PCOS

Kirtly Parker Jones MD

Objectives

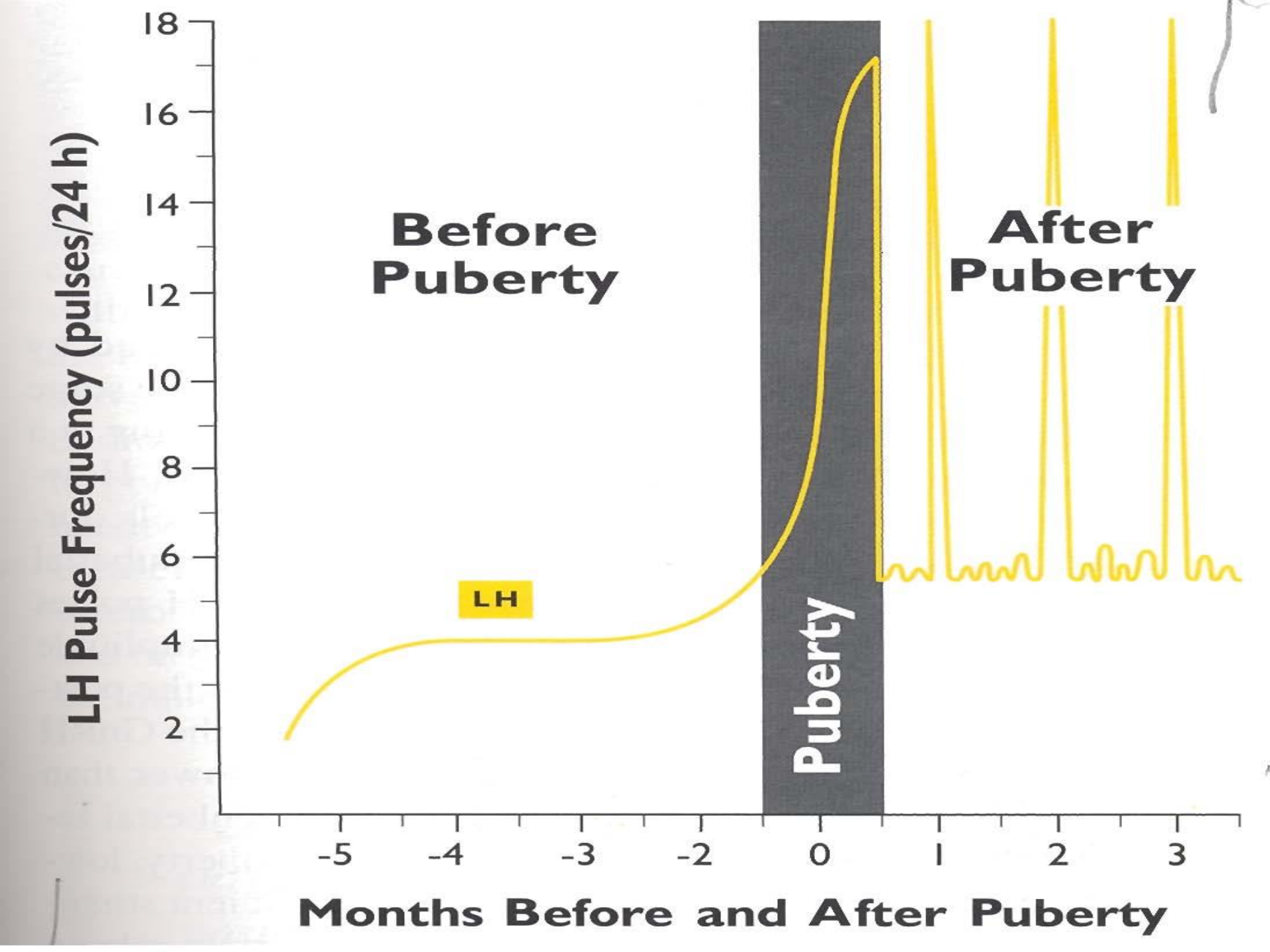
- The participant will be able to use knowledge about ovarian physiology to council perimenarchal women about irregular periods
- The participant will be able to evaluate the adolescent with irregular periods
- The participant will be able to offer therapy for the women with PCOS

Disclosures

- The lecturer has no financial conflicts of interest
- The lecturer will discuss off label use of combination hormonal contraceptives and metformin

PUBERTY

- The coordination of adrenarche and gonadarche
- The “on center” begins pulsing GnRH at night
- Gonadal steroids rise
- Early pubic hair (before age 10) may be a sign of future PCOS


LH Pulse Frequency (pulses/24 h)
18
16
14
12
10
8
6
4
2
Before Puberty
After Puberty
LH
Puberty
-5
-4
-3
-2
0
1
2
3
Months Before and After Puberty

Epidemiology

- 20% of women experience abnormal bleeding during their lifetime
- Most irregular bleeding occurs within 2-3 years after menarche
  - 85% of cycles anovulatory in first year after menarche
  - [Adolescents who have not established a 24-35 day cycle by 3 years after menarche have a 50% chance of having a persistent irregular pattern]

Anovulatory Bleeding

- Immature HPO axis
- May also be associated with
  - Sports participation
  - Stress
  - Eating disorders
  - Endocrine disorders

Anovulatory Bleeding

- PCOS
  - 5-10% of adolescents
  - Overweight
  - Insulin resistance
  - Acanthosis nigricans
  - Hirsutism
  - Acne

PCOS

- Anovulatory from puberty
- Usually <6 menses per year
- Periods are unpredictable in timing and amount
- Excessive hair growth is typical (not common in East Asian women)
- Most (60%-70%) are infertile
- At risk for diabetes, heart disease (?)
- At risk for sleep apnea, depression

ANDROGEN EXCESS DISORDERS

- Polycystic Ovary Syndrome (6% of population, 70% of androgen excess)
- Idiopathic hyperandrognism
- Idiopathic Hirsutism
- Non-Classic Congenital Adrenal Hyperplasia
- Androgen Secreting Tumors
  - Rapid onset, virilization (clitoromegaly/alopecia), defeminization (mammary atrophy)

