

# Update in Management of Polycystic Ovary Syndrome (PCOS)

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- I have/had an affiliation (financial or otherwise) with a pharmaceutical, medical device or communications organization:
  - I have received a grant(s) or an honorarium from a commercial organization:
    - **Ferring Pharmaceuticals, EMD Serono, Merck**
  - I am currently participating in or have participated in a clinical trial within the past two years:
    - **Ferring Pharmaceuticals**
- I do intend to make therapeutic recommendations for medications that have not received regulatory approval (i.e. “off-label” use of medication).
- No financial or in-kind support was received from a commercial organization to develop this presentation

## Objectives

- Diagnostic Criteria and Work-up of PCOS
- Symptomatology Management
  - Infertility
  - Hirsutism
- Long-Term Complications
  - Diabetes
  - Endometrial Cancer

## PCOS – Diagnosis

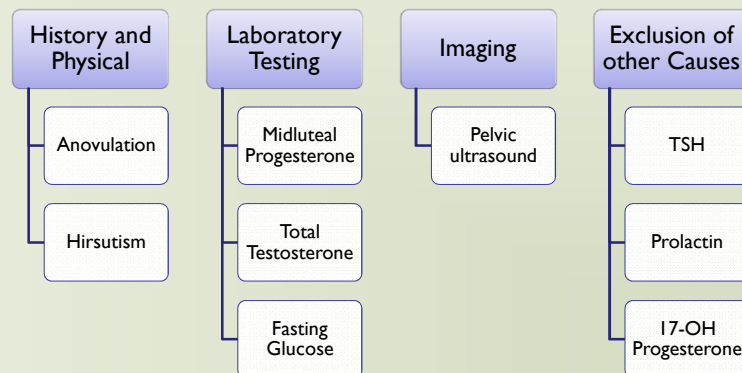
- Stein-Leventhal Syndrome
  - First Described in 1935
  - Women with amenorrhea, infertility, hirsutism, and enlarged polycystic ovaries
  - Resumption of ovulation with ovarian biopsy

Stein IF, et al. Am J Obstet Gynecol 1935. 29: 181-91

## PCOS - Diagnosis

NIH/NICHD (1990) Must meet both criteria	ESHRE/ASRM Rotterdam Criteria (2003) Must meet two of three criteria	Androgen Excess Society Criteria (2006)
Clinical and/or biochemical evidence of hyperandrogenism	Clinical and/or biochemical evidence of hyperandrogenism	Clinical and/or biochemical evidence of hyperandrogenism
Menstrual dysfunction	Oligo- or anovulation	Ovarian dysfunction or polycystic ovaries
	Polycystic ovaries	
<small>ESHRE/ASRM – European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine NIH/NICHD – National Institutes of Health/National Institute of Child Health and Human Disease</small>		

## PCOS – Diagnosis



## PCOS – Diagnosis

- What is Biochemical Hyperandrogenism
  - Free androgen index > 5
    - $FAI = (Total\ Testosterone\ (nM) / SHBG\ (nM)) \times 100$
  - Total testosterone > 1.7 nM
- What is a Polycystic Ovary?
  - Normal ovary with volume > 10 mL
  - $\geq 12$  follicles between 2- 9 mm in ovary
    - 50% normal women under age 30
  - $\geq 25$  follicles between 2-9 mm in ovary more specific

## PCOS and AMH

AMH 4.9 ng/ml – 97% specific and 92% sensitive for PCOS

Dumont A et al. *Reprod Biol and Endocrinol* 2015;13:137-47

## PCOS – Diagnosis Take Home Points

- Making diagnosis helpful but not critical
  - More important to exclude other etiologies
    - Thyroid dysfunction
    - Hyperprolactinemia
    - Congenital Adrenal Hyperplasia
    - Androgen secreting neoplasms (T usually > 2-fold upper range)
- Ultrasound helpful but not critical
  - Must be endovaginal
  - Request ovarian volume and number of follicles per ovary

## PCOS - Infertility

- Confirm Oligo-or anovulation
  - Menstrual cycle intervals > 35 days
  - Midluteal progesterone < 10 nM
- Semen testing recommended
  - Repeat if abnormal
  - Refer if total motile count (TMC) persistently < 10 million
    - $TMC = (\text{Volume (mL)} \times \text{Motility (\%)} \times \text{Conc (10}^6/\text{mL)})/100$
- Tubal patency testing optional - based on risk factors

## PCOS – Preconception Interventions

- Obese (BMI > 29) age 18-39 infertile women
- RCT to lifestyle intervention for 6 months before treatment vs immediate fertility treatment
- Primary outcome
  - Vaginal birth of healthy singleton at term within 24 months of randomization

