

Polycystic Ovarian Syndrome (PCOS)

Christina Inteso, Pharm.D., BCACP
 Community Health Network, Indianapolis, IN
 Clinical Pharmacy Specialist- Ambulatory Care
 August 1, 2019

Disclosure Statement

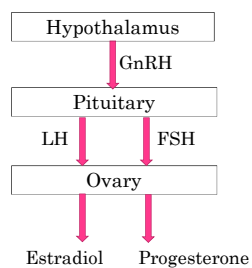
- The presenter has no conflicts of interest to disclose

Learning Objectives

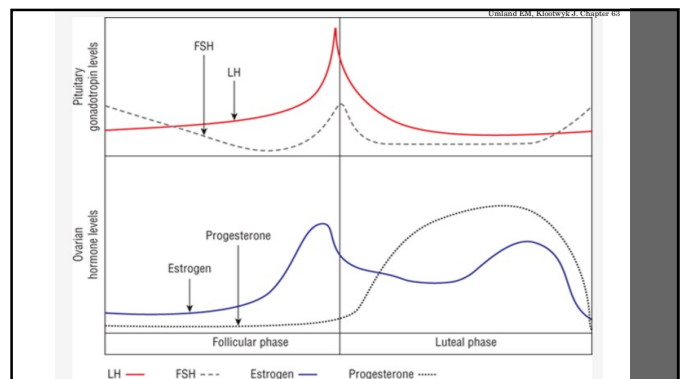
- State the PCOS diagnostic criteria
- Select a treatment regimen for a patient with PCOS
- Identify the presence of PCOS complications and explain how they are treated

Menstrual Cycle Overview

Menstrual Cycle



GnRH: Gonadotropin-releasing hormone
 LH: Luteinizing hormone
 FSH: Follicle-stimulating hormone



PCOS

What is it?

- A condition that causes irregular menstrual periods
- Accumulation of multiple small follicles/cysts in the ovaries
- Imbalance of estrogen, progesterone, LH, and FSH
- Elevated androgen levels

LH: luteinizing hormone
FSH: follicle-stimulating hormone

Etiology

- Etiology unknown
 - No specific environmental substance has been identified as the cause
- Insulin resistance may contribute
 - Obesity may amplify the effects of PCOS
 - Approximately 20% of women with PCOS are not obese
- PCOS occurs in about 6 to 8% of women
 - Most common endocrine abnormality in US women of reproductive age

Pathophysiology

- Endocrine disturbances
 - Inappropriate secretion of gonadotropins
 - Increased LH pulse frequency and amplitude
 - Follicle development is impaired due to premature stimulation of LH
 - May stimulate ovary to produce excess androgen
 - FSH secretion is normal or decreased
- Defective sex steroid synthesis or metabolism
 - Increased LH, ACTH, and insulin increase androgen production

LH: luteinizing hormone
FSH: follicle-stimulating hormone
ACTH: adrenocorticotropic hormone

Pathophysiology

- Metabolic disorder
 - Insulin resistance
 - Defect in insulin receptor signaling
 - Androgen production may worsen insulin resistance
 - Hyperinsulinemia occurs due to insulin resistance

Symptoms

- Amenorrhea or oligomenorrhea
- Hirsutism
- Obesity
- Infertility
- Acne
- Androgenic alopecia
- Acanthosis nigricans



Amenorrhea and Oligomenorrhea

Amenorrhea

- Primary- absence of menses by age 16 in the presence of normal secondary sexual development or the absence of menses by age 14 in the absence of normal secondary sexual development
- Secondary- absence of menses for 3 to 6 months in a previously menstruating woman

Oligomenorrhea

- Infrequent menstrual periods
 - Fewer than 6 to 8 per year

Amenorrhea and Oligomenorrhea

- Treatment goals
 - Restore normal menstrual cycle
 - Preserve and prevent bone loss
 - Restore ovulation
 - Improve fertility
- Non-pharmacologic therapy
 - Weight gain or weight loss
 - Psychotherapy