Prevalence

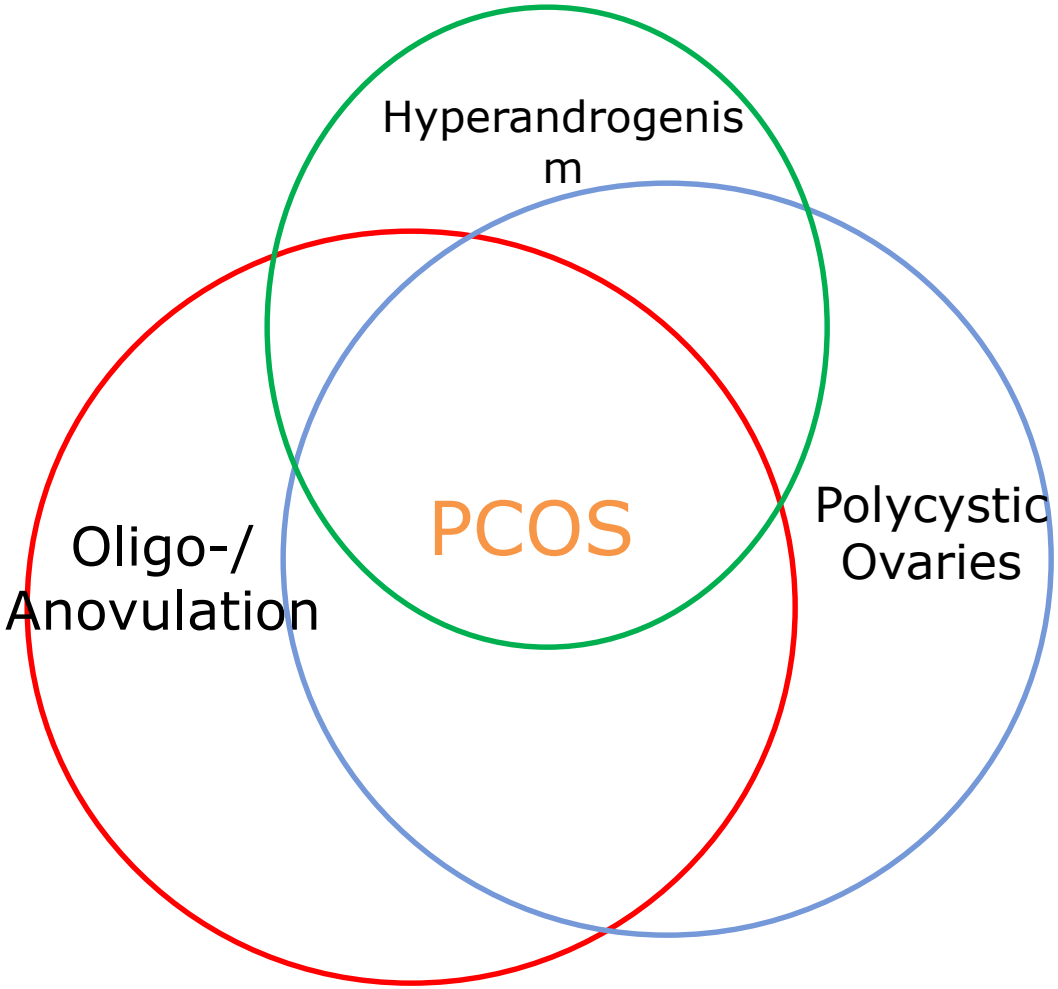
- Appears to be the same range among all races examined to date
- About 6.5% using 10 consensus definition
- About 25% using the 2003 Rotterdam criteria

Rotterdam Criteria for PCOS

Need two of the following three:

1. Irregular menstrual cycles
2. Evidence of androgen excess
3. Polycystic ovaries on ultrasound

PCOS: Rotterdam Criteria (2003)

