

**Conceiving with Confidence:
The Pharmacist's Role in Managing
Infertility and Polycystic Ovary Syndrome**

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Disclosure

Nothing to disclose

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Learning Objectives

At the end of this presentation, **pharmacists** should be able to:

1. Define infertility and polycystic ovary syndrome (PCOS)
2. Identify main causes and risk factors of infertility in males and females and PCOS
3. Compare and contrast the pharmacological agents used in infertility and PCOS
4. Given a case, recommend appropriate pharmacological and non-pharmacological regimen for the treatment of infertility and of PCOS
5. Counsel on the appropriate use, common adverse events and risks of use of a prescribed pharmacological regimen in infertility and in PCOS


At the end of this presentation, **pharmacy technicians** should be able to:

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Outline

- Epidemiology
- Risk factors
- Etiology & Pathophysiology
- Clinical presentation
- Diagnostic considerations
- Treatment
- Prevention



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Polycystic Ovary Syndrome (PCOS)




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PCOS Definition

1. Irregular periods due to irregular ovulation
+
2. Hyperandrogenism

With presence of polycystic ovaries



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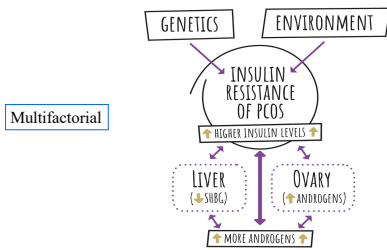
Epidemiology

- Most common endocrine pathology in reproductive-aged females worldwide
 - Affects about 5 million reproductive-aged females in the United States
- Prevalence ranges between 5% and 15%

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Etiology



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Risk Factors for PCOS

- Family history
- Ethnicity
 - Higher prevalence in Mexican-Americans than in non-Hispanic whites and African Americans
- Diet
 - High in sugar/high-glycemic index
- Sedentary lifestyle and obesity
- Environmental
- Medical conditions & medications
 - e.g. dyslipidemia
 - Valproic acid

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Clinical Presentation: PCOS

The infographic illustrates the clinical presentation of PCOS. It features a central illustration of a woman with several icons around her representing symptoms: Acne, Unaccountable hair loss, Excessive testosterone symptoms, Weight gain, Irregular menstrual cycle, Difficulty getting pregnant, and Abnormal pain. To the right, three photographs are labeled: A Hirsutism (facial hair), B Thinning hair (scalp), and C Acanthosis nigricans (skin thickening).

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Diagnostic Considerations

- History and physical exam are important for the diagnosis of PCOS.
 - Menstrual history and features of hyperandrogenism
- For the diagnosis of PCOS, depending on the guideline society, most have to meet two out of three criteria which are features of the Rotterdam Criteria:
 - chronic anovulation
 - clinical or biological hyperandrogenism
 - polycystic ovaries morphology in the absence of any other pathology
- National Institute of Health criteria also requires clinical or biochemical hyperandrogenism and oligo or anovulation
- American Excess PCOS Society requires hyperandrogenism

<https://pharmaceutical-journal.com/article/feature-based-learning-management-of-polycystic-ovary-syndrome>

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Treatment

- Goals of therapy
- Non-pharmacotherapy
- Pharmacotherapy options
- Evaluation of therapeutic outcomes

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Goals of Therapy

- Mitigation of hyperandrogenic symptoms
- Management of metabolic abnormalities and reduction of risk factors for type 2 diabetes and cardiovascular disease, prevention of endometrial hyperplasia
- Planning and obtaining a safe pregnancy if desired
- Improving general well-being and quality of life

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PCOS Non-Pharmacological

- **Behavioral interventions**
 - e.g. goal-setting, problem solving, assertiveness training, slower eating, emotional wellbeing, cognitive behavioral therapy (CBT)
- Weight loss by **5-15%**
- **Exercise**
 - For weight loss
 - For muscle strengthening to improve insulin sensitivity
- **Dietary changes**
 - e.g., low-calorie diet, low glycemic foods (e.g., bran cereals, broccoli, peppers), fruits, vegetables