Diagnosis

1990 National Institutes of Health	2003 Rotterdam	2009 Androgen Excess and PCOS Society
Hyperandrogenism (clinical or lab)	Hyperandrogenism (clinical or lab)	Hyperandrogenism (clinical or lab)
Oligomenorrhea or amenorrhea	Oligomenorrhea or amenorrhea	Ovarian dysfunction
	Polycystic ovaries	

Polycystic Ovaries



Normal ovary

Polycystic ovary

Diagnosis

DHEA-S: Dehydroepiandrosterone-sulfate
TSH: thyroid stimulating hormone

Test	Reference Range	Rule Out
Testosterone	0.1 to 6.4 pg/ml	Androgen-secreting tumor
DHEA-S	32 to 380 ug/dl	Adrenal tumor
TSH	0.5 to 4 mIU/L	Hyper- or hypo- thyroidism
Prolactin	2 to 29 ng/ml	Hyperprolactinemia
17-hydroxyprogesterone	20 to 100 ng/dl prior to ovulation 100 to 500 ng/dl during luteal phase	Adult-onset congenital adrenal hyperplasia
Cortisol	10 to 20 ug/dl	Cushing Syndrome
Dexamethasone suppression	Serum cortisol < 1.8 ug/dl	Cushing Syndrome

Think, Pair, Share

- A 28 year old female who presents with complaints of light, infrequent periods and occasional acne. Her BMI is 28.8 kg/m², A1C 5.9%, BP 122/76 mmHg. Prolactin is elevated and TSH is elevated at 9.783 mIU/L. She has not had an ultrasound completed yet. Does she meet diagnostic criteria for PCOS?

No, she does not have 2 out of 3 criteria and need to rule out other causes

- Are there other labs or symptoms you would want to ask about?

Testosterone, DHEA-S, 17-hydroxyprogesterone, cortisol

Further questions about periods, acne, hirsutism, alopecia, etc

BMI: body mass index
BP: blood pressure
TSH: thyroid stimulating hormone

Think, Pair, Share

- After the holidays and being inactive all winter, her BMI has increased to 30 kg/m², her prolactin and TSH levels are normal, as she is being treated with levothyroxine. She is now complaining of increased hair growth in various parts of her face, back, forearms, and stomach. Does she meet the diagnostic criteria for PCOS?
- Yes - has oligomenorrhea and clinical hyperandrogenism due to hirsutism

BMI: body mass index
TSH: thyroid stimulating hormone

Medications

Treatment

- Largely based on symptoms
- Combination hormonal contraceptives
- Progestin
- Insulin-Sensitizing Agents
- Clomiphene
- Aromatase Inhibitors
- Injectable gonadotropin
- Spironolactone
- Eflornithine cream

Hormonal Contraception

- Contraception is first-line if not wanting to get pregnant
- Prevents recurrent anovulatory bleeding
- Benefits
 - ↑ sex hormone-binding globulin (SHBG)
 - ↓ free androgen levels
 - Prevents pregnancy
 - Regulates cycle
 - No effect on insulin resistance

Hormonal Contraception

- No consensus on which contraceptive is the best for PCOS
 - Use ≤ 35 mcg ethinyl estradiol
- Combination estrogen and progesterone
 - Low-doses are most frequently used for long-term management and are recommended for primary treatment
 - Anti-androgenic progestones are effective for acne and hirsutism but suppress ovarian androgen production and increase SHBG

Progestins

- Medroxyprogesterone acetate 150 mg IM every 12 weeks (Depo-Provera)
- Medroxyprogesterone acetate 104 mg SC every 12 weeks (Depo-subQ Provera)
 - AE: irregular menses and amenorrhea
- Medroxyprogesterone acetate 10 mg daily PO for 10 days (Provera)
 - AE: edema, anorexia, depression, insomnia, weight gain or loss, increase in total and LDL cholesterol, decrease HDL cholesterol
- Progestin IUDs associated with abnormal bleeding patterns in 50-89% of users

