

# Integrative Medicine for Polycystic Ovarian Syndrome

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Birgit Rakel, MD  
Assistant Professor  
Brind Center for Integrative Medicine  
SKMC  
Thomas Jefferson University



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Disclosures: None

# Objectives

- An Introduction to PCOS
- Conventional Treatment
- Integrative Approaches



# Overview

- Epidemiology
- Pathogenesis/ Pathophysiology
- Clinical Manifestations
- Conventional Treatments
- Integrative Approaches

## Epidemiology

- Polycystic Ovarian Syndrome (PCOS) is a disorder of the endocrine system caused by hormonal imbalance
- It is the most common premenopausal endocrine disorder in women
- PCOS typically affects 5-10% of women of childbearing age
- Symptoms often begin in puberty
- PCOS is the leading cause of infertility

Avery JC, Braunack-Mayer AJ. Information needs of women diagnosed with PCOS. BMC Women's Health 2007

## Epidemiology

- Heterogeneous complex genetic trait of unclear etiology
- Environmental factors interact to foster the development of the disorder
- Fully expressed it causes:
  - a) ovulatory dysfunction
  - b) androgen excess
  - c) polycystic ovaries

First described in 1935 by Stein and Leventhal

## Epidemiology

- Family History

1<sup>st</sup> degree relative with PCOS  
Diabetes

- History

Diabetes (Type I, Type II, Gestational Diabetes)  
Obesity



## Epidemiology

- Valproic acid which is used in epilepsy and in bipolar disease is associated with a 1.95 fold increased risk of developing PCOS 2nd to weight gain and development of insulin resistance

Meta analysis of PCOS in women taking Valproate for epilepsy

Hu et al, J Epilepsy research 2011 Nov

# Epidemiology

- History of Premature Adrenarche

Onset of androgen-dependant body changes like axillary and pubic hair, body odor and acne before the age of 8

20% develop PCOS

Kousta et al. Premature Adrenarche leads to PCOS; Am Acad Sci 2006 Dec

## Epidemiology

- Mexican- American ethnicity
- 13% = twice the prevalence reported in other populations

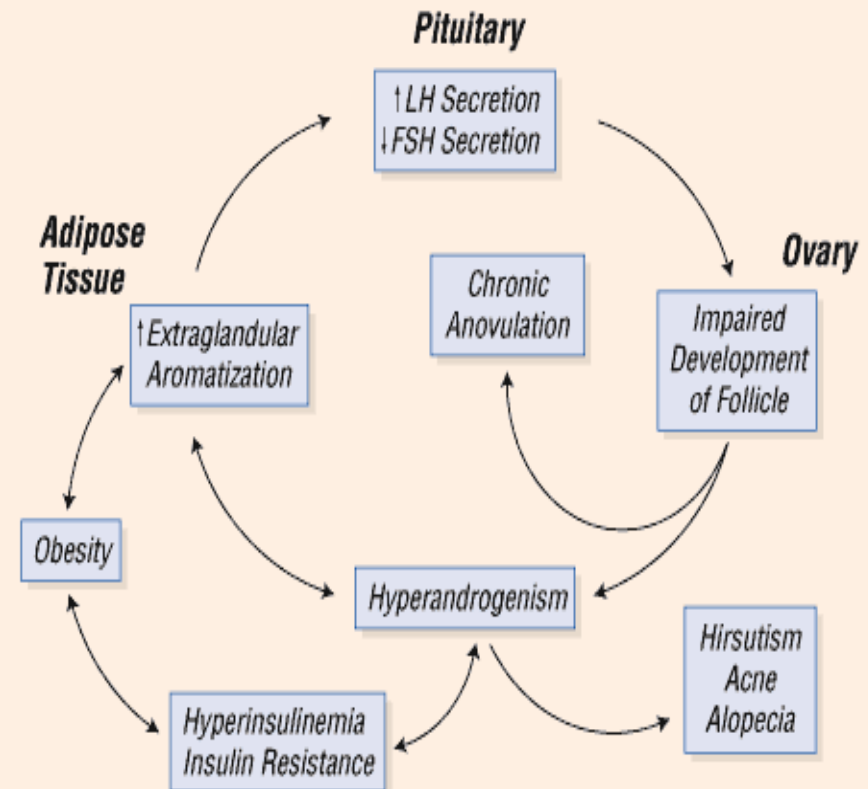
Chandrika et al. Ethnic specific PCOS and variation in prevalence, Expert Rev Endocrin August 2013