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PCOS Pharmacotherapy

Hormonal contraceptives	Metformin & Potentially GLP-1 Agonists	Clomiphene & Aromatase Inhibitors	Spiroglactone & Eflornithine
<ul style="list-style-type: none"> • First line for management of menstrual abnormalities and hirsutism/acne • 20 mcg of ethinyl estradiol combined with progestin • Progestin with neutral/minimal or anti-androgenic activity (e.g. desogestrel and drospirenone or norethindrone acetate) • For patients who do not want to become pregnant • Screen for contraindications • For full effect, trial of at least 6 months 	<ul style="list-style-type: none"> • First line for management of insulin resistance, assists with prevention of pregnancy complications, or treatment of obesity • Type 2 Diabetes Mellitus or impaired glucose tolerance • Second line in women with menstrual abnormalities who cannot tolerate contraceptives • GLP-1 agonist associated with decreased BMI and testosterone and improved ovulation rate in obese women with PCOS 	<ul style="list-style-type: none"> • First line for treatment of anovulatory infertility • Metformin may be used as adjunct therapy • Letrozole compared to clomiphene, was associated with higher live-birth and ovulation rates among infertile women with polycystic ovary syndrome 	<ul style="list-style-type: none"> • Spiroglactone - anti-androgen that inhibits excessive hair growth and acne by blocking androgens • Use contraception • Eflornithine - cream applied to slow hair growth

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Assessment Question #1

Which of the following is considered first line for the management of insulin resistance, and treatment of obesity in women with PCOS?

- A. CHOC
- B. Metformin
- C. Clomiphene
- D. Spironolactone

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Assessment Question #2

Which of the following is true regarding Eflorithine (Vaniqa®)?

- A. It is an injectable agent
- B. It inhibits hair growth
- C. It is used on facial or chin hair
- D. Both A & C

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Case Presentation

- JJ is a 25 years old female who presents to the pharmacy for recommendations about managing the hair growth and acne on her face
- Past Medical History is significant for PCOS, no other medical conditions
- Medications: Started the combined oral contraceptive pill three months ago, which helped with most of her symptoms (e.g. her periods are more regular and less painful). However, the acne on her face and the hair on her chin are still present and bothersome
- She is currently not sexually active nor has partner, and does anticipate becoming pregnant soon
- She confirms she eats healthy and exercises to remain fit

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Question #1

What would you recommend to JJ at this time?

- A. Discontinue her OCP as it is ineffective
- B. Start Semaglutide 0.25 mg SQ weekly
- C. Start clomiphene 50 mg PO daily
- D. None of the above

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PCOS Associated Morbidities

- | | |
|---|---|
| Infertility | Obstructive sleep apnea (OSA) |
| Metabolic syndrome | Endometrial cancer |
| Obesity | Nonalcoholic fatty liver disease/
nonalcoholic steatohepatitis
(NAFLD/NASH) |
| Impaired glucose tolerance/type
2 diabetes mellitus (DM-2) | |
| Cardiovascular risk | |
| Depression | |

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Infertility

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Epidemiology of Infertility

- Women have an 85% chance of pregnancy over 1 year when using no birth control method
 - Probability of having a baby decreases 3%–5% every year after age 30
- Married women aged 15 to 49 years with no prior births, about:
 - 1 in 5 (19%) are unable to get pregnant after one year of trying
 - 1 in 4 (26%) have difficulty getting pregnant or carrying a pregnancy to term
- In women aged:
 - 15 to 34 years, infertility rates = 7.3 to 9.1%.
 - 35 to 39 years, infertility rates increased to 25%.
 - 40 to 44 years had a 30% chance of infertility.
- Infertility rates are higher in Eastern Europe, North Africa, and the Middle East