AE: adverse effects
LDL: low-density lipoprotein
HDL: high-density lipoprotein
IUD: intrauterine device

Progestins

- Can be used in women with contraindications to estrogen or if side effects are unacceptable
- No studies have evaluated long-term use of depot-MPA and intermittent oral MPA to treat hirsutism
- Benefits
 - ↑ progestin
 - ↓ free androgen levels
 - Prevents pregnancy
 - Regulates cycle
 - No effect on insulin resistance

MPA: medroxyprogesterone acetate

Insulin-Sensitizing Agents

- Metformin, pioglitazone, rosiglitazone
- Benefits
 - ↑ SHBG
 - ↓ free androgen levels
 - Improve ovulation
 - Improve insulin resistance
 - Improve glucose tolerance
 - Rarely associated with hypoglycemia

SHBG: sex hormone binding globulin

Insulin Sensitizing Agents

- Metformin
 - Dosing:
 - 1500 to 2000 mg daily in 2 to 3 divided doses
 - Adverse Events
 - Anorexia, N/V/D, flatulence, lactic acidosis (rare)
- Pioglitazone 15 to 45 mg daily
- Rosiglitazone 4 to 8 mg daily
- Adverse Events
 - Weight gain, edema, headache, fatigue, hepatic injury (rare)
 - Rosiglitazone: increase in total, LDL, and HDL cholesterol

N/V/D: nausea, vomiting, diarrhea
 LDL: low-density lipoprotein
 HDL: high-density lipoprotein

Spirolactone

- Diuretic and aldosterone antagonist, inhibits ovarian and adrenal steroidogenesis, competes for androgen receptors in hair follicles, and directly inhibits 5-alpha-reductase activity
- 25 to 100 mg BID with a goal of balancing efficacy and avoiding side effects
- May take 6 months to see effects
- 20% of women experience increased menstrual frequency
- Decreases androgenic symptoms
- Pregnancy considerations
 - Can adversely affect male sex differentiation

Benefits of Medications

Medication	Decrease Androgen levels	Reduce Androgen effects	Increase SHBG	Increase Progestin	Decrease insulin resistance
E + P Contraceptives	X	X	X	X	
Progestins	X	X		X	
Metformin	X	X	X		X
TZDs	X	X	X		X
Spirolactone	X	X			

E+P: estrogen and progesterone
 TZDs: thiazolidinedione

Eflornithine cream (Vaniqa)

- Reduces unwanted facial hair on women
- MOA: inhibits ornithine decarboxylase (ODC) which inhibits cell division and synthetic functions which slows hair growth
- Dosing: Apply a thin layer to affected areas and rub in thoroughly
 - Use BID and at least 8 hours apart
 - Do not wash for at least 4 hours
- Adverse Events
 - Acne, pseudofolliculitis barbae

Infertility

Infertility

- Weight reduction, exercise, smoking cessation, reduction in alcohol consumption
- Clomiphene and metformin are first-line
- Exogenous gonadotropins or ovarian surgery are second-line

Infertility

- Aromatase inhibitors have been proposed as primary and secondary treatment
 - Letrozole appears to be comparable to clomiphene
 - Anastrozole not as effective as clomiphene
- Shorter half-life, higher implantation rates, lower multiple pregnancy rates are potential benefits
- Need more studies
- Not FDA approved for this use

Clomiphene

- Selective-estrogen receptor modulator (SERM)
- MOA: Increases GnRH which stimulates the pituitary to release more FSH and LH
 - This stimulates the ovaries to produce oocyte follicles and stimulates the development and function of the corpus luteum
- Adverse Events
 - Typically dose-related
 - Ovarian enlargement, vasomotor flushes, vision changes

GnRH: Gonadotropin-releasing hormone
LH: luteinizing hormone
FSH: follicle-stimulating hormone