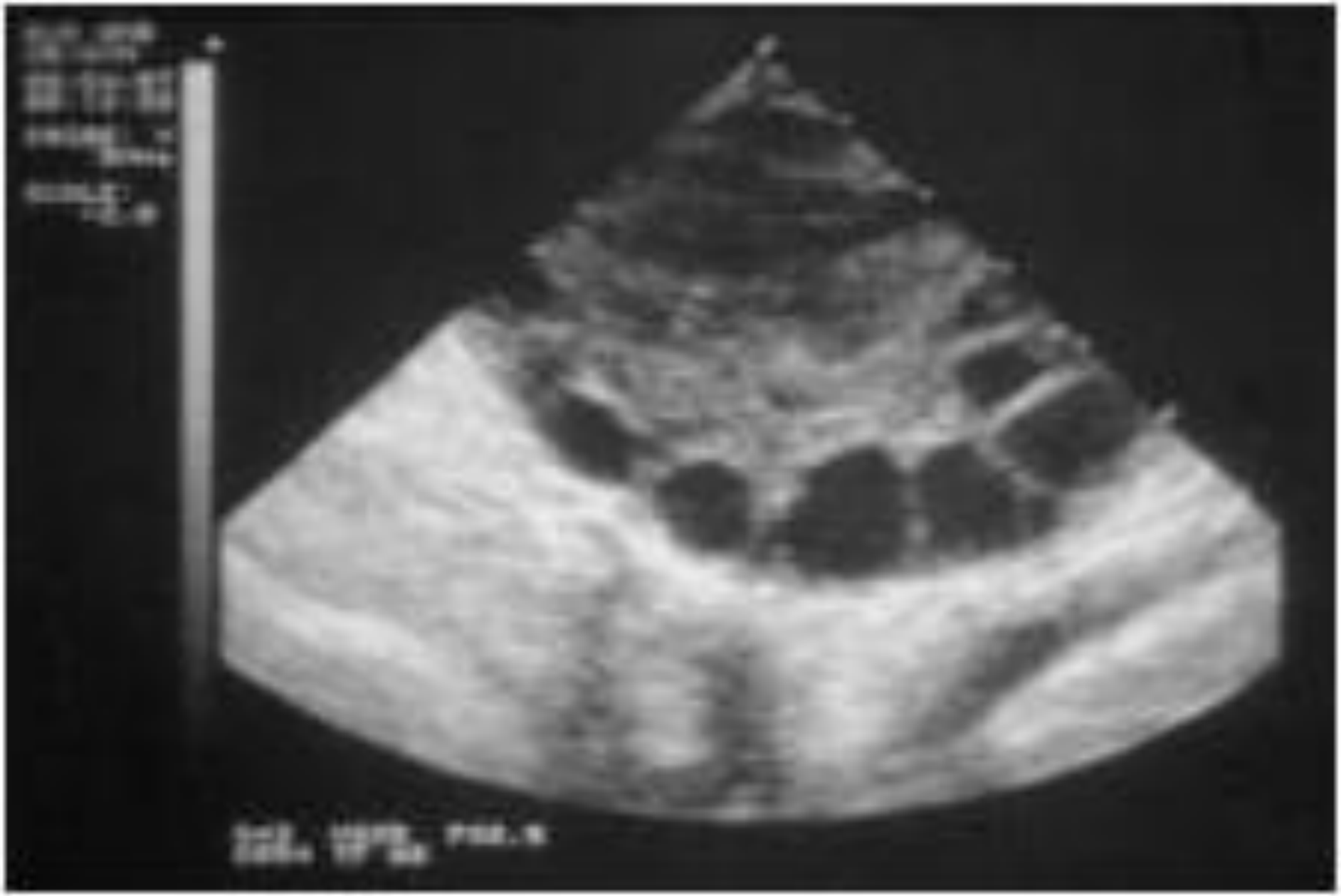


Ultrasound Criteria….

- >12 follicles 2-9 mm in at least one of the ovaries
- Increased volume (>10cc)

- Excluded are those on OCPs and those with follicle >10mm).
- “Chain of Pearls sign” is not required

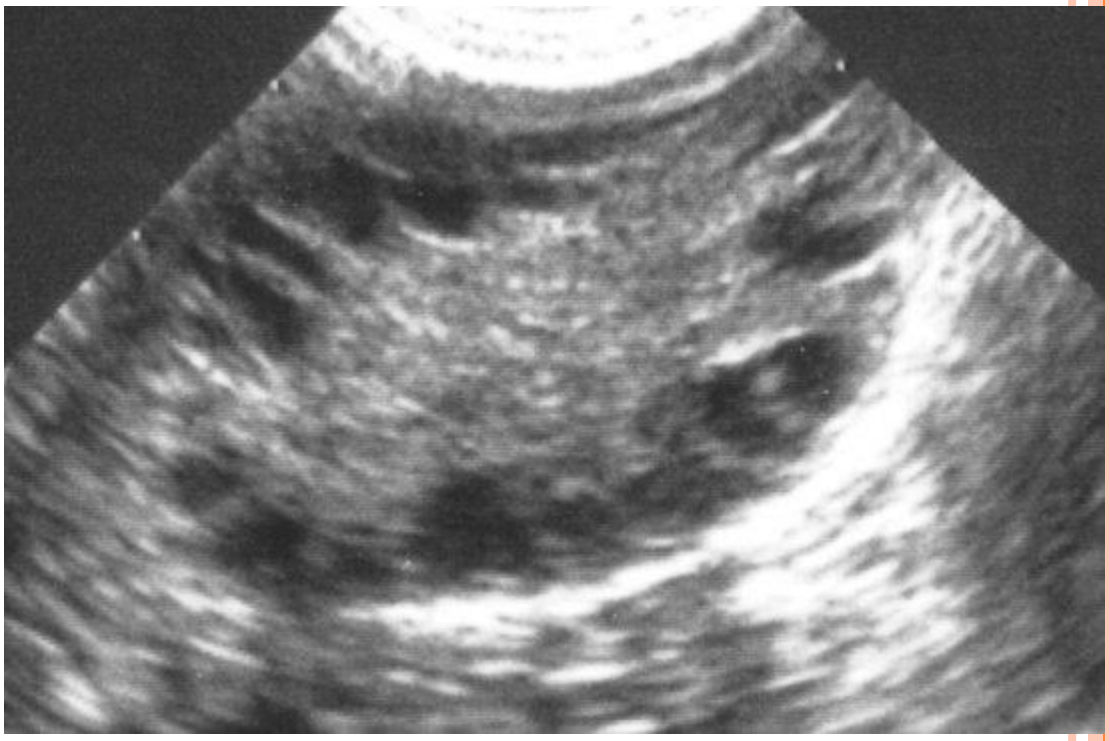
If you are using ultrasound criteria….and I don’t



PCOS Sonogram

Ultrasound Criteria

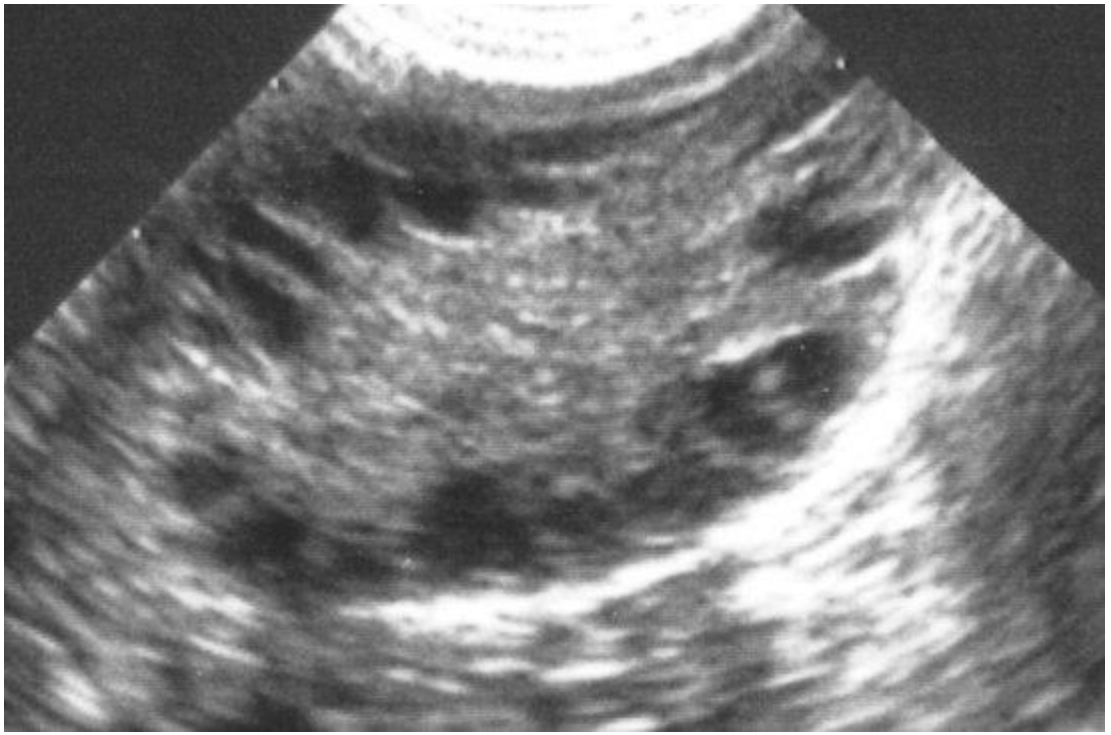
- Only 2 of three women with this criteria will have PCOS, and probably even fewer adolsecents
- About 25% of ovulatory women have this morphology (most of our good fertile young egg donors)

