

Boosting the Chances of Conception: Fertility Medications and the Pharmacist

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Disclosure

Dr. Giara has no financial relationships with ineligible companies.

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Learning Objectives

- Review the prevalence and major causes of infertility
- Explain the role of medications in infertility treatment, including those for assisted reproductive procedures
- Optimize care and counseling for patients experiencing infertility

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Infertility Primer

PREVALENCE AND CAUSES

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QUESTION 1

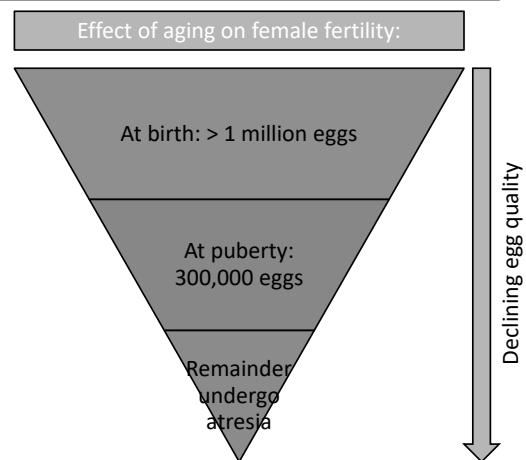
Which of the following is TRUE about infertility?

- A. Infertility affects 1 in 8 heterosexual couples
- B. Every cause of infertility is identifiable and treatable
- C. People should seek assistance after 6 months of trying to conceive

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What is Infertility?

- Diminished capacity to bear offspring
- Inability to conceive after 1 year or longer of unprotected heterosexual intercourse
 - People should typically see a fertility specialist after 1 year of trying to conceive
 - 6 months for women > 35 years old or those with a known condition affecting fertility
- Affects 1 in 8 heterosexual couples
 - 10% of men
 - 13% of women



Infertility FAQs. <https://www.cdc.gov/reproductivehealth/infertility/index.htm>;
How your chances of conception are affected by your cycle, age, birth control, health conditions (and more). <https://modernfertility.com/blog/chances-of-conception/>

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Psychosocial & Economic Impact

- Inability to fulfill biological role of parenthood can be socially, mentally, and physically damaging
- Stressful and often heartbreaking
- Often becomes the focal point of daily conversations and tasks
- EXPENSIVE!
 - ART industry was a \$3.3 billion business in 2005
 - Anticipated to surpass \$32.5 billion worldwide by 2024
 - Artificial reproduction procedures can average \$17,000 per cycle (with no guarantee of success)

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Menstrual
cycle

Conception

Causes of
Infertility

Where Do Babies Come From?

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Menstrual Cycle

- **MYTH:** Every woman's menstrual cycle is 28-days long
 - Cycle length varies from 21 to 40 days
 - Only about 13% of women naturally experience a 28-day cycle
- Hormone-regulated process
 - **Follicle-stimulating hormone (FSH):** recruits follicles in the ovaries for growth and development
 - **Luteinizing hormone (LH):** triggers egg release from the ovary
 - **Gonadotropin-releasing hormone (GnRH):** stimulates pituitary gland to produce FSH and LH

Bull JR, et al. *NPJ Digit Med.* 2019;2:83.