Clomiphene

- 25 mg per day for 5 days between days 3 and 5 of the menstrual cycle
- Doses up to 100 mg daily have been used in significantly obese patients or if ovulation doesn't occur at 50 mg/day
- If ovulation occurs, there is no advantage to increase dose
 - If ovulation occurs, but not followed by a pregnancy, can continue for up to 6 treatments
- If ovulation doesn't occur after first course, a second course of 100 mg daily for 5 days can be given
 - If ovulatory menses don't occur, stop after 3 cycles total at higher dose
 - If ovulation occurs, but isn't followed by pregnancy, use a max of 6 treatments

Clomiphene

- Contraindications:
 - Known or history of liver disease
 - Hormone-dependent tumors or patients with abnormal uterine bleeding of undetermined origin
 - Pregnancy
 - Ovarian cysts
- Precautions
 - Long-term therapy beyond 6 cycles is not recommended
 - Ovarian hyperstimulation syndrome (OHSS)
 - Visual symptoms
 - Uterine fibroids
 - Hypertriglyceridemia

Letrozole (Femara)

- MOA: inhibits aromatase which blocks estradiol production and increases the release of FSH to induce ovulation
 - Androgens may accumulate in the ovaries, which increases sensitivity of ovarian follicles to FSH
 - Does not deplete estrogen receptors like clomiphene
- Dosing
 - 2.5 mg, 5 mg or 7.5 mg daily for 5 days on days 3 to 7 of menstrual cycle
- Contraindications
 - Pregnancy
 - One cohort study has shown similar rate of miscarriage and ectopic pregnancy when used to improve ovulation
- Precautions: hepatic disease and decrease in BMD

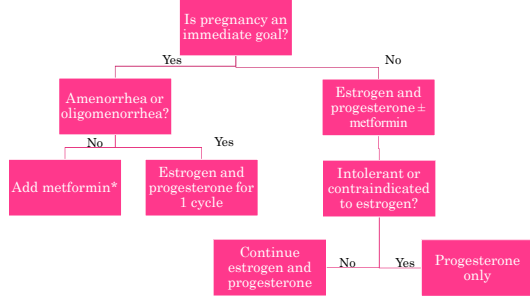
FSH: follicle-stimulating hormone
BMD: bone mineral density

Letrozole (Femara)

- Drug Interactions
 - Estrogens, oral contraceptives, tamoxifen
- Adverse Events
 - Hot flashes, arthralgia, flushing, asthenia, edema, headache, dizziness, hypercholesterolemia, increased sweating, bone pain, musculoskeletal pain
- Monitoring
 - LFTs: baseline and periodically

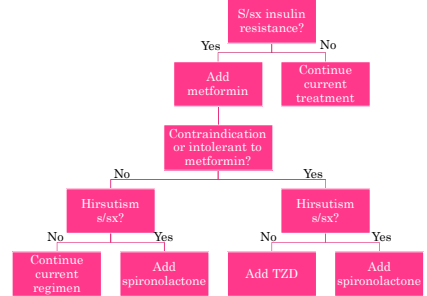
LFTs: liver function tests

Treatment Algorithm



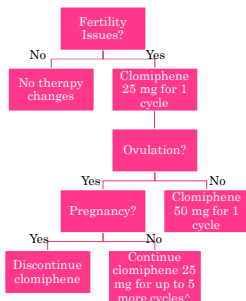
*see upcoming slide

Treatment Algorithm



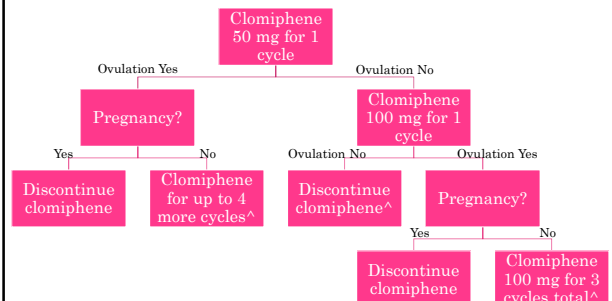
s/sx: signs and symptoms
TZD: thiazolidinedione

