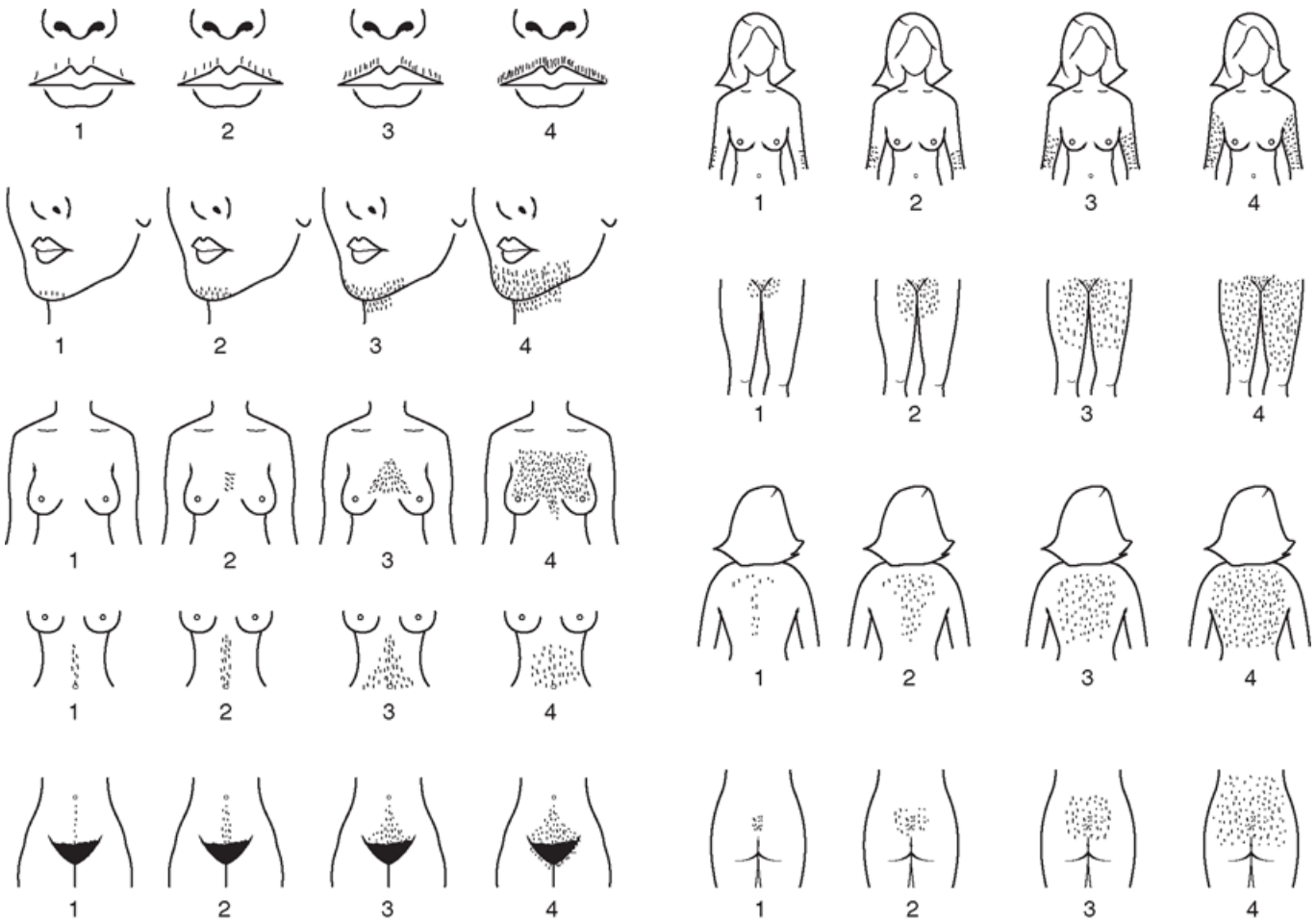
HIRSUTISM

- Defined as excess terminal (thick pigmented) body hair in a male distribution and is commonly noted on the upper lip, around the breast nipples and along the linea alba of the lower abdomen



MODIFIED FERRIMAN-GALLWAY SCORING



Source: DeCherney AH, Nathan L, Laufer N, Roman AS: *CURRENT Diagnosis & Treatment: Obstetrics & Gynecology*, 11th Edition: www.accessmedicine.com

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HYPERTRICHOSIS

Defined as increase in total body hair

Can be medication induced (e.g. phenytoin, cyclosporine)

Also occurs in patients with systemic illnesses such as the following:

1. hypothyroidism
2. anorexia nervosa / malnutrition
3. porphyria cutanea tarda
4. dermatomyositis