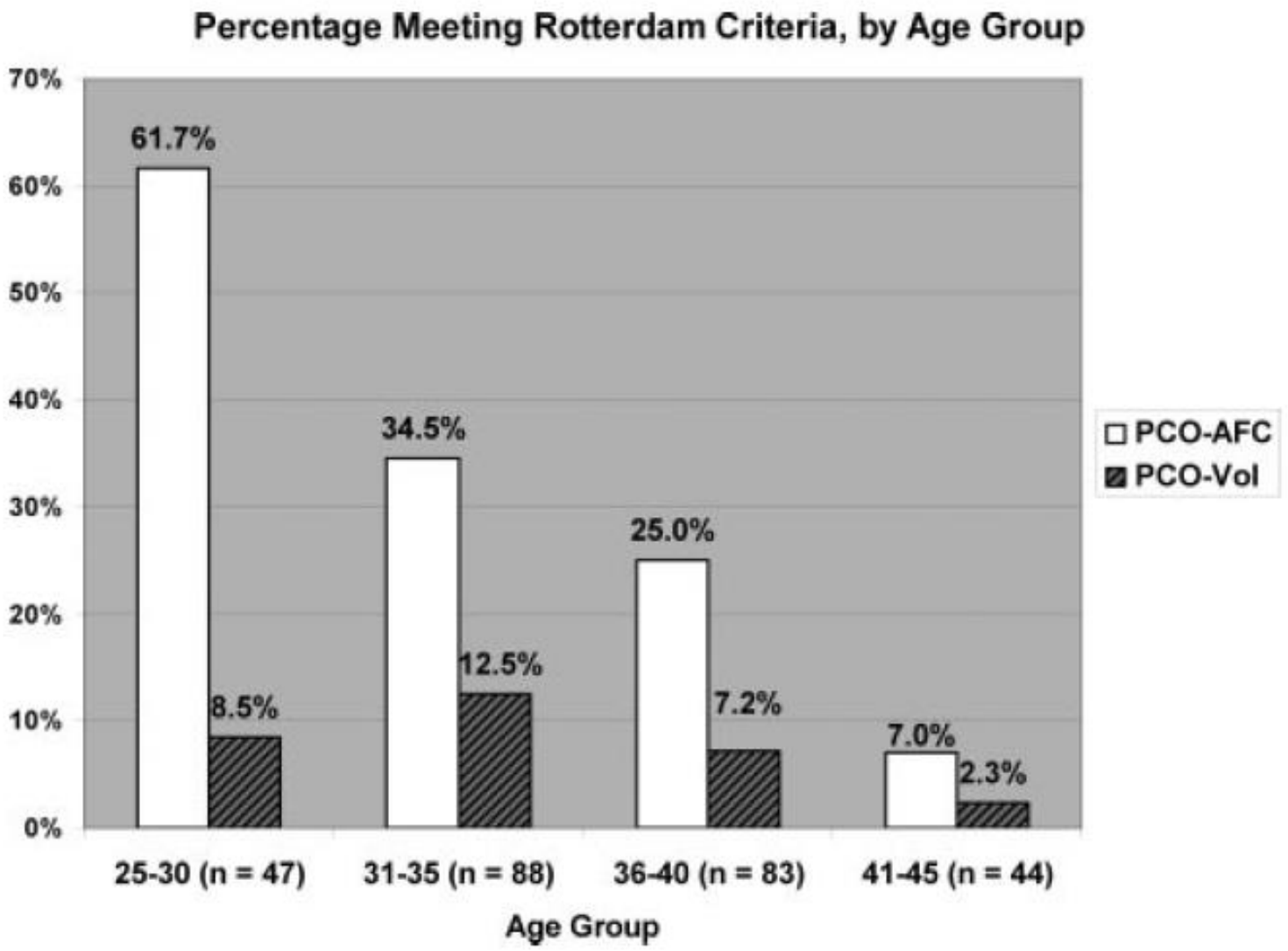


High Androgens

Anovulation/PCO

1. Many Antral Follicles indicate GOOD OVARIAN Function
2. Need to Rule out other causes of Anovulation
3. Radiologists do not understand this.





Johnstone et al, 2010, JCEM

Consensus Diagnosis of PCOS

- "There is lack of consensus with even the latest consensus statement"
- Obesity is not even part of the diagnostic criteria but it does add to the clinical suspicion