<https://www.cdc.gov/reproductivehealth/infertility/index.html> - text=infertility&utm_source=gov&utm_medium=year&utm_campaign=infertility
<https://www.merckmanuals.com/infertility/infertility/infertility>
<https://www.fertilitypreservation.org/blog/what-to-know-about-pregnancy-after-40/> - text=Though&utm_source=infertility&utm_medium=year&utm_campaign=infertility
<https://www.ncbi.nlm.nih.gov/books/NBK55653/>

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Global Statistics

48,500,000
THE NUMBER OF COUPLES AROUND THE WORLD EXPERIENCING FERTILITY PROBLEMS

30% 30% 30% 10%

GLOBAL STATISTICS

- 48.5 Million Couples unable to have a Child
- 19.2 Million First Child
- 29.3 Million Second Child
- US: 6.7 Million Women are Suffering from Infertility

<https://screenme.co.uk/infertility-facts-you-should-know>

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Infertility Definition

- < 35** Unable to get pregnant (conceive) after **12 months (1 year)** or more of unprotected sex
- > 35** Unable to get pregnant (conceive) after **6 months** of unprotected sex


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Infertility Definition

Primary Infertility
When neither partner has attained a pregnancy in current or prior relationship(s)



Secondary Infertility
A pregnancy was attained in the past with current or previous partner(s)



<https://www.facebook.com/tryghy/photos/primary-infertility-refers-to-couples-who-have-not-been-able-to-become-pregnant-1515762946-157431177-28>
https://www.medicinenet.com/infertility/secondary_infertility_150_tu0417/

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Risk Factors For Infertility

HIGH RISKS	MEDIUM RISKS	LOW RISKS
AGE	POOR NUTRITION	CAFFEINE
OVERWEIGHT	PHYSICAL EXERCISE	RECREATIONAL DRUG USE
UNDERWEIGHT	FREQUENCY OF INTERCOURSE	STD's
ALCOHOL		
SMOKING		
STRESS		

<https://screenme.co.uk/infertility-facts-you-should-know/>

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Etiology: Female

The most common identifiable factors of **female** infertility are:

- Ovulatory disorders - 25%
- Endometriosis - 15%
- Pelvic adhesions - 12%
- Tubal blockage - 11%
- Other tubal/uterine abnormalities - 11%
- Hyperprolactinemia - 7%

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Etiology: Male

The most common identifiable factors of **male** infertility are:

- Primary testicular defects (which include abnormal sperm parameters without any identifiable cause) - 65% to 80%
- Idiopathic (where an infertile male has normal sperm and semen parameters) - 10% to 20%
- Sperm transport disorders (such as vasectomy) - 5%
- Endocrine disorders (usually due to hypogonadism) - 2% to 5%

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Fertility & COVID-19 Vaccine

Per the CDC, no evidence exists that COVID-19 vaccines cause or contribute to infertility

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Diagnostic Considerations

Females

- Assessment of ovarian function and reserve
- Assessment of uterine cavity
- Assessment of fallopian tubes

Males

- Semen analysis
- Endocrinological serum studies

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Diagnostic Considerations: Males

- Semen analysis using WHO criteria or Kruger-Tygerberg criteria
 - At least 3 days of abstinence
 - 2 samples at least 1 week apart
- Other tests
 - Antisperm Antibodies – suspected with sperm agglutination or isolated asthenozoospermia
 - DNA integrity test – assess the degree of DNA fragmentation in sperm
 - Genetic Screening – indicated with azoospermia or severe oligozoospermia
 - Karyotype, Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), and Y chromosome testing
 - Hormonal tests – low sperm count and concentration or suggestive endocrine disorder or impaired sexual function
 - Post-coital test – hyperviscosity of semen, normal sperm density with low or high semen volumes, and in cases of idiopathic infertility
 - Post-ejaculatory urinalysis – semen volume below 1 mL
 - Ultrasound/biopsy – masses, obstructions, etc...