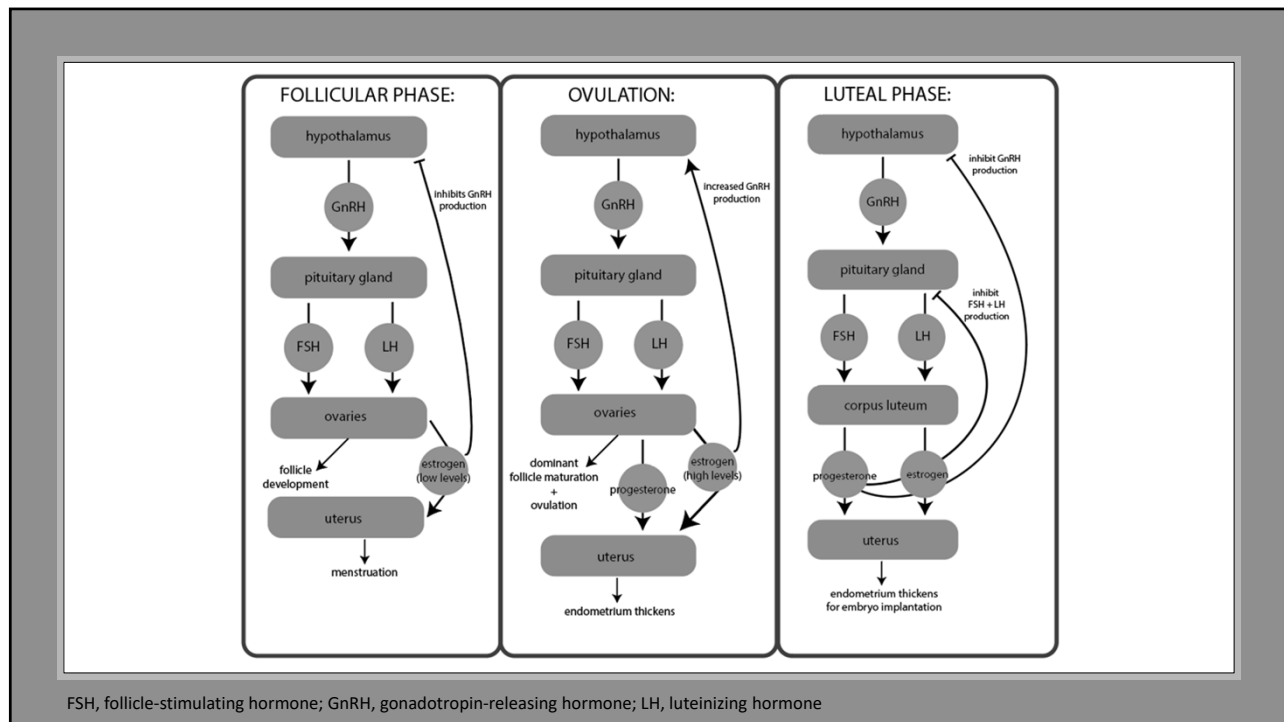
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Menstrual Cycle (Based on 28-Day Cycle)

Follicular Phase (~day 1 to 14)	Ovulatory Phase (~day 14)	Luteal Phase (~days 14-28)
<ul style="list-style-type: none"> • Day 1 to day 14 • FSH rises to recruit a small number of follicles for growth and development • Days 5 to 7: one follicle dominates and secretes estrogen to signal the body to stop menstrual flow • Sustained FSH causes LH to surge around day 14 	<ul style="list-style-type: none"> • Release of a mature oocyte • 28 to 32 hours after LH surge (around day 14) • Egg travels down the fallopian tube towards the uterus 	<ul style="list-style-type: none"> • Corpus luteum (CL) forms <ul style="list-style-type: none"> • Remaining follicles that developed but did not release an egg • Produces progesterone to prepare the uterus for embryo implantation • <i>Fertilization fails:</i> CL degenerates, decreased progesterone triggers menstruation • <i>Conception occurs:</i> fertilized embryo produces hCG to prevent CL regression

hCG = human chorionic gonadotropin

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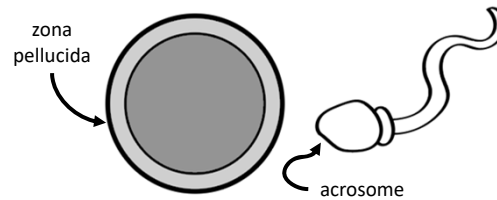
Conception

- Minimum requirements to conceive:
 - Production of competent sperm
 - Production and ovulation of competent oocyte (egg)
 - Sperm proximity to the oocyte in the reproductive tract
 - Embryo transport into the uterine cavity
 - Embryo implantation into the endometrium

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Conception

- Competent sperm swims up through woman's vagina and uterus to join with the oocyte in the fallopian tube
 - Sperm already in the tract before ovulation can survive up to 5 days



- Acrosome reaction: sperm binding to ZP triggers enzymatic reactions that create a “lock and key” recognition
 - Acrosome releases enzymes to harden the ZP, making it impenetrable to other sperm