NOT A CONSENSUS CONFERENCE

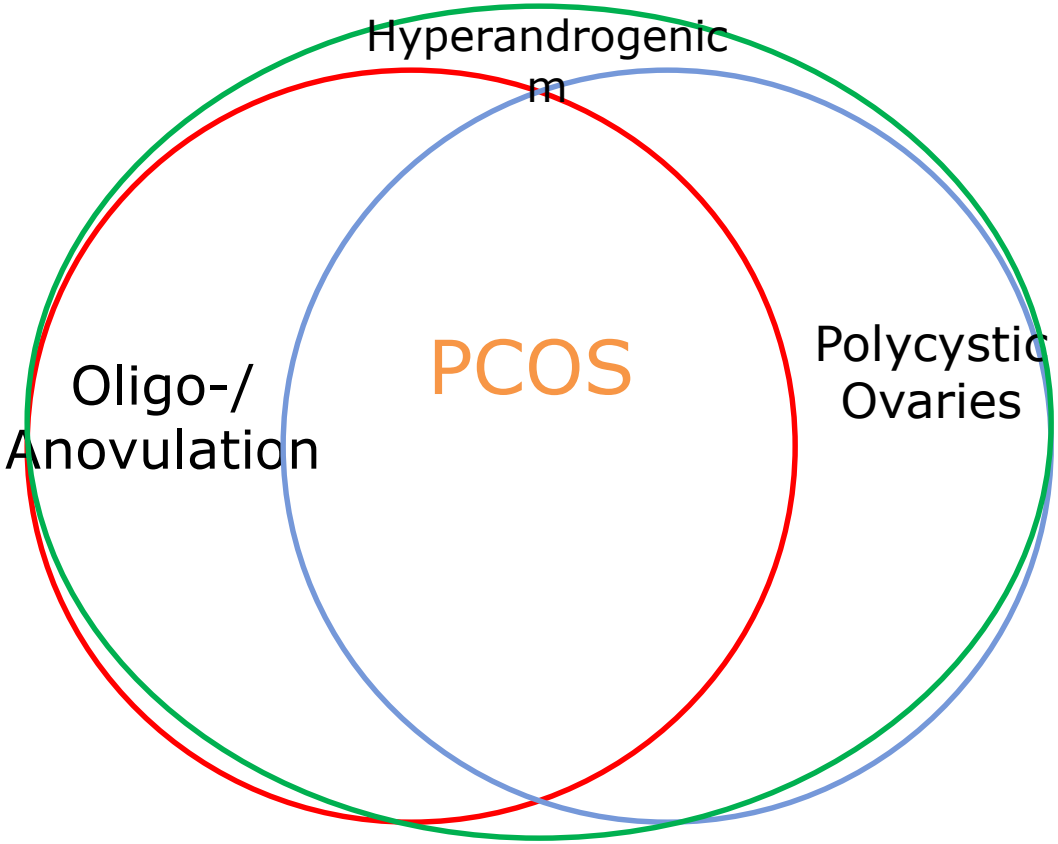
- Clearly Little Consensus Concerning
  - Whether PCOS will retain its name.
  - Diagnostic Criteria.
  - Utility of the diagnosis – How does it help understanding/treatment?
  - Long-term effects

PCOS - 2008

- Hyperandrogenism –(clinical and/or biochemical
- Ovarian dysfunction – as reflected by oligo-anovulation and/or polycystic appearing ovaries
- Exlusion of other androgen excess disorders

The Androgen Excess and PCOS Society criteria for PCOS: the Complete taskforce report. Fertil and Steril Oct 2008:1-33, e-pub

PCOS: Androgen Excess Society 2006



PCOS 2008

- Clinical or biochemical signs of androgen excess are prerequisites of PCOS
- If an adolescent doesn't have hyperandrogenism, don't order ultrasound
- (I never order the ultrasound in women with irregular periods or amenorrhea)

PCOS

- The diagnostic approach in adolescents should be based on history and physical exam
- Avoid numerous laboratory tests that do not contribute to clinical management

Guzick DA. Clinical Updates in Women's Health Care. ACOG 2009

Million Dollar Workup

- TSH, Prolactin, Total testosterone (female), Free Testosterone, SHBG, androstenedione, DHEAS, Plasma free testosterone, overnight Dexamethasone Suppression test, IGF-1, 17-hydroxyprogesterone in the follicular phase, fasting insulin and glucose
- Ultrasound

Measurement of Serum Androgens:

- Useful when ruling out tumor (rapid onset):
  - Total Testosterone > 150 ng/dL Adrenal vs Ovarian
  - DHEAS >700 ug/dL Likely Adrenal
- Otherwise, can be helpful for making a diagnosis of PCOS, but rarely changes clinical management

Ruling out rare causes of Hyperandrogenism

- NCCAH:
  - Screening: Morning 17-OHP>200 ng/dL.
  - Can be reserved for childhood/early onset of moderate/severe hirsutism, Women with family history and high-risk ethnicities (Hispanic, Mediterranian, Ashkenazi Jewish, Slavic)
  - Rare: Carrier rate in NYC 1/100, in Utah, ?

Ruling out rare causes of Hyperandrogenism

- Cushings Syndrome:
  - Extremely rare
  - Measure 24 hour urinary free cortisol (>3 times upper limit of normal positive screen) only when hirsutism accompanied by signs of hypercortisolism. (Moon face, buffalo hump, hypertension, severe fatigue and weakness, skin atrophy/easy bruising/striae), diabetes
  - Refer to Endocrinologist for positive screen.
  - Overnight Dex supression may be better screen, but less practical.

Hundred Dollar workup

- Testosterone (female) to rule out tumors (free testosterone may be elevated in the face of normal total but you know that by looking) but only in women with virilization or rapidly increasing hirsutism
- Prolactin and TSH (for other causes of anovulation)
- 17-hydroxyprogesterone in the follicular phase?
- Serum glucose if diabetes is clinically suspected

And in the Face of Clinical Suspicion…

- 24 hour urinary free cortisol to rule out Cushing's
- IGF-1 for acromegaly
- DHEAS for adrenal tumors (but I have never seen one)
- If 17-hydroxyprogesterone is very high (check your lab's normals) and you are sure it was follicular – refer)

Insulin and PCOS

- 50% of obese teens with PCOS have insulin resistance by the most sensitive tests (insulin euglycemic clamp test)
- 17% of normal weight women with PCOS have insulin resistance by the most sensitive tests
- Frank diabetes is very uncommon
- Diet and exercise is a primary recommendation no matter what their fasting insulin is

Metformin and Adolescents with PCOS

- No real data on long term use of metformin in adolescents
- One small randomized trial in morbidly obese teens showed improvement in glucose, insulin, BMI, and menstrual cyclicity
- All effects gone within 3 months of discontinuing metformin

Ibanez L. JCEM 2001;86:3595-3598

PCOS Treatment
The complicated way

- The big work up
- The big therapy
  - Metformin
  - Lifestyle modifications

Add OCPs if cycles do not regulate (and they often don't)

Repeat the big workup yearly

Trials of Metformin, Oral Contraceptives, Lifestyle modification

- Both Lifestyle modification (if weight was lost) and OCs significantly reduce androgens and increase SHBG in obese adolescents with PCO
- Metformin alone lowered testosterone (but not hirsutism score) but didn't change weight

Hoeger K et al. JCEM.2008

PCOS Treatment The Easy Way

- Diet and exercise
- OCPs
- Check fasting glucose (or two hour post prandial….or random) if they are still gaining weight

- How do you put the fear of the mirror without creating self loathing?