Treatment Algorithm*



*If fail clomiphene, discontinue and consider letrozole

Treatment Algorithm



*If fail clomiphene, discontinue and consider letrozole

Think, Pair, Share

- The patient states that she would like to start trying to become pregnant in 2 years. She is not taking any medications at this point in time. Her symptoms have remained about the same.
- What do you recommend for her today?
 - Estrogen and progesterone
 - Metformin

Think, Pair, Share

- A few years have gone by and she has been unable to conceive a baby for about 6 months
- What do you recommend?
 - Clomiphene 25 mg for 1 cycle for 5 days between days 3 to 5

Complications of PCOS

Complications

- Type 2 diabetes
- Hypertension
- Dyslipidemia
- Cardiovascular disease
- Metabolic syndrome
- Nonalcoholic fatty liver disease (NAFLD)
- Sleep apnea
- Mostly caused by insulin resistance and obesity

Diabetes

- Risk Factors:
 - Age > 45 yo
 - BMI ≥ 25 kg/m² or 23 kg/m² in Asian Americans
 - First-degree relative with DM
 - Physical inactivity
 - Race/ethnicity (African American, Latino, Native American, Asian American, Pacific Islander)
 - History of GDM or delivering a baby > 9 pounds
 - BP $\geq 140/90$ mmHg or on therapy
 - HDL < 35 mg/dl
 - TG > 250 mg/dl

BMI: body mass index, DM: diabetes mellitus, GDM: gestational diabetes
BP: blood pressure, HDL: high-density lipoprotein, TG: triglycerides

Diabetes

- Diagnosis

Test	Normal	Impaired	Diabetes
FBG	< 100 mg/dl	100 to 125 mg/dl	≥ 126 mg/dl
2 hour OGTT with 75 g glucose	< 140 mg/dl	140 to 199 mg/dl	≥ 200 mg/dl
A1C	< 5.6%	5.7 to 6.4%	$\geq 6.5\%$

- Random plasma glucose ≥ 200 mg/dl with classic hyperglycemia symptoms

FBG: fasting blood glucose
OGTT: oral glucose tolerance test

Diabetes

- Manage diabetes the same as non-PCOS patient
 - Start lifestyle modifications ± medications at diagnosis
 - Consider metformin first-line
- Pregnancy considerations:
 - Metformin, glyburide, insulin can be used in pregnancy
 - GLP-1 agonists, DPP-IV inhibitors, SGLT-2 inhibitors: not well-studied in humans

GLP-1: glucagon-like peptide 1
DPP-IV: dipeptidyl peptidase IV
SGLT-2: sodium-glucose cotransporter 2

Hypertension

- Check blood pressure at every visit
- Lifestyle changes
 - Weight loss, DASH diet, limit sodium intake to less than 2,400 mg per day, moderate to vigorous aerobic physical activity, eliminate nicotine use, limit alcohol consumption to 1 serving a day
- Follow current treatment guidelines
- Pregnancy considerations
 - ACEIs and ARBs are contraindicated
 - Methyldopa, labetalol, nifedipine

ACEi: angiotensin converting enzyme inhibitor
ARB: angiotensin II receptor blocker

Dyslipidemia

- Strongly suspected that there is an increased risk and early onset of CVD in women with PCOS
- Having abnormal lipid profiles is about 70% in women with PCOS
- LDL is disproportionately elevated in women with PCOS
- Start screening at age 20
 - Rescreening every year

CVD: cardiovascular disease
LDL: low-density lipoprotein

Dyslipidemia

- Lifestyle changes
 - Saturated fat < 7% of calories, cholesterol < 200 mg/day, 10 to 25 g/day soluble fiber, 2 g/day plant stanols/sterols
- Start therapy if triglycerides > 500 mg/dl
- Statins are first-line therapy in most recent guidelines
 - Likely don't fit into statin benefit groups
 - Consider fibrates, ezetimibe, nicotinic acid, bile acid sequestrants, and omega-3 fatty acids