# Pathophysiology

- Excess production of LH by pituitary
- Abnormal function of the hypothalamic-pituitary-ovarian axis
  - Increased androgen and decreased FSH
  - Prevention of egg release from ovary
  - Egg remains in ovary and develops into cyst

**Figure 1**

## Pathophysiology of Polycystic Ovary Syndrome



Source: Rasgon NL (2001)



## Pathophysiology Cardiovascular Risk Factors

- Hyperinsulinemia stimulates IGF 1 contributes to smooth muscle hypertrophy
- Hyperandrogenism contributes to endothelial dysfunction associated with atherosclerosis
- Elevated insulin causes sodium retention which enhances the production of angiotensin II

Cho et al. Cardiometabolic aspects of PCOS .  
Vasc Health Risk Manag 2007

# Pathophysiology Inflammatory Risk Factors

- Fat cells are metabolically active and secrete inflammatory agents
- TNF
- IL6
- Adiponectin

Stimulating the production of CRP and hs-CRP

Cho et al. Cardiometabolic aspects of PCOS .  
Vasc Health Risk Manag 2007

## Clinical Manifestations

- Amenorrhea
- Acne
- Abnormal hair growth patterns
  - Alopecia and /or Hirsutism
- Weight gain
  - Excess visceral fat accumulation
- Insulin resistance

# Evaluation After Initial Diagnosis

## Metabolic risk assessments

- Insulin resistance/Type II Diabetes
  - Fasting blood sugar and HbA1C or oral GTT
- Heart disease
  - Patients with PCOS are at increased risk of developing Obesity, Hypertension, Hyperlipidemia and CAD
  - It is important to monitor weight, lipids, BP frequently



## Further Screening After Initial Diagnosis

- Depression and anxiety
- Eating disorder
- Sleep apnea

Dokras, A. Mood and anxiety disorders in women with PCOS.  
Steroids 2012; 10(77):338-41.

# Complications

## Infertility and Recurrent Miscarriages

- Infertility
  - Patients with PCOS have poorly developed follicles within their ovaries. These follicles cannot be released during the menstrual cycle
- Recurrent miscarriages
- Prevalence of recurrent miscarriages as high as 40%

Sheehan MT , PCOS: Diagnosis and management.  
Clin Med Res 2004

Rai R et al .Polycystic Ovaries and recurrent miscarriages. Oxford J  
Human Reproduction 1999

## Complications Endometrial Cancer

- 3 fold increased endometrial cancer risk
- 9% lifetime risk
- Oral contraceptives will reduce risk by 50-70 %

Dumesic et al .Cancer risk and PCOS.Steroids;2013

## Complications Endometrial Cancer

- The exact mechanism of action leading from estrogen overexposure to hyperplasia is not fully understood
- Due to amenorrhea, the endometrial lining hypertrophies over time leading to endometrial hyperplasia
- Increase in endogenous estrogen PCOS/Obesity/Diabetes leads to unopposed estrogen stimulation

Shan W et al. Hyperinsulinemia is associated with endometrial hyperplasia. Gyn Oncol, 2014



# Conventional Treatment

- Metformin
- OCP
- Spironolactone

# Conventional Treatment

## Metformin



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- Oral diabetes medication: Dosage 500 mg 1-2 x day
  - Affects expression of glycolase I
  - Stimulates AMPK phosphorylation
  - Decreases phosphorylation of S6
- Off Label Therapy:
  - No prospective, randomized, placebo-controlled, double-blind studies to support it's use
- “complete knowledge of MOA in PCOS has not yet been achieved”