Mutsaerts MAQ et al. N Engl J Med 2016;374:1942-1953

## PCOS – Preconception Interventions

	Intervention Group N = 289	Control Group N = 285	RATE RATIO
Anovulation	128 (44.3%)	141 (49.5%)	
Vaginal Birth Healthy Live Singleton	76 (27.1%)	100 (35.2%)	0.77 (0.60-0.99)
Live Birth	123 (43.9%)	153 (53.9%)	0.82 (0.69-0.97)
Natural Conception	73 (26.1%)	46 (16.2%)	1.61 (1.16-2.24)
Ovulation Induction	34 (12.1%)	64 (22.5%)	0.54 (0.37-0.79)

Mutsaerts MAQ et al. N Engl J Med 2016;374:1942-1953

## PCOS – Preconception Interventions



Van Oers AM et al. Hum Reprod 2016;31:2704-13

## PCOS - Infertility

### **For Primary Care Provider**

- Ovulation Induction
  - Metformin (off-label)
  - Clomiphene (on-label)
  - Letrozole (off-label)

### **For Fertility Specialist**

- Ovulation Induction
  - Gonadotropins
  - Laparoscopic Ovarian Drilling
- IVF

## PCOS-Ovulation Induction

- Metformin
  - Oral biguanide/insulin sensitizer
  
  - May be used alone, or in conjunction with clomiphene
  
  - Initial studies
    - Ovulation rates 90% with metformin and clomiphene
    - Ovulation up to 75% with metformin and clomiphene in clomiphene resistant patients

Nestler JE et al, 1998. N Engl J Med; 336: 1876-1880

Vandermolen DT et al, 2001. Fertil Steril; 75: 310-315

## PCOS-Ovulation Induction

- Clomiphene Citrate
  - Selective Estrogen Receptive Modulator (SERM)
  
  - Shown to induce ovulation in 1961
  
  - Ovulation rates of 70-80%
  
  - Pregnancy rates of 30-40%
  
  - Twin pregnancy rates 5-7%



## PCOS-Ovulation Induction

- Letrozole
  - Aromatase inhibitor
  - Adjuvant treatment estrogen receptor positive breast cancer
  - First described in 2000 for ovulation induction
  - Number of small studies showing similar success to clomiphene

Mitwally MF et al. Reprod Technol 2000. 10:244-47

## PCOS – Ovulation Induction

- Practical questions for the Family Physician/OBGYN
  - What drug is “best”
  - How do I use the drugs
  - How do I monitor for effectiveness
  - How should I counsel my patients

## PPCOS I -Ovulation Induction

	Clomiphene N = 209	Metformin N = 208	Combination therapy N = 209
Ovulation	49.0%	29.0%	60.4%
Conception	29.7%	12.0%	38.3%
Pregnancy	23.9%	8.7%	31.1%
Twins	4.0%	0%	3.1%
Live Birth	22.5%	7.2%	26.8%

Legro R et al., N Eng J Med; Feb 8, 2007

## PPCOS 2 -Ovulation Induction

	Clomiphene N = 376	Letrozole N = 374	P value
Ovulation	48.3%	61.7%	<0.001
Conception	35.8%	46.5%	<0.007
Twin birth	6.9%	3.9%	0.49
Live Birth	19.1%	27.5%	0.007

Legro R et al., N Eng J Med; July 10, 2014

## PPCOS – Ovulation induction

How to Use the Ovulation Induction Medications		
Drug	Letrozole	Clomiphene
Initial dose	2.5 mg daily	50 mg daily
Dosing regimen	Cycle day 3-7 (5 days)	
Recommended maximum cycles	6 ovulatory cycles	
Confirmation of ovulation	Cycle day 21-23 progesterone > 10 nM	
Indication for dosage increase	Absence of ovulation	
Dosage increase	2.5 mg daily increment	50 mg daily increment
Maximal daily dose	7.5 mg daily	150 mg daily

## PCOS – Ovulation Induction

- **Practical Points**
  - Remind intercourse timing – one of:
    - Ovulation predictor kits
      - Day before and day of ovulation best chance of conception
      - Kits typically positive 1-2 days before ovulation
      - 7% false positive rate
    - Intercourse every other day from cycle day 10-20
      - Greater frequency neither helpful or harmful
  - Multiple pregnancy rate
    - 4-7% twins
    - Higher order multiples <1%

## PCOS – Persistent Anovulation

- Refer to Fertility Specialist
- Management Options
  - Addition of Metformin to oral ovulation induction agents
  - Laparoscopic ovarian drilling
  - Gonadotropins
  - IVF