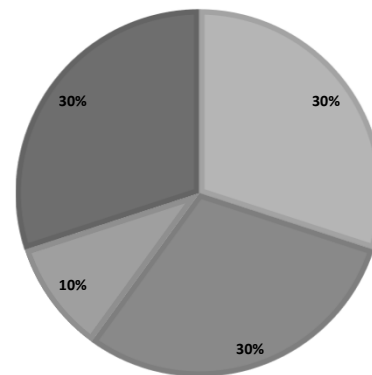
ZP = zona pellucida; Fertilization. <https://www.malecontraceptive.org/fertilization.html>

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Miscarriage

- Clinical miscarriage:** pregnancy loss after positive hCG and ultrasound confirmation
- Generally considered a “physiological phenomenon”
- Body prevents conceptions with structural abnormalities/serious chromosomal aberrations incompatible with life from progressing to viability
- About 2/3 of all fertilized oocytes do not produce live birth
- Age is a significant risk factor
 - 20 to 24 years old: 10%
 - 40 to 44 years old: 51%
 - 45 years and older: 53%

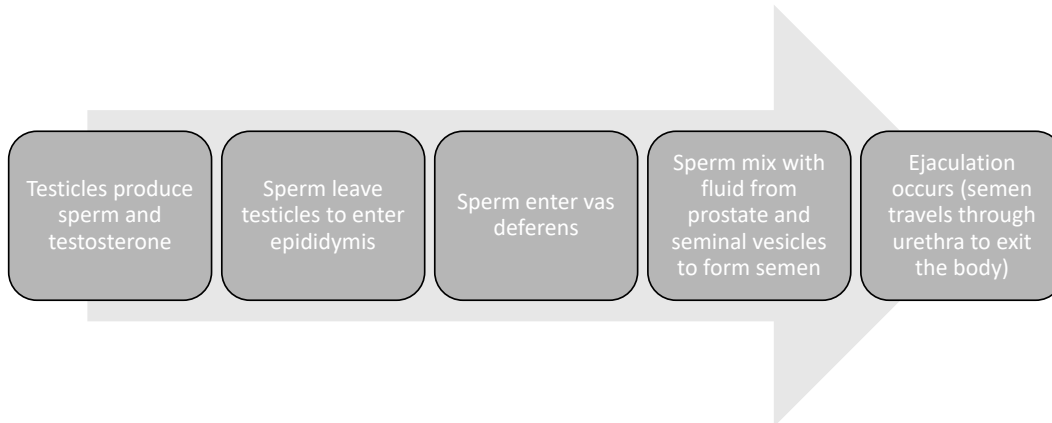
■ Pre-implantation ■ Post-implantation
■ Clinical miscarriage ■ Live birth



hCG = human chorionic gonadotropin; Larsen EC, et al. *BMC Med.* 2013;11:154.

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Male Fertility: Normal Conditions



What is male infertility? <https://www.urologyhealth.org/urology-a-z/m/male-infertility>

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Major Causes of Infertility

- Five major processes can be affected:
 1. Competent oocyte production
 2. Reproductive tract transport of sperm, oocyte, and/or embryo
 3. Embryo implantation
 4. Sperm production
 5. Immunological factors
- Most common causes are abnormal semen parameters, ovulation problems, endometriosis, pelvic adhesions, and tubal disease
- **Unexplained infertility:** no identifiable cause

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Female Causes: Ovarian Dysfunction

POLYCYSTIC OVARY SYNDROME (PCOS)

- Multisystem reproductive-metabolic disorder
- Cardinal signs:
 - Excess androgen (e.g., acne, excess hair growth)
 - Irregular menstrual bleeding (e.g., infrequent or prolonged cycles)
 - Polycystic ovaries (i.e., fluid collections [follicles] on imaging)
 - Weight gain
- Leading cause of anovulatory infertility
- 75% to 85% of women with PCOS have some degree of ovarian dysfunction

OTHER CAUSES

- Diminished ovarian reserve
- Functional hypothalamic amenorrhea
- Improper hypothalamus or pituitary gland function
- Premature ovarian insufficiency

Shufelt CL, et al. *Semin Reprod Med.* 2017;35(3):256-262.