Motta, AB et al. Mechanism involved in Metformin action in Tx of PCOS  
.Curr Pharm 2009

Campagnoli C et al. Lifestyle and Metformin for the prevention of  
endometrial pathology. Gyn Endocrinology 2013

# Conventional Treatments

## Oral Contraceptive Pills

- Ethinyl Estradiol with Drospirenone
  - Ensures cyclical shedding of the endometrium
  - Helps regulate menstrual cycle
  - Treats acne
- Progestins
  - For women who are unable to take estrogen replacement, progestins help to build the endometrial lining. The endometrial lining then sheds, similar to a menstrual cycle

## Conventional Treatment Spironolactone

- Potassium-sparing diuretic
  - Lowers androgen levels
  - Is often used in conjunction with OCPs to treat acne, alopecia and hirsutism
- Spironolactone 50-100 mg daily for at least 6-12 month
- Improves hirsutism by up to 22%
- FDA Black Box warning reads:  
“Spironolactone has been shown cause tumors in rats.  
Unnecessary use of this drug should be avoided”  
Journal of Family Practice April Vol 64, April 2015



## Conventional Treatment Infertility

- Clomiphene citrate
- Selective Estrogen Receptor Modulator
  - Stimulates pituitary to release FSH
- Brown J et al. Clomiphene for ovulation induction in PCOS;Cochrane Database Syst Rev 2009

## Why Integrative Therapies?

- Conventional treatments can lead to:
  - Intolerable side effects
    - Metformin > nausea and vomiting
    - Spironolactone > tumors
  - Can be not as effective
    - Up to 30% of women with PCOS on clomiphene fail to respond

# Lifestyle Changes Diet and Exercise

THE ONLY BAD  
WORKOUT IS THE  
ONE THAT DIDN'T  
HAPPEN

REUVEK TOADREVE.TUMBLR



**Food** is the  
most abused  
anxiety drug.  
**Exercise**  
is the most  
underutilized  
antidepressant.



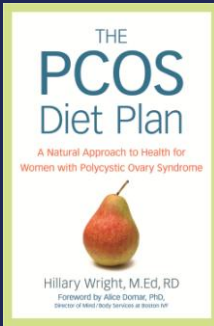


## Diet

- Patients with PCOS should eat an anti-inflammatory diet fruits, vegetables and whole grains
  - Avoid red meat and dairy
  - Increase intake of whole soy foods, which contain isoflavones may help regulate hormonal imbalance
  - Nuts ,Lentils and Soy are rich in L-arginine which improve fertility
  - Flaxseed /Lignans increase SHBG, lower testosterone
  - Low glycemic index diet to prevent insulin resistance

Ravn et al. Overweight in PCOS .Endocrinology 2013





## Diet

## Weight Loss

- Low-carb ,high protein diets help promote weight loss
- Weight loss reduces hyperinsulinemia, insulin resistance and subsequently hyperandrogenemia
- Helps to stimulate ovulation and improves fertility rates

Ravn et al. Overweight in PCOS .Endocrinology 2013

Moran L J et al .Dietary Composition in Restoring Reproductive Health and Metabolic Physiology in women with PCOS.J of Clin Endo and Metab 2013

## Exercise

**WARNING:**  
EXERCISE HAS  
BEEN KNOWN TO  
CAUSE HEALTH  
AND HAPPINESS

LoveThePc.com

- Multiple studies on correlation of Metabolic syndrome, PCOS and exercise
- Improves insulin sensitivity

Cho et al. Cardiometabolic aspects of PCOS.  
Vasc Health Management 2007

## Supplements

- Chromium
- L-Arginine
- N-acetyl cysteine
- D-Chiro-Inositol
- Alpha Lipoic Acid
- Vitamin D