Sometimes idiopathic

METABOLIC SYNDROME AND PCOS

- The prevalence of **metabolic syndrome in women with PCOS is approximately 43-46%** (NCEP 2002) vs. 18% in general reproductive age population (Ford et al. 2004)

- Almost **70% of patients with PCOS have an abnormal lipid profile** and **high triglycerides and HDL cholesterol** are often found (Legro et al. 2001)

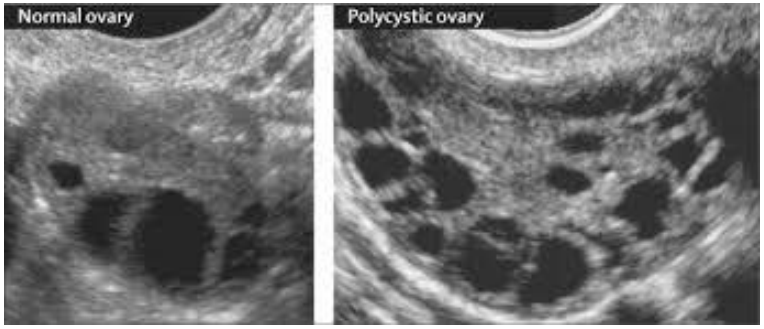
- 35-45 % had impaired glucose tolerance
- Of obese women with PCOS, **10% have undiagnosed diabetes** (Dunaif 1997)

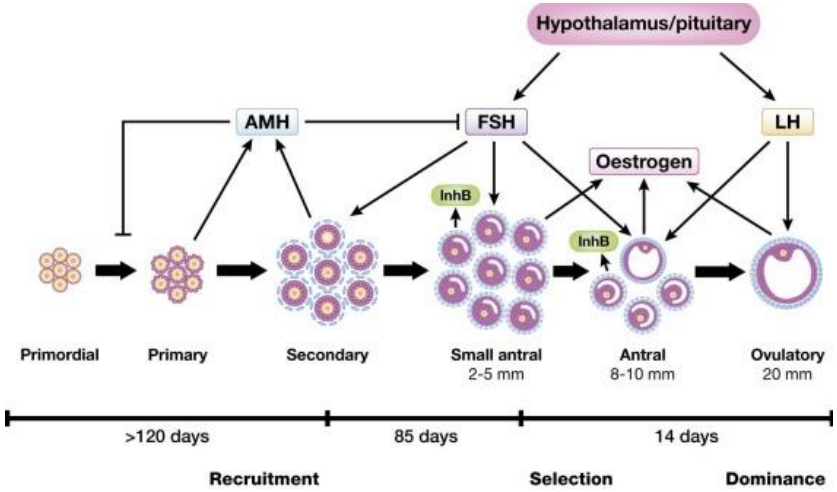
- **Non-alcoholic steatohepatitis (NASH)**
- Up to 30% of PCOS patients have elevated ALT (Schwimmer et al 2005)
- Sleep apnea (OR 30.6) in PCOS (Vgontzas et al. JCEM 2001)

LABORATORY EVALUATION

- Although not essential to the diagnosis, insulin resistance is common and may affect treatment decisions
- Therefore, 2-hr oral glucose tolerance test and/or Hemoglobin A1C can be measured for hyperinsulinemia
- Additionally, a fasting lipid panel can be done to r/o hyperlipidemia.