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Female Causes: Fallopian Tube Dysfunction

▪ **Salpingitis:** fallopian tube inflammation

- Causes:
 - Infections in the pelvic area (e.g., vaginal or cervical), including sexually transmitted infections
 - Ruptured appendicitis

▪ **Hydrosalpinx:** fallopian tube blocked with watery fluid

- Caused by previous salpingitis
- Blocks the transport of eggs, sperm, or embryos through the fallopian tube(s)

Chalazonitis A, et al. *Curr Probl Diagn Radiol.* 2009;38(5):199-205.

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Female Causes: Abnormal Uterine Growth

- **Endometriosis:** estrogen-dependent, chronic inflammatory disease that causes endometrial tissue growth outside the uterine cavity
 - Can cause dysmenorrhea, non-menstrual pelvic pain, and dyspareunia
 - Incidence is 10-fold higher in women with infertility than those without (20% to 50% versus 0.5% to 5%)

- **Uterine fibroids:** the most common benign tumors in women of reproductive age
 - Can cause abnormal uterine bleeding, bowel dysfunction, dyspareunia, low back pain, pelvic pressure, and urinary frequency, urgency, and/or retention

Chalazonitis A, et al. *Curr Probl Diagn Radiol.* 2009;38(5):199-205.; De La Cruz MS, Buchanan EM. *Am Fam Physician.* 2017;95(2):100-107.

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Male Causes: Sperm Production & Transport

- Sperm analysis for quantity and quality
 - Evaluate sperm volume, number of sperm present, concentration, motility, and morphology
- **Varicoceles:** swollen veins in the scrotum, which houses the testicles
 - Present in about 16% of men, but 40% of infertile men
 - Harm sperm growth by blocking proper blood drainage, making the environment too warm for making sperm
- Any part of the male reproductive tract can be blocked, trapping sperm from being ejaculated
 - Repeated infections, surgery (e.g., vasectomy), swelling, or developmental defects

What is male infertility? <https://www.urologyhealth.org/urology-a-z/m/male-infertility>

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Male Causes: Genetics & Environment

▪Genetics:

- Most commonly causes azoospermia (lack of sperm in ejaculatory fluid)
- **Klinefelter's syndrome:** chromosomal variation causing an extra X chromosome in males (sometimes referred to as XXY)
 - Not inherited; randomly occurs during sex chromosome division in the egg or sperm
 - Usually results in primary testicular failure, leading to androgen deficiency and infertility

▪Environmental factors:

- Anabolic steroid use
- Cigarette smoking
- Diabetes
- Heavy alcohol use
- Heavy metal, pesticide, or radiation exposure
- History of mumps infection
- Marijuana and other recreational drugs

What is male infertility? <https://www.urologyhealth.org/urology-a-z/m/male-infertility/>; Rare disease database: 47,XXY (Klinefelter Syndrome). <https://rarediseases.org/rare-diseases/47-xy-klinefelter-syndrome/>

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History of Assisted Reproduction

- Encompasses a range of technologies used to enhance probability of conception
- Involves direct handling of oocytes, sperm, and/or resulting embryos outside the body
- First baby born through *in vitro* fertilization (IVF) was Louise Brown in 1978
 - British medical researcher Robert Edwards and gynecologist Patrick Steptoe
 - Edwards later won a share of the 2010 Nobel Prize for his work developing IVF technique
- Over the next 3 decades, ART produced about 5 million babies worldwide

ART = assisted reproductive technology

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Ovulation-Inducing Medications

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QUESTION 2

Which of the following accurately describes cetrorelix acetate?

- A. It is a GnRH agonist used for IVF stimulation
- B. It increases ovarian FSH and LH production
- C. It prevents spontaneous ovulation during IVF

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Ovulation Induction

- About 25% of infertile women have ovulation problems (i.e., ovulate less often or not at all)
- For anovulatory women, the goal is to develop and ovulate one follicle

[No author]. *Med Lett Drugs Ther.* 2011;53(1376):86-88.