## Supplements Chromium

- 1,000 mcg daily
- May help to improve glucose tolerance in women with PCOS

Lydic ML et al .Chromium piccolinate improves insulin resistance in obese patients with PCOS.Fertil Steril 2006



## Supplements L-Arginine

- 1,600mg daily
- Helps to improve ovarian function in women with PCOS

Masha A et al .Prolonged treatment with NAC and L-Arginine restores gonadal function in patients with PCOS.J Endocrin Invest 12/2009

## Supplements N-acetyl cysteine

- Amino acid
- 600mg 2x day
  - May increase ovulation and fertility
  - Improves insulin level

Fulghesu AM et al

NAC treatment improves insulin resistance in women with PCOS. *Fert Steril* 2002

Rizk AY et al NAC as adjuvant to clomiphene in clomiphene resistant patients with PCOS. *Fert Ster.* 2005

## Supplements

# D-chiro-Inositol

- Occurs naturally in the body and is found in citrus fruit and beans
- It appears to be low in women with PCOS
- 1,200 mg daily
- Decreases insulin resistance
- Decreases androgen concentration
- Improves ovarian function

Nestler et al. Ovulatory and metabolic effects of D- chiro Inositol in PCOS.  
Engl J Med 1999

## Supplements

### Alpha Lipoic Acid

- ALA 400 mg 2xday
- Improves Insulin sensitivity

Masharani U et al .Effects of ALA in lean non-diabetic women with PCOS.J of Diabet Science 2010



## Supplements Vitamin D

- Has been linked to Insulin resistance, inflammation, obesity, Type II Diabetes and cardiovascular disease
- All commonly found in PCOS
- Helps lower 2 hour insulin level and has a protective effect on blood pressure
- Improves ovulatory function and decreases androgen concentration

High-dose vitamin supplementation and measures of insulin sensitivity in PCOS. Raja-Khan,N et al. Fertil Steril June 2014

Thys -Jacobs et al. Vit D and Calcium dysregulation in PCOS.Steroids 1999

## Botanicals for Hormonal Imbalance

- *Vitex agnus-castus*
- *Cimicifuga Racemosa*
- *Paeonia Lactiflora*
- *Cinnamomum Cassia*
- *Glycyrrhiza Uralensis*
- *Serenoa Repens*
- *Mentha Spicata Labiatae*



## Botanicals

### Chaste Tree

### Vitex Agnus-Castus

- Pre-clinical and clinical evidence for lowered prolactin, improved menstrual regularity and treatment of infertility
- Shown in 3 placebo-controlled RCT
- 20-40 mg per day

Meier B, Berger D, Hoberg E, Sticher O, Schaffner W:  
Pharmacological activities of Vitex agnus-castus extracts in vitro.  
*Phytomedicine* 2000, 7(5):373-381.

Kamel HH. Role of phyto-oestrogens in ovulation induction in women with polycystic ovarian syndrome. *Eur J Obstet Gynecol Reprod Biol* 2013; 168(1):60-63.





## Botanicals

### Black Cohosh

### *Cimicifuga Racemosa*

- Lowered LH in pre-clinical and clinical studies
- Increased fertility alone and in conjunction with clomiphene in RCTs
- Women receiving combined therapy (clomiphene 150 mg plus *Cimicifuga racemosa* 20 mg per day) were 43.3% more likely to become pregnant compared to 20.3% for women receiving only clomiphene

Shahin AY et al. Adding cimicifuga Racemosa to Clomiphene induction cycle Improves pregnancy rates ;Gyn Endo 2014

Sierra O, Bodinet C, Kolba S, Wulf M, Vollmer G: Anti estrogenic activities of Cimicifuga racemosa extracts. J Steroid Biochem Mol Biol 2002