PCOS and Adolescents

- Prevent severe DUB and endometrial cancer
- Suppress ovarian androgen production and bind up the rest
- Be prepared to detect and treat diabetes

PCOS and Adolescents

- Low dose OCPs
- Any ones will do
- Norgestimate, desogestrel, drospirnone are non androgenic progestins and have theoretical advantages

Can't Take OCPs

- Cyclic progestins
- Androgen blocking therapies (spironolactone)

Cosmetic therapy

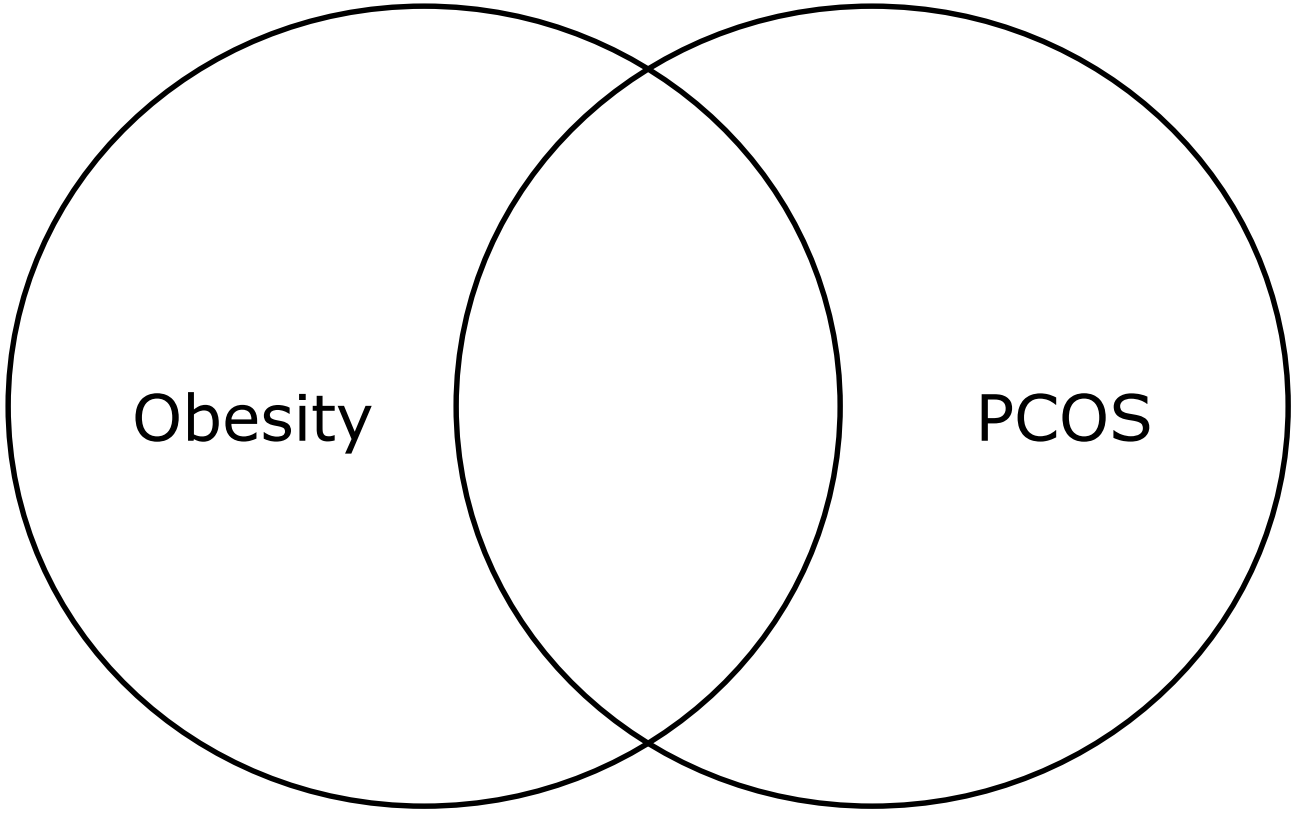
- OCPs for Acne
- Laser for Hair
- Vaniqa?

Reccomended treatment, hirsutism

- Lifestyle modification, possible insulin sensitization with obesity/insulin resistance
- OCP's and topical measures (laser/efluornithine)
- If inadequate response in 3-6 months, add spironolactone 50-100 mg BID
- Flutamide, Finasteride third line.
- Follow up is subjective, patient satisfaction, with little benefit to measuring serum androgens.

Hirsutism Treatment

- OCP's: 60-100% with improvement
  - 3-6 months before effect
  - Androgenicity of progesterone likely of little clinical importance.
    - Drosperinone has anti-androgenic properties, so theoretically superior.
- Should start an OCP (or LARC) before adding an antiandrogen in reproductive age women due to teratogenicity.
- Antiandrogens: Sprironolactone, flutamide, finasteride
  - Similar efficacy, alone or enhanced in combo with OCP's
  - Reccomended as second-line to OCP's due to increased toxicity/reproductive risk.
- For NCCAH, corticosteroid needed.



The incidence of PCOS in the normal weight population is 5%. In the obese population, the incidence is 32% (Azevedo, Archives of Internal Medicine, 2006)

Treatment for Obesity

- Diet – there is some evidence in adults that low carb is more sustainable than low fat
- A to Z weight loss Study compared: Atkins (High protein, low carb, hi fat

  Zone (balanced carb and protein, fat

  Ornish (high carb, low fat)

  Weight Watchers – (portion)

Gardiner et al: JAMA 2007;297:298-178

Lifestyle Interventions

- Lifestyle interventions: structured, medically-based programs intended to assist with weight-loss.
  - Frequent contact with Physicians, Nutritionists, Behavior counsellors.
  - Studies range from 6 to 50 visits.
  - Frequency of contact is common denominator among studies.
  - Most studies uncontrolled, but showed weight loss between 5-10% of body weight, with improvements in metabolic parameters.
- Cochrane Review (Moran et al, 2011) looked at 6 RCT's
  - Lifestyle Intervention (6-50 visits) vs minimal lifestyle counseling (3-6 visits).
  - Interventions ranged from exercise only to diet/exercise/behavioral interventions.
  - Controls all received minimal lifestyle counseling.