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Clomiphene Citrate

Mechanism of Action

- Nonsteroidal estrogen agonist-antagonist
- Blocks estrogen production → hypothalamus releases GnRH → pituitary gland releases FSH and LH

Dosing

- 50 mg orally at bedtime for 5 days starting between cycle days 2 and 5
- If patient does not ovulate, can increase to 100 mg daily (manufacturer max 100 mg/day, ASRM max 200 mg/day)

Adverse Effects

- Abnormal uterine bleeding, breast discomfort, gastrointestinal disturbances, headaches, hot flashes, mood swings, visual changes (rarely, OHSS)

ASRM = American Society for Reproductive Medicine; OHSS = ovarian hyperstimulation syndrome
Clomid [prescribing information]. 2012.; [No author]. *Med Lett Drugs Ther.* 2011;53(1376):86-88.

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Clomiphene Citrate: Clinical Pearls

- About 80% of anovulatory women taking clomiphene will ovulate
 - Only 10% to 13% will get pregnant per cycle, so multiple courses often required
- When to discontinue use and consider other options:
 - If ovulation does not occur after 3 courses of treatment
 - If 3 ovulatory responses occur but the patient does not conceive, further treat
- Tendency to cause multiple eggs to ovulate, so incidence of multiple pregnancies (e.g., twins, triplets) is increased
 - 7.98% chance of multiples (6.9% twins, 0.5% triplets, 0.3% quadruplets, 0.1% quintuplets)
 - Risk is dose-dependent

9 things you should know about Clomid. <https://www.freedomfertility.com/blog/9-things-you-should-know-about-clomid/>; Clomid [prescribing information]. 2012.

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Clomiphene Citrate: Male Use

- Pharmacy teams may encounter clomiphene prescriptions for male patients
- Male patients with low sperm count due to low testosterone may use clomiphene to support spermatogenesis
 - FSH: supports sperm maturation
 - LH: increases testosterone levels
- Typical starting dose is 25 mg daily

Clomid for Men: Can it Cure Low Sperm Count? <https://www.malefertility.com/blog/clomid-for-men-can-it-cure-low-sperm-count>

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Letrozole (Off-Label)

Mechanism of Action

- Nonsteroidal aromatase inhibitor
- Aromatase converts androgens to estrogen, so letrozole suppresses estrogen production → pituitary gland releases FSH + LH → follicle development

Dosing

- 2.5 mg once daily on cycle days 5 through 9
- Some patients take 5 mg or 7.5 mg

Adverse Effects

- Arthralgia, asthenia, bone pain, dizziness, edema, flushing, headache, hot flashes, hypercholesterolemia, increased sweating
- Generally better tolerated than clomiphene citrate

[No author]. *Med Lett Drugs Ther.* 2011;53(1376):86-88.; Femara (letrozole) for infertility, ovulation problems and PCOS treatment. <https://advancedfertility.com/fertility-medications/femara-letrozole-treatment/>; Femara [prescribing information].

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Letrozole: Clinical Pearls

- About 65% to 80% of anovulatory women taking clomiphene will ovulate
- No official recommendation for a maximum number of cycles
 - Women with breast cancer use letrozole daily, so some providers may be comfortable with longer-term use
- In 2005, fertility doctors in Canada raised concerns about birth defects
 - Clears from the bloodstream long before a fertilized embryo is present, so this is unlikely
 - ASRM indicates that providers can confidently advise patients that ovulation-inducing medications are not associated with increased risk of birth defects
- Rarely, REs use other aromatase inhibitors (e.g., anastrozole) to induce ovulation, but none are approved for this indication

[No author]. *Med Lett Drugs Ther.* 2011;53(1376):86-88.; Femara (letrozole) for infertility, ovulation problems and PCOS treatment. <https://advancedfertility.com/fertility-medications/femara-letrozole-treatment/>;

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Correcting Hyperprolactinemia

- Some women do not ovulate due to hyperprolactinemia (i.e., pituitary gland secretes too much prolactin)
 - Inhibits FSH and LH release
- Many causes, including adenoma, use of certain drugs (e.g., alcohol, hallucinogens, oral contraceptives, painkillers, tranquilizers), and kidney or thyroid disease
- Bromocriptine (once daily) or cabergoline (twice daily) reduce amount of prolactin secreted by pituitary gland
 - Prolactin levels return to normal for 90% of patients
 - 85% will ovulate and potentially conceive if no other infertility causes present
 - If prolactin levels normal but no ovulation, may use concurrently with clomiphene or gonadotropins
- Adverse effects: dizziness, drowsiness, fainting, fatigue, headaches, hypotension, nasal congestion, nausea, and vomiting