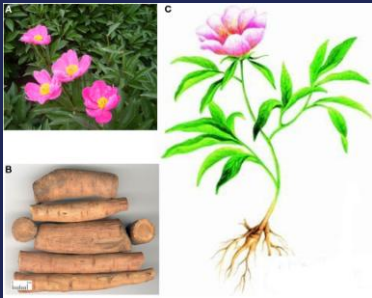


## Botanicals

### Chinese Peony and Chinese Licorice *Paeonia Lactiflora* and *Glycyrrhiza Uralensis*

- Evidence in 1 lab and 2 clinical studies
- Reductions in free and total testosterone
- 75 grams per day for 24 weeks and 5-10 grams per day for 2-8 weeks respectively

Arentz S, et al. Herbal medicine for the management of PCOS, associated oligo/amenorrhoea and hyperandrogenism; BMC Comp and Alt Med 2014



## Botanicals

### Chinese Peony and Cinnamon

### *Paeonia Lactiflora* and *Cinnamomum Cassia*

- Japanese Preparation called Unkei-to
- 1 clinical trial of 157 infertile women aged 17-29
  - Subgroup of 42 women with PCOS /amenorrhoea
- Treatment with Unkei-to 7.5 grams per day for eight weeks
- Showed significant reductions of LH in the PCOS subgroup of 49.7%
- Ovulation confirmed in 30 of 42 amenorrheic women

Ushiroyama T et al .Osaka Medical College. Effects of Unkei-to on endocrine function and ovulation in women with high LH levels.J Reprod Med 2001



# Botanicals

## Cinnamon

### Cinnamomum Cassia

- Placebo controlled RCT with 45 women at Columbia University
- Overweight women with oligo/amenorrhoea and PCOS
- 1,500 mg Cinnamon for 6 months
- Decreased testosterone, LH and insulin resistance

Kort, D MD. Preliminary evidence that cinnamon improves menstrual cycle in PCOS. Am J Obstet Gyn Nov 2014





## Botanicals Saw Palmetto *Serenoa Repens*

- Dosage 320 mg per day
- Inhibits 5-alpha-reductase
- Reduces conversion of testosterone to di-hydrotestosterone
- Helps in reducing acne, excess facial hair and male pattern hair loss

Tori Hudson ND. Women's Encyclopedia of Natural Medicine





## Botanicals

### *Mentha Spicata* Labiatae

### Spearmint

- 2 cups day of spearmint tea decreased free testosterone and facial hair growth

Akdogan M et al. Effect of spearmint teas on androgen levels in women with hirsutism

Phytother Res 2007

Grant P. et al. Spearmint herbal tea has significant anti-androgen effects in PCOS

Phytother Res 2009



## Acupuncture

- Can help increase ovulation by lowering sympathetic nervous system tone
- Increase in blood flow to the ovaries and thus improving ovulation
- Decrease circulating testosterone and improves menstrual cycles
- Improves Infertility

Stener-Victorin et al effects of electro-acupuncture on ovulation in women with PCOS. Acta Obstet Gynecol Scand 2000

Johansson et al. Acupuncture for ovulation induction in PCOS.  
Am J Physiol Endocrinol Metab 2013

## Mind Body Therapies

- Mindfulness Based Stress Reduction and PCOS

Dr Nazia Raja-Khan Endocrinologist

Assistant Professor at Penn State University

Fellow Integrative Medicine

Principal Investigator of NIH funded study on effects of mindfulness in women with PCOS



## Mind Body Therapies

- Visualization
  - Hypnosis
  - Biofeedback
  - Yoga
  - Psychotherapy
- 
- No data specific to PCOS available
  - Reduction inflammation
  - Reduction anxiety and depression
  - Balance autonomic nervous system





## Conclusions

- PCOS is a complex syndrome that has significant clinical implications for reproductive, metabolic and psychological health
- PCOS can take a physical and emotional toll on women
- Take an individualized approach to treatment depending on the severity of symptoms
- Use of integrative approaches may reduce morbidity associated with the disease
- May help increase fertility
- Improvement in quality of life