Dyslipidemia

Drug Class	LDL Effects	HDL Effects	TG Effects
Statins	↓ 18 to 55%	↑ 5 to 15%	↓ 7 to 30%
Ezetimibe	↓ 18%	↑ 1%	↓ 8%
Fibrates	↓ 5 to 20%	↑ 10 to 20%	↓ 20 to 50%
Nicotinic acid	↓ 5 to 25%	↑ 15 to 35%	↓ 20 to 50%
Bile acid sequestrants	↓ 15 to 30%	↑ 3 to 5%	↑ or no change
Omega-3 fatty acids	↑ 5 to 10%	↓ 1 to 3%	↓ 25 to 30%

LDL: low-density lipoprotein
HDL: high-density lipoprotein

Dyslipidemia

- Pregnancy Considerations
 - Statins are contraindicated
 - Small recent studies report use of pravastatin 10 mg daily for pre-eclampsia
 - Omega-3 fatty acids or fibrates can be used in second trimester if needed
 - If a patient is trying to become pregnant, remove dyslipidemia agent
 - Treat with non-pharmacologic options while pregnant

Obesity Management

- Weight loss decreases androgen levels
 - Can cause spontaneous resumption of menses
 - Improve fertility, decrease hirsutism, improve glucose and lipid levels
- Weight loss of 5%
 - Calorie restriction
 - Physical activity
- Pharmacologic agents
- Gastric bypass surgery
 - Normalization of reproductive and metabolic abnormalities at 5%

Metabolic Syndrome

- NCEP ATP III criteria
 - Any 3 of the 5
 - Waist circumference
 - > 40 inches for men
 - > 35 inches for women
 - FBG \geq 100 mg/dl or prescription
 - TG \geq 150 mg/dl or prescription
 - HDL
 - < 40 mg/dl for men
 - < 50 mg/dl for women
 - > 130 mmHg systolic or > 85 mmHg diastolic or prescription

NCEP ATP: National Cholesterol Education Program Adult Treatment Panel
FBG: fasting blood glucose, TG: triglycerides, HDL: high-density lipoprotein

Think, Pair, Share

- The patient returns to your clinical to have labs drawn. Her results are as follows: A1C 5.8%, FBG 105, total cholesterol 380, LDL 132, HDL 45, TG 350, BP 118/66, waist circumference 47.5 inches. Her husband states she has been snoring so loudly at night that it wakes him up.
- What PCOS complications does this patient have?
 - Pre-Diabetes, metabolic syndrome, dyslipidemia, obstructive sleep apnea?

FBG: fasting blood glucose, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglycerides, BP: blood pressure.

Think, Pair, Share

- The patient returns to your clinical to have labs drawn. Her results are as follows: A1C 5.8%, FBG 105, total cholesterol 380, LDL 132, HDL 45, TG 350, BP 118/66, waist circumference 47.5 inches. Her husband states she has been snoring so loudly at night that it wakes him up.
- How do you want to manage those conditions?
 - Lifestyle modifications, weight loss, statin (if not planning pregnancy), sleep study

FBG: fasting blood glucose, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglycerides, BP: blood pressure.

Self-Assessment Question

A patient presents with polycystic ovaries and ovarian dysfunction. She denies hirsutism, acne, and alopecia. She states she has a regular menstrual cycle. Upon physical exam, you notice she has acanthosis nigricans. She has a BMI of 35.6 kg/m² and a free testosterone level of 2.3 pg/ml (reference range: 0.1 to 6.4 pg/ml). Does the patient have PCOS based on the 2003 Rotterdam diagnostic criteria?