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Injectable Gonadotropins

Mechanism of Action

- Contain FSH alone or in combination with LH
- Work directly on the ovaries to develop multiple follicles, rather than working with the brain to stimulate ovaries
- Combination products are referred to as menotropins or human menopausal gonadotropin (hMG)

Dosing

- Variable depending on product

Adverse Effects

- Abdominal pain, breast tenderness, headache, injection-site reactions, mood swings (milder than with clomiphene), nausea
- OHSS is the most serious adverse effect, requiring hospitalization in up to 2% of gonadotropin cycles

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Injectable Gonadotropins

Medication Class	Examples
Follicle stimulating hormone (FSH)	urofollitropin (urinary-derived) follitropin alpha (recombinant) follitropin beta (recombinant)
Luteinizing hormone (LH)*	lutropin alpha (recombinant)
Human chorionic gonadotropin (hCG)	chorionic gonadotropin (urinary-derived) choriogonadotropin alfa (recombinant)
Human menopausal gonadotropin (hMG)	menotropins for injection (multiple products, all urinary-derived)

*used in conjunction with FSH, not alone

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Injectable Gonadotropins

- Used in women of advanced fertility age (35 years or older) or those who have not conceived after oral treatment
- Patients may be concerned about “using up” or “wasting” more eggs due to maturation of multiple follicles
 - Rescue the eggs that would normally die off, allowing them to be available for retrieval (discussed later) or conception
- Risk of multiple births is 30% when used alone or in combination with IUI
 - Compared with 1% to 2% of naturally-occurring pregnancies

IUI = intrauterine insemination

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Human Chorionic Gonadotropin (hCG)

- Used to induce final follicular maturation and ovulation
- Often referred to as a “trigger shot”
- Injecting hCG subcutaneously or intramuscularly also stimulates ovaries to produce progesterone
 - Important for uterus to prepare for embryo implantation
- If too many follicles develop or estrogen levels are too high, RE may withhold hCG to reduce risk of OHSS or high-order (i.e., more than twins) multiple pregnancy

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Ovarian Hyperstimulation Syndrome (OHSS)

- Symptoms appear a few days after ovulation
- Excessive response to medications used to make eggs grow (especially injectable gonadotropins)
 - Large number of growing follicles + high estrogen levels
 - Ovaries swell and leak fluid into the abdomen
- Can be mild, moderate or severe
 - Severe cases cause vascular permeability and ascites, potentially leading to blood clots, decreased renal perfusion, hypovolemia, hyperkalemia, and respiratory difficulty
 - Rarely, OHSS is fatal
- **Advise women to seek medical attention following ovarian stimulation if they experience:**
 - abdominal swelling
 - continued nausea and/or vomiting
 - decreased urination
 - difficulty breathing
 - difficulty tolerating fluids
 - facial numbness
 - lower extremity swelling
 - sudden abdominal pain onset
 - weight gain more than 3 pounds in 2 days
 - weakness

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Gonadotropin-Releasing Hormone (GnRH) Analogs

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GnRH and Conception

- Hypothalamus naturally releases small amounts of GnRH about every 90 minutes
 - This stimulates pituitary gland to produce FSH and LH
- **GnRH analogs (agonists and antagonists):** synthetic hormones similar to naturally-occurring GnRH that are chemically modified to make them last longer in the body
- Used to prevent spontaneous natural ovulation in women undergoing reproductive procedures