Treatments for Obesity: Diet

ORIGINAL CONTRIBUTION

Comparison of the Atkins, Zone, Ornish, and LEARN Diets for Change in Weight and Related Risk Factors Among Overweight Premenopausal Women

The A TO Z Weight Loss Study: A Randomized Trial

Christopher D. Gardner, PhD
Alexandre Kiazand, MD
Sofiya Alhassan, PhD
Soowon Kim, PhD
Randall S. Stafford, MD, PhD
Raymond R. Balise, PhD
Helena C. Kraemer, PhD
Abby C. King, PhD

Context Popular diets, particularly those low in carbohydrates, have challenged current recommendations advising a low-fat, high-carbohydrate diet for weight loss. Potential benefits and risks have not been tested adequately.

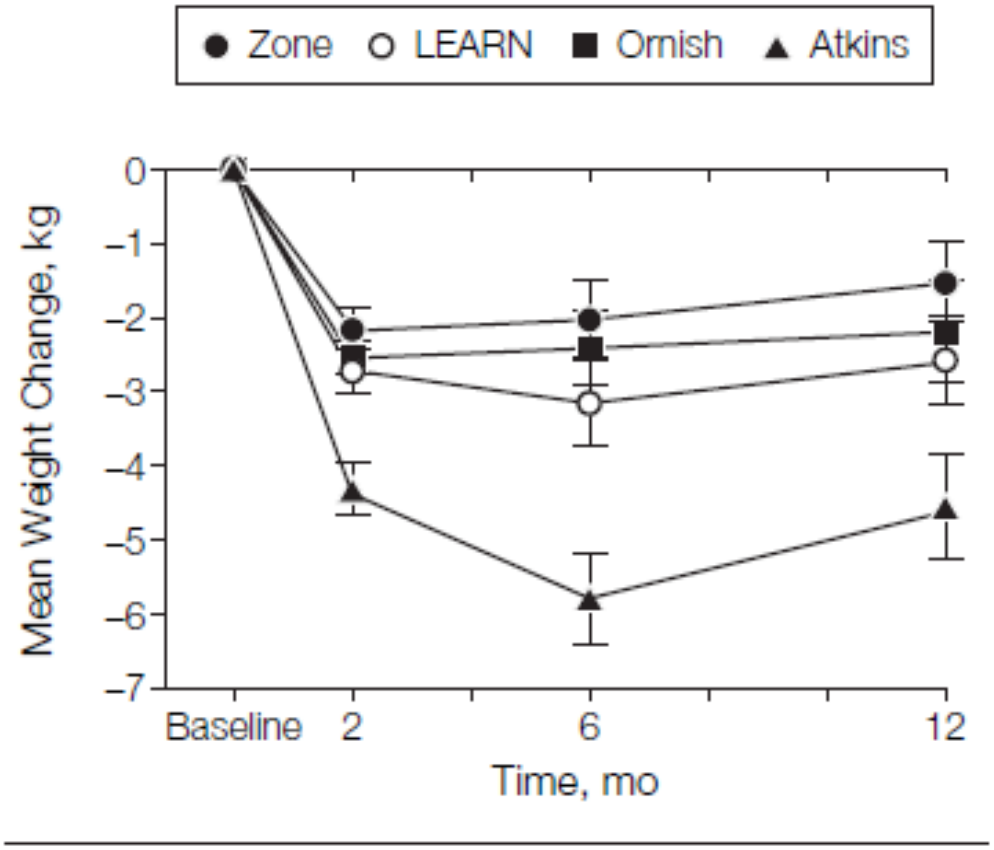
Objective To compare 4 weight-loss diets representing a spectrum of low to high carbohydrate intake for effects on weight loss and related metabolic variables.

Design, Setting, and Participants Twelve-month randomized trial conducted in the United States from February 2003 to October 2005 among 311 free-living, overweight/obese (body mass index, 27-40) nondiabetic, premenopausal women.

Intervention Participants were randomly assigned to follow the Atkins (n=77), Zone (n=79), LEARN (n=79), or Ornish (n=76) diets and received weekly instruction for 2

A TO Z PRIMARY OUTCOME.

Figure 2. Weight Change Relative to Baseline



Diet for PCOS

- Some websites and some science suggest low carb (or low glycemic index) high protein, high fat diets are more appropriate for PCOS

- Decrease glycemic load, decrease insulin, decrease androgens

Diets

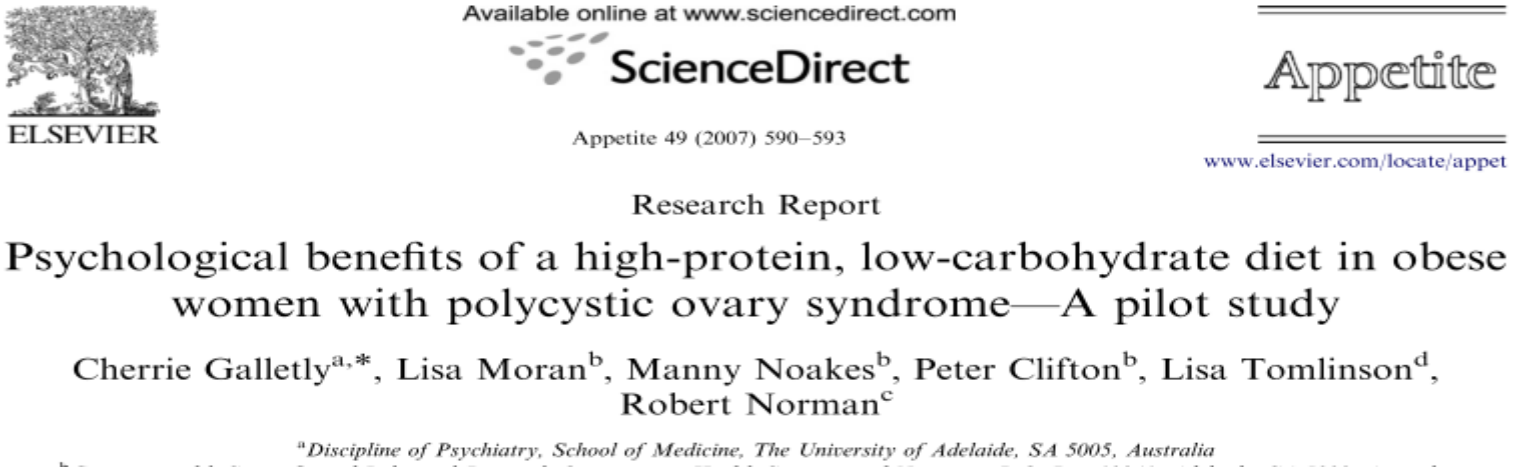
- Large (811) 2 year randomized trial of various diets with counseling
- No real difference in weight loss (about 6kg at 6 months, about 3.3kg at 2 years)
- Only calories counted….
- Best predictor of success was attendance at group sessions