- Yes, she has at least 2 criteria
- Yes, she has at least 3 criteria
- No, she has only 1 criterion
- No, she does not have any criteria

Self-Assessment Question

A patient presents with polycystic ovaries and ovarian dysfunction. She denies hirsutism, acne, and alopecia. She states she has a regular menstrual cycle. Upon physical exam, you notice she has acanthosis nigricans. She has a BMI of 35.6 kg/m² and a free testosterone level of 2.3 pg/ml (reference range: 0.1 to 6.4 pg/ml). Does the patient have PCOS based on the 2003 Rotterdam diagnostic criteria?

- Yes, she has at least 2 criteria
- Yes, she has at least 3 criteria
- No, she has only 1 criterion**
- No, she does not have any criteria

Self-Assessment Question

A patient has PCOS and is not wanting to become pregnant for several years. She has tried estrogen therapy and experienced unacceptable side effects. Which of the following is the best first-line option for this patient?

- A. Ethinyl estradiol alone
- B. Ethinyl estradiol + progesterone
- C. Progesterone alone
- D. Metformin

Self-Assessment Question

A patient has PCOS and is not wanting to become pregnant for several years. She has tried estrogen therapy and experienced unacceptable side effects. Which of the following is the best first-line option for this patient?

- A. Ethinyl estradiol alone
- B. Ethinyl estradiol + progesterone
- C. Progesterone alone**
- D. Metformin

References

- American Diabetes Association. *Standards of Medical Care in Diabetes - 2015*. *Diabetes Care* 2015;38(1):8-16.
- Brough L. What pharmacists need to know about polycystic ovary syndrome (PCOS). <http://www.frees.com/for/consultation.pdf>
- *Cholest [package insert]*. Ridgecrest, NJ: Sanofi-Santaris; 2012.
- *Finaster [package insert]*. East Rutherford, NJ: Novartis; 2014.
- Hirschak PR, Tappin RB. Chapter 7. Folate Deficiency and Ovarian Classification in Digital Ultrasound Images of Ovaries. In: *Gynecologic GPP 8th*. Advancements and Breakthroughs in Ultrasound Imaging. InTech; 2013. DOI: 10.5772/526218.
- Huang PL. A comprehensive definition for metabolic syndrome. *Dis Model Mech*. 2009;2(2):211-217.
- Anderson TA, Ho MK, Hahn EC, et al. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 1: full report. *J Clin Lipidol*. 2012; 1(4): 1-14.
- Anderson TA, Hahn EC, Orszag CR, et al. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. *J Clin Lipidol*. 2012; 1(4):151-172.
- Polycystic ovary syndrome. *ACOG Practice Bulletin* No. 188. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2008;111:930-48.
- National Heart, Lung, and Blood Institute. *ATP III A-I-A-Glossary: Quick Desk Reference*. Available from: <http://www.nhlbi.nih.gov/files/docs/atp3/atp3glossary.pdf>. Accessed 2015 Jan 3.
- Clinical Endocrinology. *Chapter 46: Metabolic/Endocrine Disorders*. In: *Diagnosis & Treatment of Endocrine Disorders*. 2nd ed. Mosby; 2004. Pp 1-10. *Pharmacotherapy: A Clinical Approach*. 4th ed. New York, NY: McGraw-Hill; 2014. http://accessmedicine.mhprofessional.com/content/9780323094103/9780323094103_ch46. Accessed December 17, 2015.
- United EM, Wintstein LC, Barakett S. Chapter 48. *Menstruation-Related Disorders*. In: *Chapman-Russell MA, Schillinghouse TL, Webb-BG, Mahon PM, Kibben JM, Rhee JC, eds. Pharmacotherapy: Principles and Practice*. 2e. New York, NY: McGraw-Hill; 2010.

Polycystic Ovarian Syndrome (PCOS)

Christina Inteso, Pharm.D., BCACP

Community Health Network, Indianapolis, IN

Clinical Pharmacy Specialist- Ambulatory Care

August 1, 2019