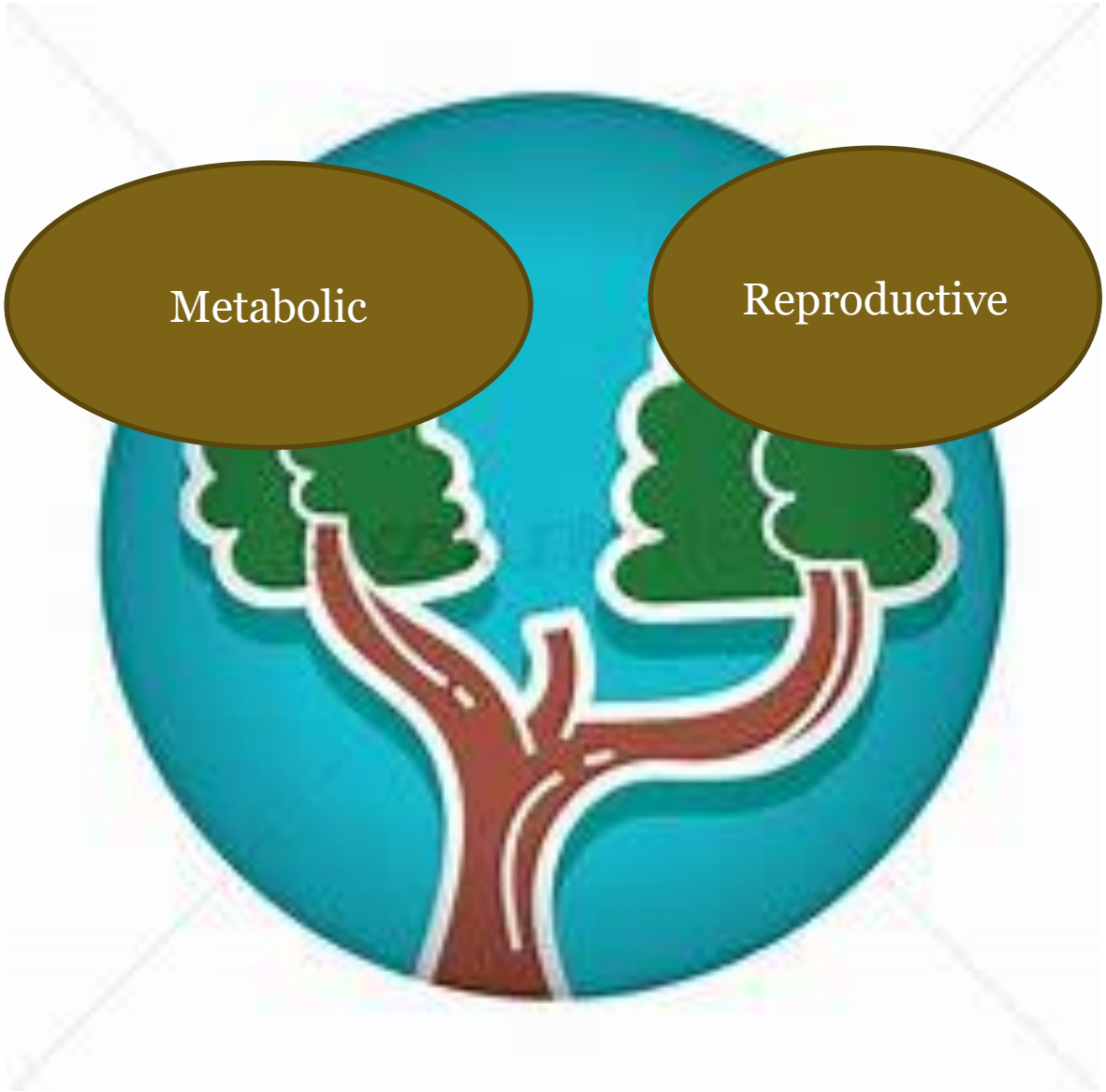
ANTI-MULLERIAN HORMONE LEVEL





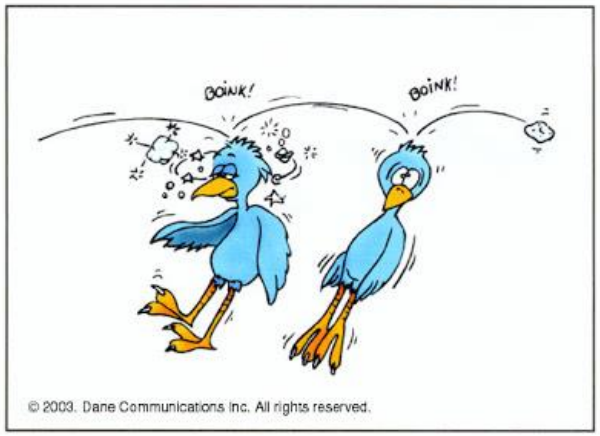
- Anti-Müllerian Hormone (AMH)
- Synthesized by granulosa cells of resting primary through preantral follicles (2-6 mm)
- 2 -3 fold higher levels than normovulatory women (Laven et al. JCEM 2004)
- Proposed diagnostic ‘marker’ for PCOS but limited specificity and sensitivity (Quinn 2017)
- Correlates with number of follicles on ultrasound and response to ovulation induction and risk for OHSS (Mumford et al. 2016)

THERAPEUTIC MANAGEMENT



ORAL CONTRACEPTIVE (OCP)

- Often first line management
- Accomplishes multiple therapeutic goals:



1) Menstrual cycle regulation

2) Reliable contraceptive

3) Protection against endometrial hyperplasia/cancer

4) Lowers serum androgen levels & symptoms

METFORMIN

- Biguanide antihyperglycemic lowers insulin resistance
- Prevention of diabetes & weight reduction (Nestler 2008)
- May reduce serum androgen concentrations (Elter et al. 2002) but has limited benefit treatment of hirsutism (Harborne et al. 2003)
- **Available data does not support use of metformin as primary agent for hyperandrogenism**
- May be used as alternative or **adjunct** for management of PCOS pts with insulin resistance

SPIRONOLACTONE

- Oral aldosterone antagonist with antiandrogenic properties
- Dosage 25 mg to 200mg/day
- Potential side effects: GI disturbances, liver toxicity (check LFTs once per year), dizziness and hyperkalemia.
- Should be given with reliable contraceptives because of the above and the risk of teratogenicity
- Mechanical (e.g plucking, laser therapy) Eflornithine (Vaniqa), a topical agent, interferes with an enzyme in the hair follicle and slows hair growth. Takes 6-8 wks to work but the hair will reappear after stopping treatment.