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Treatment

- Goals of therapy
- Non-pharmacotherapy
- Pharmacotherapy options
- Evaluation of therapeutic outcomes

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Goals of Therapy

- Stimulate the development of a single follicle and release of a single egg
- Improve the physical, emotional, social and interpersonal stressors of infertility

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Infertility Treatment Overview


- Nonpharmacological
 - Varies based on underlying cause of infertility
- Pharmacological Trigger ovulation
 - Clomiphene (Clomid®) ± metformin
 - Gonadotropins, for example:
 - Follicle stimulating hormone-recombinant
 - Human chorionic gonadotropin (hCG)
 - Gonadotropin releasing hormone agonists (GnRHA) e.g. leuprolide (Lupron®)
 - Aromatase inhibitors (Letrozole, anastrozole) – not FDA-approved, but used 1st line in women with PCOS related infertility

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No Treatment – Male Infertility

When left untreated, couples may still produce a pregnancy










- 23% of untreated infertile couples conceived after 2 years
- 33% after 4 years



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Non-pharmacological

FERTILITY-BOOSTING TIPS

 <small>BALANCE BLOOD SUGAR</small>	 <small>EAT A DIET RICH IN PROTEIN</small>	 <small>DEFENDERS: WEAR FOOD</small>
 <small>LIMIT CAFFEINE + ALCOHOL</small>	 <small>GET A LITTLE SUN</small>	 <small>LIMIT TOXIN EXPOSURE</small>
 <small>MANAGE STRESS</small>	 <small>MOVE REGULARLY</small>	 <small>TRANSITION OR REASSURE WITH COUNSEL</small>

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Non-Pharmacological

- Dependent on underlying cause
- If secondary to anorexia → recommend weight gain
- If secondary to obesity → lose weight without strenuous exercise or unhealthy dieting
 - BMI < 27 is ideal
- If secondary to excessive exercise → reduce exercise intensity
- Avoid medications known to interfere with infertility
 - Review with both male and female
- Avoid excess alcohol, smoking/nicotine, and illicit drugs
- Take a daily multivitamin that contains at least 0.4 mg of folic acid



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Pharmacotherapy



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Clomiphene: Clomid®, Serophene®

- Infertility in Males
- Anti-estrogen, and in small doses can ↑ FSH and LH secretion → spermatogenesis
 - May add tamoxifen 10 mg BID as an estrogen receptor antagonist

- Infertility in Females
- Indication
 - Ovulation induction
 - Inhibits the negative feedback of estrogen, ↑ FSH and LH secretion
 - Works best in women who have normal FSH and estrogen productions
 - Must time intercourse to coincide with the expected time of ovulation (~5-10 days after clomiphene course)

On the ISMP
high alert
medication
list!

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Clomiphene Dosing

Females

- Dose: 50 mg PO daily
 - Begin on day 3-5 of cycle (if recent bleeding)
 - Duration: 5 days
- If no ovulation occurs
 - ↑ to 100 mg PO daily x 5 days during next cycle
- Max: 100 mg PO daily x 5 days per month up to 6 cycles
 - D/c if no ovulation after 3 course of tx OR 3 ovulatory response but no pregnancy

Males: Small doses of 25-50 mg 3x/week

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Clomiphene Side Effects & Warnings - Females

Common side effects

- Ovary enlargement
- Multiple pregnancies
- Abdominal bloating/discomfort
- Hot flashes
- Clotting risk

Precautions

- Multiple births
- Hyperlipidemia
- Visual disturbances
- Use > 12 months ↑ risk of ovarian cancer

Contraindications

- Pregnancy
- Ovarian cyst (not d/t PCOS)
- Abnormal uterine bleeding
- Uncontrolled thyroid or adrenal dysfunction
- Current or history of hepatic disease
- Certain types of cancer or lesion