## PCOS - Hirsutism

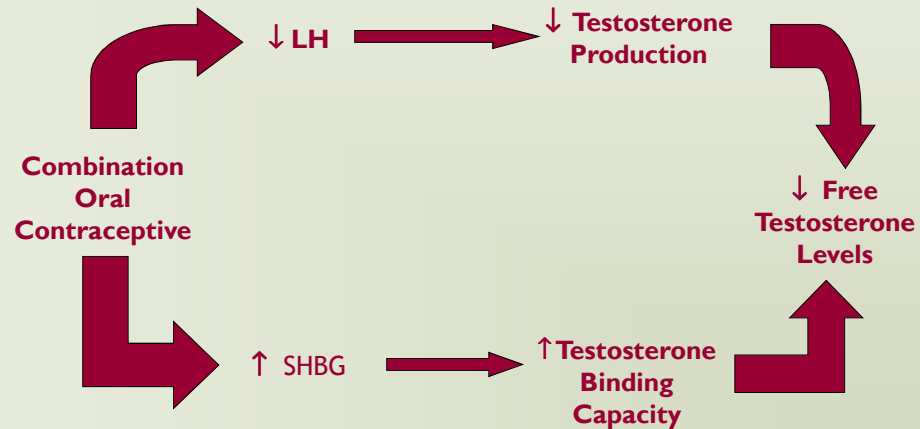
## PCOS - Hirsutism

- Therapy includes
  - Androgen suppression
  - Peripheral androgen blockade
  - Mechanical/cosmetic destruction of unwanted hairs
- Hormonal/Medical therapy requires > 6 months
- Removal of unwanted hairs most effective after medical therapy

## PCOS - Hirsutism

- Oral Contraceptive Pill (OCP) first line treatment
- No clinical differences between OCPs for hirsutism
- Yaz/Yasmin have theoretical advantages
  - Drospirenone 3 mg has spironolactone activity
- Diane 35 has theoretical advantages
  - Cyproterone acetate an antiandrogen

## PCOS - Hirsutism



## PCOS - Hirsutism

- Spironolactone
  - Aldosterone-antagonist, mild-diuretic
  - Better effect seen with dose 100-200 mg daily
    - After time, can lower dose to maintenance 25-50 mg daily
  - Hyperkalemia risk
    - Use with caution in elderly and diabetic

## PCOS - Hirsutism

Van Zuuren EJ et al. *Cochrane Database Syst Rev.* 2015;4:CD010334

## PCOS – Diabetes IGT

DM2

Lisa J. Moran et al. *Hum. Reprod. Update* 2010;16:347-363

## PCOS - Diabetes

- Screening for DM2 for PCOS
  - BMI > 30
  - BMI > 25 for Asian population
  - Acanthosis nigricans
  - Family History of GDM or DM2
- Fasting glucose vs 75 g-OGTT

## PCOS - Diabetes

- Prevention of Type 2 Diabetes
  - RCT of 3234 people at risk for DM2
    - Fasting glucose 5.3-6.9 mM or
    - Glucose 7.8-11 mM - 2 hr post 75g glucose load
  - Three groups
    - Lifestyle Modification (goal of 7% weight loss and 150 minutes physical activity/week)
    - Metformin 850 mg po bid
    - Placebo

Diabetes Prevention Program Research Group; N Engl J Med; 346: 393-403



## PCOS and Diabetes

Diabetes Prevention Program Research Group; N Engl J Med; 346: 393-403

## PCOS and Endometrial Cancer

## PCOS and Endometrial Cancer

- Risk Factors for Endometrial Cancer (EC)
  - Obesity
  - Unopposed Estrogen
  - Infertility
  - Hypertension
  - Type 2 Diabetes
- 2.9- fold greater risk of EC with PCOS
- 9% Absolute Lifetime Risk

Barry JA et al. Hum Reprod Update. 2014; 20:748-58.

Haoula Z et al. Hum Reprod 2012; 27:1327-31

## PCOS and Endometrial Cancer

- Preventative measures for EC in PCOS not known
- OCP treatment of menstrual irregularity protective against endometrial cancer
  - 50% reduction in ever users of OCP
  - Greater risk reduction with longer OCP use
  - Risk reduction lasts even > 20 years after discontinuing
- Levonorgestrel IUS may have similar reduction risk

Cibula D et al. Hum Reprod Update. 2010; 16:631-50.

Bahamondes L et al. Hum Reprod Update 2015 21:640-51

# PCOS and Endometrial Cancer

Chandra V et al. Gynecol Oncol. 2016 Jan; 27(1): e8.

*QUESTIONS?*