INOSITOL

- Complimentary therapy to reduce insulin resistance, not a prescription
- Nutrient derived from food-based sources
- Some growing evidence it can be helpful in women with PCOS
- Alternative if metformin is not well tolerated

PRECONCEPTUAL MANAGEMENT LIFESTYLE MODIFICATION & WEIGHT LOSS

- Optimize metabolic status prior to conception
- Preconceptual consultation for risks with elevated BMI, diabetes, hypertension
- Referral to nutrition
- Strategies
  - Don’t leave the patient to her own devices!
  - See at least every 6 weeks
  - Active follow up for ‘weigh-ins’; address and expect recidivism and plateaus
  - Encourage fitness if weight loss is not easily achieved
- Bariatric surgery
  - decrease in hirsutism, androgen levels, insulin and resumption of ovulatory cycles (Escobar-Morreale et al. JCEM 2005, Christ & Falcone 2018)

OWL PCOS TRIAL

ORIGINAL ARTICLE

Randomized Controlled Trial of Preconception Interventions in Infertile Women With Polycystic Ovary Syndrome

Richard S. Legro, William C. Dodson, Penny M. Kris-Etherton, Allen R. Kunselman, Christy M. Stetter, Nancy I. Williams, Carol L. Gnatuk, Stephanie J. Estes, Jennifer Fleming, Kelly C. Allison, David B. Sarwer, Christos Coutifaris, and Anuja Dokras

Departments of Obstetrics and Gynecology (R.S.L., W.C.D., C.L.G., S.J.E.) and Public Health Sciences (R.S.L., A.R.K., C.M.S.), Penn State College of Medicine, Hershey, PA, Departments of Nutritional Sciences (P.M.K., J.F.) and Kinesiology (N.I.W.), Penn State College of Health and Human Development, University Park, Pennsylvania 16802; and Departments of Psychiatry (D.B.S., K.C.A.), Surgery (D.B.S.), and Obstetrics and Gynecology (A.D., C.C.), Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania 19104

Context: Lifestyle modification is recommended in women with polycystic ovary syndrome (PCOS) prior to conception but there are few randomized trials to support its implementation or benefit.

Objective: This study aimed to determine the relative efficacy of preconception intervention on reproductive and metabolic abnormalities in overweight/obese women with PCOS.

Design, Setting, and Participants: This was a randomized controlled trial of preconception and infertility treatment at Academic Health Centers in women with infertility due to PCOS, age 18–40 y and body mass index 27–42 kg/m^2.

Intervention: Women were randomly assigned to receive either 16 weeks of 1) continuous oral contraceptive pills (OCPs) (ethinyl estradiol 20 mcg/1 mg norethindrone acetate) ("OCP"); 2) lifestyle modification consisting of caloric restriction with meal replacements, weight loss medication (either sibutramine, or orlistat), and increased physical activity to promote a 7% weight loss ("Lifestyle"); or 3) combined treatment with both OCP and lifestyle modification ("Combined"). After preconception intervention, women underwent standardized ovulation induction with clomiphene citrate and timed intercourse for four cycles. Pregnancies were followed with trimester visits until delivery.

Main Outcome Measures: Weight, ovulation, and live birth were measured.

Results: We consented 216 and randomly assigned 149 women (Lifestyle: n = 50; OCP: n = 49; Combined: n = 50). We achieved significant weight loss with both Lifestyle (mean weight loss, −6.2%; 95% confidence interval (CI), −7.4–−5.0; and Combined (mean weight loss, −6.4%; 95% CI, −7.6–−5.2) compared with baseline and OCP (both $P < .001$). There was a significant increase in the prevalence of metabolic syndrome at the end of preconception treatment compared with baseline within OCP (odds ratio [OR, 2.47; 95% CI, 1.42–4.27) whereas no change in metabolic syndrome was detected in the Lifestyle (OR, 1.18; 95% CI, 0.63–2.19) or Combined (OR, 0.72; 95% CI, 0.44–1.17) groups. Cumulative ovulation rates were superior after weight loss: OCP, 46%; Lifestyle, 60%; and Combined, 67% ($P < .05$). Live birth rates were OCP, 12%; Lifestyle, 26%; and Combined, 24% ($P = .13$).