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Nasal Testosterone Gel - Males

- Testosterone replacement supplement – unique minimal effect on semen parameters unlike all other forms of testosterone
- Applied very low dose 2-3x/day
- Estradiol levels remain normal

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Aromatase Inhibitors – Not FDA approved Males; Off-label in Females

- Steroidals: Testolactone
- Nonsteroidals:
 - Anastrozole - 1 mg 3x/week in males
 - Letrozole
 - 2.5 mg 3x/week in males
 - 2.5 or 5 mg/day on cycle days 3-7 with intercourse every other day 5 days after completing the medication)
- Improve abnormal semen and hormonal parameters, not proven to improve rates of pregnancy
- Most useful when testosterone levels are normal but estradiols are relatively high
- Can be used with clomiphene in males
- ACOG recommends letrozole over clomiphene for women with PCOS

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Others - Males

- L-Carnitine – amino acid and antioxidant (3g daily)
- Antioxidants
 - Coenzyme Q10 (300 mg daily)
 - Vitamins C, E, folic acid, selenium, and zinc
- Vitamin D supplement (5000 IU) may help sperm motility

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Metformin - Females

- Purpose – assist in ovulation (especially in women with PCOS)
 - Improves insulin sensitivity, reduces circulating insulin levels which helps to normalize follicular development
 - When used in combination with clomiphene, ovulation rate = 90%
- Dosing:
 - 500 mg po daily with meals
 - titrate to 1000 mg po BID with meals as tolerated
- Potential side effects:
 - GI upset (nausea, diarrhea, constipation)
 - NQ** risk associated with use

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Gonadotropins - FSH + LH or FSH

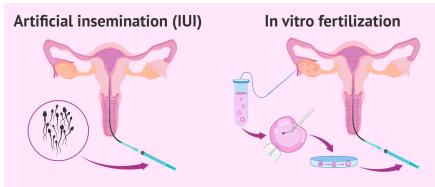
- Purpose – assist with follicle growth and maturation as well as ovulation
 - Used after a poor response to clomiphene or to spur egg release
- Dose:
 - Dose customized to patient
 - Requires luteal support (progesterone)
 - Requires ultrasound monitoring for follicular development
- Potential side effects:
 - Multiple births
 - Hyperstimulation
 - Febrile reaction
 - Injection site reaction
 - Abdominal pain, N/V/D
 - Ovarian hyperstimulation syndrome risk

Cannot be taken orally – administer via IM or SQ injection

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Other Options



<https://www.invivo.com/en/artificial-insemination-or-in-vitro-fertilization>

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Assessment Question #3

Clomiphene is the only FDA-approved for infertility available as oral pills.

- A. True
- B. False

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Assessment Question #4

What counseling points would you provide a female patient starting clomiphene for infertility?

- A. Used when metformin failed
- B. Usually started on days 3-5 of your cycle
- C. Take 50 mg PO QDAY for 14 days
- D. It carries the highest risk of multiple births



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Case Presentation

N.T. is a 27-year-old female who has been trying to conceive for 14 months without success. She and her husband would like to conceive in the next year or so. She is 62 inches tall and weighs 171 lb (78 kg); her BMI is 33 kg/m². Her past medical history is significant for moderate acne and hirsutism, and polycystic ovaries. She reports regular menstrual cycles, and ultrasound does not show any anatomical problems. Her insulin/glucose ratio is elevated. Her husband also underwent a physical examination and semen analysis which are normal.

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Question #1

What is the preferred recommendation for NT that might help her ovulate?

- A. No treatment at this time. Continue trying to conceive naturally
- B. Weight loss and start Metformin
- C. In vitro fertilization
- D. Start FSH injections

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Question #2

Which of the following a potential cause of infertility in this patient?

- A. Irregular menstrual cycles
- B. Husband's sperms
- C. Polycystic ovaries
- D. Her age

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Thank You!

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Key References

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