Sacks et al. NEJM 2009;360:859-73

Lifestyle Changes

- Exercise (good luck) – 2400 calories out a week minimum
- Bariatric surgery is the only thing that reliably works: instant reversal of diabetes, long term success in many
- Bariatric surgery recommended for morbidly obese adolescents

Effects of low carb diet on mood in PCOS
Galletly et al, 2007, Appetite



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Research Report

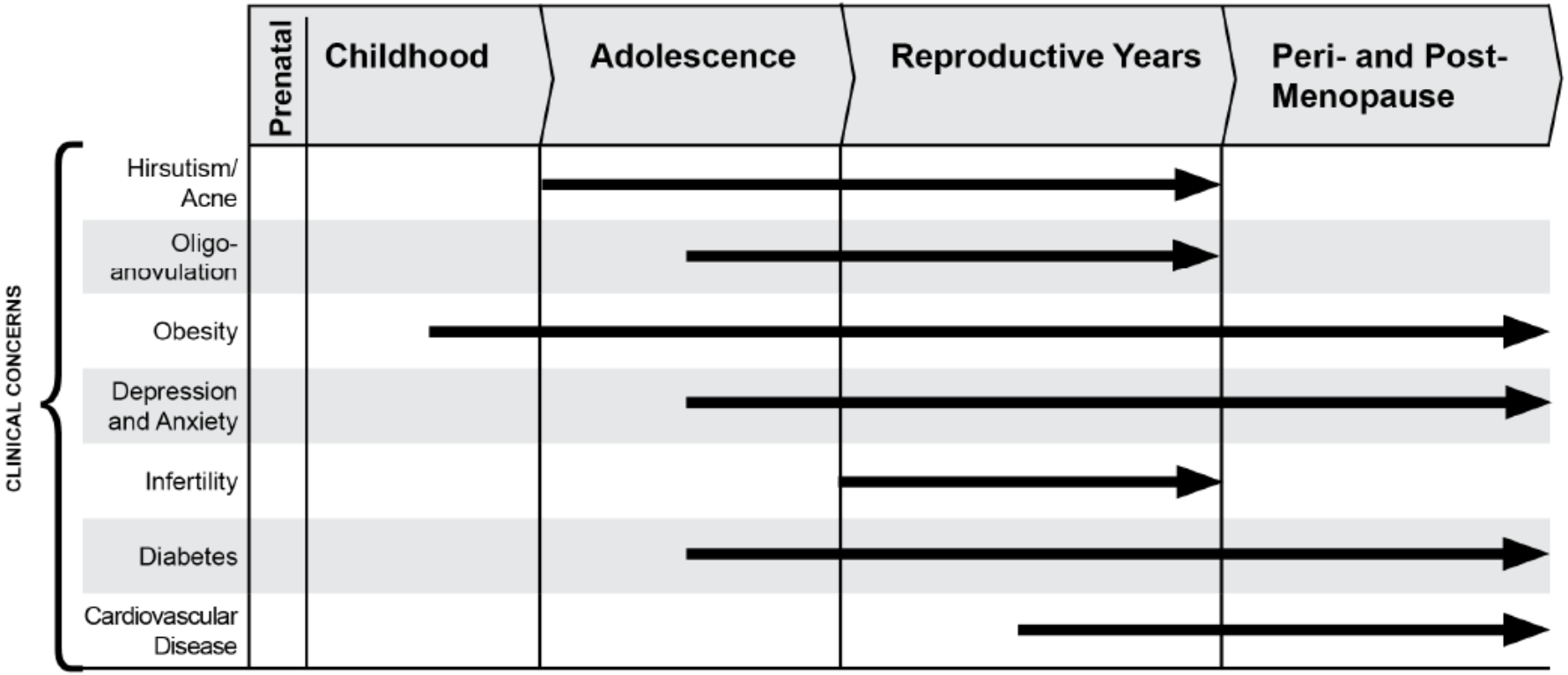
Psychological benefits of a high-protein, low-carbohydrate diet in obese women with polycystic ovary syndrome—A pilot study

Cherrie Galletly[a,*], Lisa Moran[b], Manny Noakes[b], Peter Clifton[b], Lisa Tomlinson[d], Robert Norman[c]

[a]Discipline of Psychiatry, School of Medicine, The University of Adelaide, SA 5005, Australia

- 25 overweight PCOS women randomized for 16 weeks to low carb, high protein, or low protein, high carb
- Low carb/High protein had less depression ($p<0.01$)
  - Explanation? Amino acid serotonin precursors, greater satiety/less deprivation, less reactive hypoglycemia.

Less Useful: "PCOS"
More Useful: What is patient complaint/goal?



Summary and Recommendations

- PCOS definitions/name controversial, likely to change
- Important that those treating PCOS and androgen excess disorders understand hormone pathways that can lead to PCOS.
- PCO morphology is a normal finding and indicative of excellent ovarian reserve. It is only useful in predicting ovarian hyperstimulation with IVF.
- Incidence of "PCOS" is rising due to obesity epidemic and likely due to increases in obese mothers giving birth.
- OCP's First line treatment for PCOS symptoms in non-obese, non-fertility seeking patients, but many do not like.
- Metformin may increase ovulatory regularity in PCO women with insulin resistance, but doesn't increase fertility.