Conclusions: A preconception weight loss intervention eliminates the adverse metabolic oral con-

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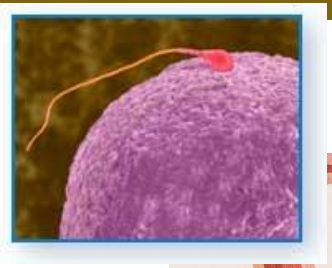
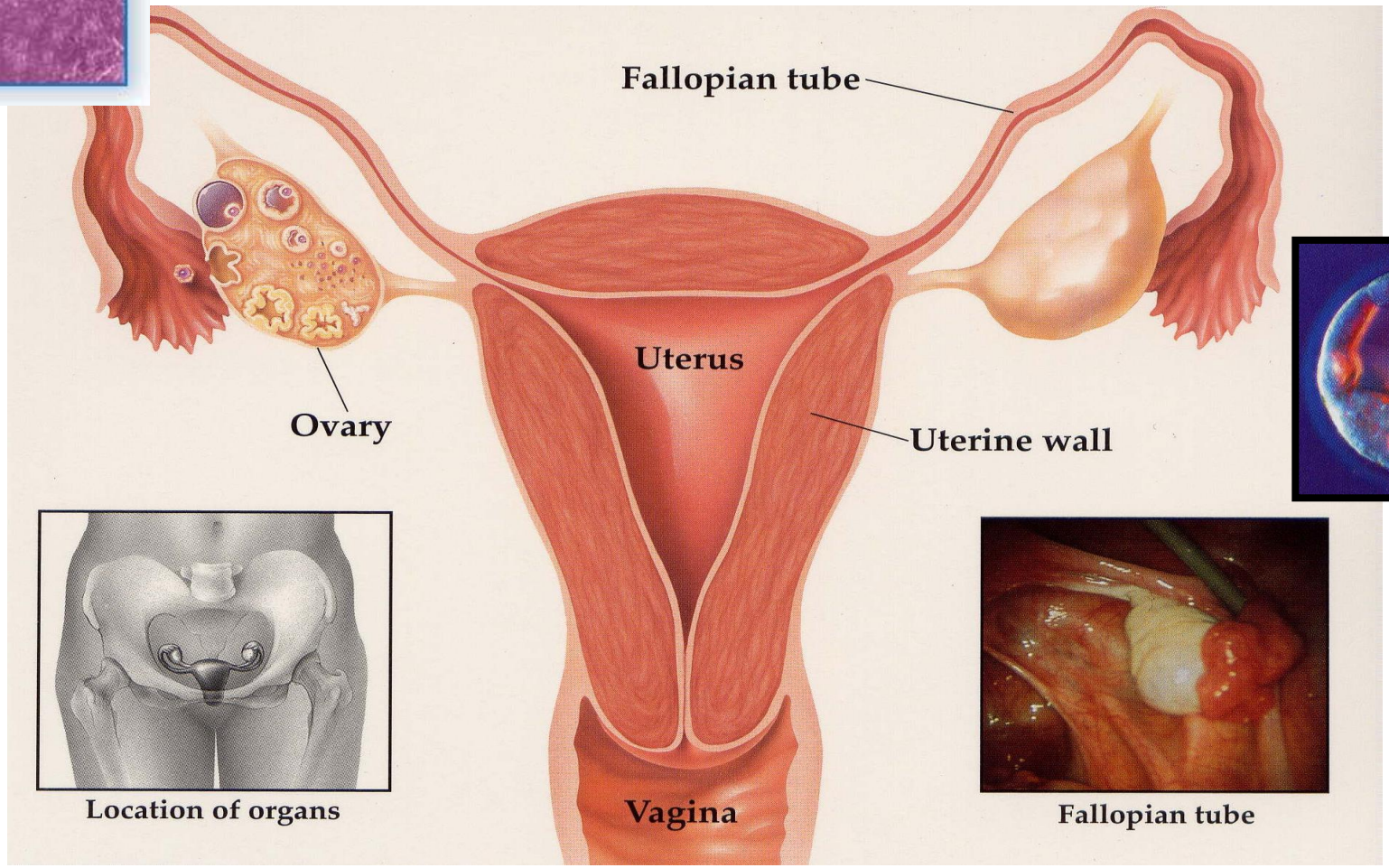
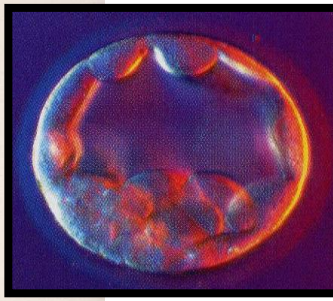
WHEN TO DO FULL FERTILITY EVALUATION?







Location of organs

Fallopian tube

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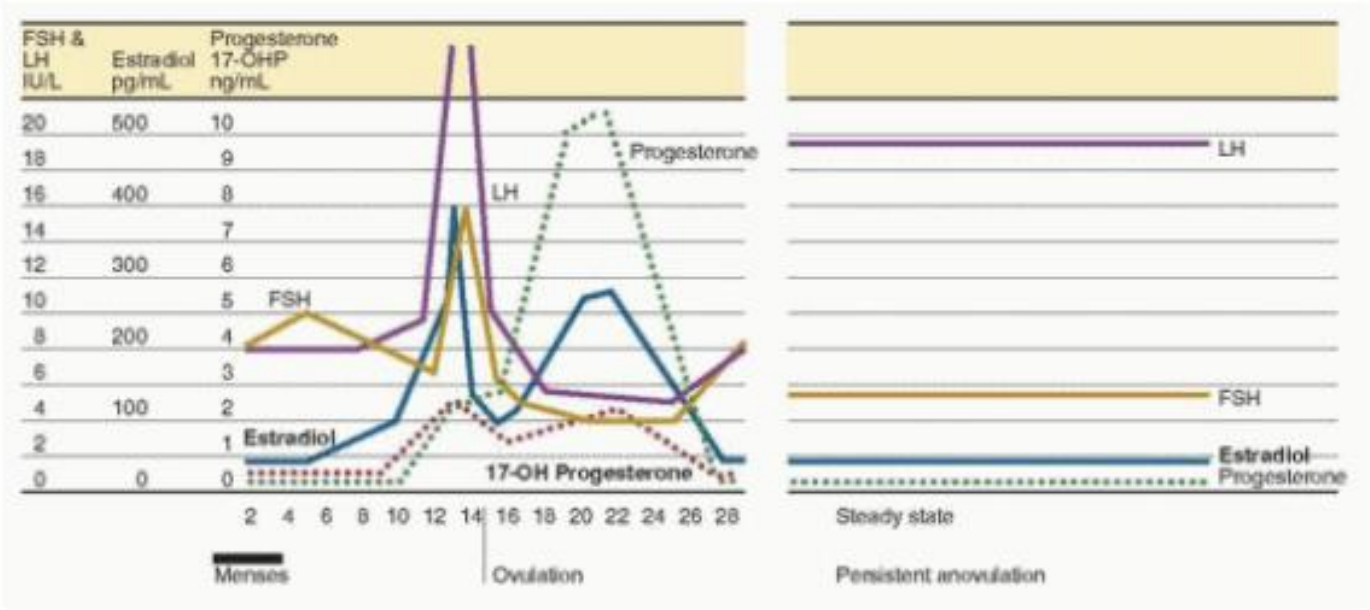
OVULATION INDUCTION FOR PCOS



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OVULATION INDUCTION IN PCOS

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 8, 2007 VOL. 356 NO. 6

Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome

Richard S. Legro, M.D., Huiman X. Barnhart, Ph.D., William D. Schlaff, M.D., Bruce R. Carr, M.D., Michael P. Diamond, M.D., Sandra A. Carson, M.D., Michael P. Steinkampf, M.D., Christos Coutifaris, M.D., Ph.D., Peter G. McGovern, M.D., Nicholas A. Cataldo, M.D., Gabriella G. Gosman, M.D., John E. Nestler, M.D., Linda C. Giudice, M.D., Ph.D., Phyllis C. Leppert, M.D., Ph.D., and Evan R. Myers, M.D., M.P.H., for the Cooperative Multicenter Reproductive Medicine Network*

ABSTRACT

BACKGROUND

The polycystic ovary syndrome is a common cause of infertility. Clomiphene and insulin sensitizers are used alone and in combination to induce ovulation, but it is unknown whether one approach is superior.

METHODS

We randomly assigned 626 infertile women with the polycystic ovary syndrome to receive clomiphene citrate plus placebo, extended-release metformin plus placebo, or a combination of metformin and clomiphene for up to 6 months. Medication was discontinued when pregnancy was confirmed, and subjects were followed until delivery.

RESULTS

The live-birth rate was 22.5% (47 of 209 subjects) in the clomiphene group, 7.2% (15 of 208) in the metformin group, and 26.8% (56 of 209) in the combination-therapy group ($P<0.001$ for metformin vs. both clomiphene and combination therapy; $P=0.31$ for clomiphene vs. combination therapy). Among pregnancies, the rate of multiple pregnancy was 6.0% in the clomiphene group, 0% in the metformin group, and 3.1% in the combination-therapy group. The rates of first-trimester pregnancy loss did not differ significantly among the groups. However, the conception rate among subjects who ovulated was significantly lower in the metformin group (21.7%) than in either the clomiphene group (39.5%, $P=0.002$) or the combination-therapy group (46.0%, $P<0.001$). With the exception of pregnancy complications, adverse-event rates were similar in all groups, though gastrointestinal side effects were more frequent, and vasomotor and ovulatory symptoms less frequent, in the metformin group than in the clomiphene group.

CONCLUSIONS

Clomiphene is superior to metformin in achieving live birth in infertile women with the polycystic ovary syndrome, although multiple birth is a complication. (ClinicalTrials.gov number, NCT00068861.)

From Pennsylvania State University College of Medicine, Hershey (R.S.L.); Duke University Medical Center, Durham, NC (H.X.B., E.R.M.); University of Colorado, Denver (W.D.S.); University of Texas Southwestern Medical Center, Dallas (B.R.C.); Wayne State University, Detroit (M.P.D.); Baylor College of Medicine, Houston (S.A.C.); University of Alabama, Birmingham (M.P.S.); University of Pennsylvania School of Medicine, Philadelphia (C.C.); University of Medicine and Dentistry of New Jersey, Newark (P.G.M.); Stanford University, Stanford, CA (N.A.C.); University of Pittsburgh, Pittsburgh (G.G.G.); Virginia Commonwealth University School of Medicine, Richmond (J.E.N.); University of California at San Francisco, San Francisco (L.C.G.); and the National Institute of Child Health and Human Development, Bethesda, MD (P.C.L.). Address reprint requests to Dr. Legro at the Department of Obstetrics and Gynecology, Pennsylvania State University College of Medicine, M.S. Hershey Medical Center, 500 University Dr., H103, Hershey, PA 17033, or at rsl1@psu.edu.

*Other members of the Cooperative Multicenter Reproductive Medicine Network are listed in the Appendix.

N Engl J Med 2007;356:551-66.

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PCOS OVULATION INDUCTION

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome

Richard S. Legro, M.D., Robert G. Brzyski, M.D., Ph.D., Michael P. Diamond, M.D., Christos Coutifaris, M.D., Ph.D., William D. Schlaff, M.D., Peter Casson, M.D., Gregory M. Christman, M.D., Hao Huang, M.D., M.P.H., Qingshang Yan, Ph.D., Ruben Alvero, M.D., Daniel J. Haisenleder, Ph.D., Kurt T. Barnhart, M.D., G. Wright Bates, M.D., Rebecca Usadi, M.D., Scott Lucidi, M.D., Valerie Baker, M.D., J.C. Trussell, M.D., Stephen A. Krawetz, Ph.D., Peter Snyder, M.D., Dana Ohl, M.D., Nanette Santoro, M.D., Esther Eisenberg, M.D., M.P.H., and Heping Zhang, Ph.D., for the NICHD Reproductive Medicine Network*

ABSTRACT

BACKGROUND

Clomiphene is the current first-line infertility treatment in women with the polycystic ovary syndrome, but aromatase inhibitors, including letrozole, might result in better pregnancy outcomes.

METHODS

In this double-blind, multicenter trial, we randomly assigned 750 women, in a 1:1 ratio, to receive letrozole or clomiphene for up to five treatment cycles, with visits to determine ovulation and pregnancy, followed by tracking of pregnancies. The polycystic ovary syndrome was defined according to modified Rotterdam criteria (anovulation with either hyperandrogenism or polycystic ovaries). Participants were 18 to 40 years of age, had at least one patent fallopian tube and a normal uterine cavity, and had a male partner with a sperm concentration of at least 14 million per milliliter; the women and their partners agreed to have regular intercourse with the intent of conception during the study. The primary outcome was live birth during the treatment period.

RESULTS

Women who received letrozole had more cumulative live births than those who received clomiphene (103 of 374 [27.5%] vs. 72 of 376 [19.1%], P=0.007; rate ratio for live birth, 1.44; 95% confidence interval, 1.10 to 1.87) without significant differences in overall congenital anomalies, though there were four major congenital anomalies in the letrozole group versus one in the clomiphene group (P=0.65). The cumulative ovulation rate was higher with letrozole than with clomiphene (834 of 1352 treatment cycles [61.7%] vs. 688 of 1425 treatment cycles [48.3%], P<0.001). There were no significant between-group differences in pregnancy loss (49 of 154 pregnancies in the letrozole group [31.8%] and 30 of 103 pregnancies in the clomiphene group [29.1%]) or twin pregnancy (3.4% and 7.4%, respectively). Clomiphene was associated with a higher incidence of hot flushes, and letrozole was associated with higher incidences of fatigue and dizziness. Rates of other adverse events were similar in the two treatment groups.

CONCLUSIONS

As compared with clomiphene, letrozole was associated with higher live-birth and ovulation rates among infertile women with the polycystic ovary syndrome. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and others; ClinicalTrials.gov number, NCT00719186.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Legro at the Department of Obstetrics and Gynecology, Penn State College of Medicine, M.S. Hershey Medical Center, 500 University Dr., H103, Hershey PA, 17033, or at rsl1@psu.edu.

*Additional members of the National Institute of Child Health and Human Development (NICHD) Reproductive Medicine Network are listed in the Supplementary Appendix, available at NEJM.org.

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UW Medicine

HOW TO GIVE LETROZOLE OR CLOMIPHENE

- Not necessary to start with menses; can induce with provera 10mg x 10 - 12 days
- Confirm lack of pregnancy (Pregnancy category X)
- Start with 2.5 mg letrozole or 50 mg clomiphene for 5 days (can be cycle day 3 through 7)
- Clomiphene historically used more often but evidence establishes superiority of letrozole with PCOS; letrozole is off-label and patients must be informed
- Anticipate ovulation 8-12 days after last pill
- Monitoring ovulation (home OPKs, ultrasound)
- Check luteal (~day 21-23) progesterone, if mid-luteal P <3 ng/ml, increase dose by 2.5 mg (letrozole) or 50 mg (clomiphene) increment and repeat
- If ovulatory response, give 3 to 6 months

ORAL OVULATION INDUCTION AGENTS

- Side effects
  - Vasomotor (15%)
  - Abdominal pain (5.5%)
  - Nausea and vomiting (2.2%)
  - Visual changes (2%)
- Contraindications
  - Pregnancy/ Hypersensitivity / adverse effects
- Risks
  - 5 – 8% twins; 1% triplets
- Ovulation rates (on clomiphene)
  - 50% at 50 mg clomiphene
  - 20% at 100 mg
  - 8-10% 150 mg

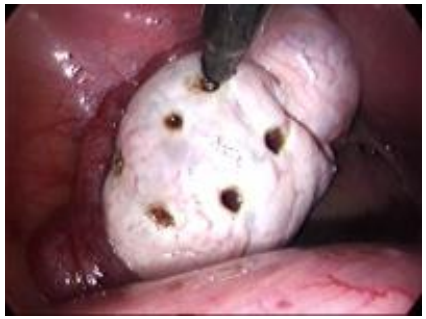
20 % will not respond

CLOMIPHENE / LETROZOLE RESISTANT PCOS

- Gonadotropin-based ovulation induction
  - High risks of multiple gestation, ovarian hyperstimulation syndrome (OHSS), cycle cancellation
  - Traditional long low dose gonadotropins vs. sequential protocols

CLOMIPHENE / LETROZOLE RESISTANT PCOS

- Historical paper on 75 women who underwent bilateral wedge resections
- Nearly 90% of whom began to have spontaneous menstrual cycles and 65% of those seeking fertility conceived (Stein, Cohen and Elson 1948)



- Laparoscopic ovarian drilling
  - Ovulation rates ~70-90%
  - Cautery or laser
  - 3-6 sites per ovary at depth 4 to 10mm
  - Risk for adhesions / decline of ovarian reserve – uncertain impact

PCOS ACROSS REPRODUCTIVE YEARS

Adolescence:

- How to be make an early diagnosis?
- Reduction/avoidance of excess hair growth
- Reduction/avoidance of weight gain
- Addressing menstrual irregularity
- Identifying and treating dyslipidemia and insulin resistance (less likely)
- Addressing quality of life/psychosocial issues

PCOS ACROSS REPRODUCTIVE YEARS

Reproductive years:

- Treatment of anovulatory infertility
- Prevention of progression of hirsutism and weight gain
- Delay/avoid T2DM, GDM or dyslipidemia
- Mental health
- Increased risk of pregnancy-related hypertension or preeclampsia (OR 3.4, 2.2) [Qin et al. 2013]
- Increased risk of gestational diabetes (OR 3.4)
- Increased risk of preterm delivery (OR 1.9)
- Increased risk (20-40%) for miscarriages (Glueck et al. 2002) -mechanisms not understood may relate to obesity
- Elevated rates of CRP in pregnancy (Palomba et al. 2014)

PCOS ACROSS REPRODUCTIVE YEARS

Late Reproductive Years:

- Cycles may become regular
- Androgens may not remain elevated
- Risks of T2DM and accelerated atherosclerosis

PCOS ACROSS REPRODUCTIVE YEARS

Post-reproductive Life:

- Other women ‘catch up’ to many PCOS women post-menopause
- Long term risk may be less than previously believed
- Which PCOS phenotype is at greatest long term risk?
- Very few studies have focused on this age group
- Fewer studies have longitudinally tracked the natural history over the vital transition time between 45 to 55 year of age.

CONCLUSION

- PCOS is not a single disease but a syndrome
- Multifactorial and with variable presentation
- No single definitive lab test or noninvasive procedure can make the diagnosis
- Important to establish correctly diagnosis of PCOS and assess future health risks
- Individualized treatment plan based patient's concerns
- Management through an interdisciplinary team
- Optimize pre-pregnancy health to optimize efficient conception and safe pregnancy

THANK YOU!