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GnRH Analogs

	GnRH Agonists	GnRH Antagonists*
Examples	<ul style="list-style-type: none"> ▪ Nafarelin acetate ▪ Goserelin acetate ▪ Leuprolide acetate** 	<ul style="list-style-type: none"> ▪ Ganirelix acetate ▪ Cetrorelix acetate
Mechanism	<ul style="list-style-type: none"> ▪ Provide constant GnRH exposure to produce initial FSH and LH release followed by decline to prevent spontaneous ovulation 	<ul style="list-style-type: none"> ▪ Suppress FSH and LH production without the initial rise seen with GnRH agonists
Adverse Effects	<p style="text-align: center;"><i>Temporary:</i> hot flashes, mood swings, and vaginal dryness <i>Long-term:</i> bone loss, decreased breast size, headaches, insomnia, painful intercourse</p>	

*oral relugolix and elagolix are available, but they are approved for prostate cancer and endometriosis pain, respectively

**not approved for infertility treatment, but used off label for this indication

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Insulin-Sensitizing Agents

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Role of Insulin in Fertility

- About 70% of women with PCOS experience insulin resistance and hyperinsulinemia due to increased weight
- Hyperinsulinemia may contribute to excess testosterone production and can lead to ovulatory issues
- Some will benefit from insulin-sensitizing agents

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Metformin (Off-Label)

- Metformin alone for 4-6 months can regulate menstrual periods/ovulation in some women with PCOS
 - May also increase effectiveness of clomiphene for women with PCOS
- Most common adverse effect is gastrointestinal irritation (e.g., diarrhea, nausea)
 - Usually improves after a few weeks of use
- Rare but serious adverse effect is lactic acidosis
 - Monitor for abdominal pain, deep and rapid breathing, heart-rhythm disturbances, lethargy, and vomiting
- Other insulin-sensitizing agents (e.g., pioglitazone, rosiglitazone) have also been used off-label

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QUESTION 3

A 32-year-old female patient is filling progesterone in oil at your pharmacy, and she indicates that she is two weeks post-embryo transfer after IVF. She complains that the injection is very painful and asks if you have any advice. Which of the following is the best counseling point for this patient?

- A. Apply a heating pad to the injection site after injection
- B. Keep the medication in the refrigerator until it is time to inject
- C. You should only need this one more week, try to stick it out

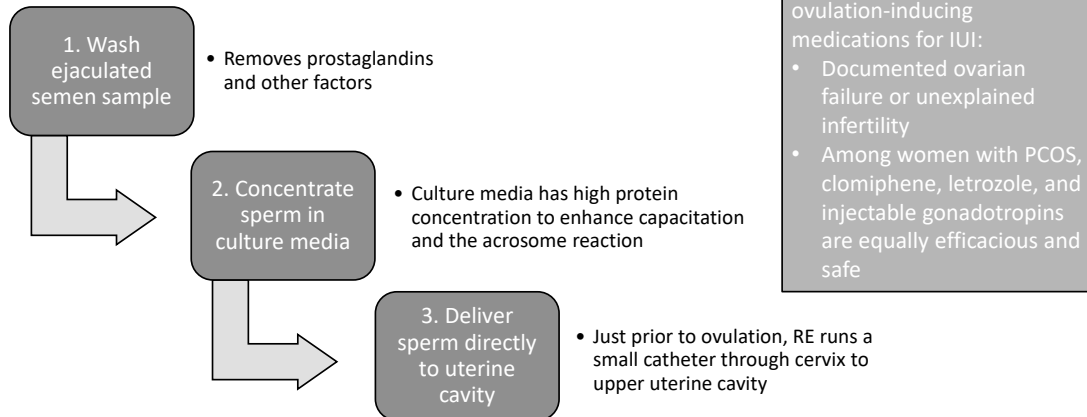
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Assisted Reproductive Technology

PROCEDURES FOR INFERTILITY AND WHERE MEDICATIONS FIT IN

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Intrauterine Insemination (IUI)



Huang S, et al. *Eur J Obstet Gynecol Reprod Biol.* 2018;231:117-121.

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Who is IUI Ideal for?

- Male factor infertility
 - More than doubles the pregnancy rate
- Cervical factor infertility
 - Sperm cannot swim through cervical mucus or anti-sperm antibodies are present
- Utilizing sperm donor
- Unexplained infertility (sometimes)

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In Vitro Fertilization (IVF)

1. Ovarian Stimulation: Medications to stimulate multiple eggs to mature and grow

2. Egg Retrieval: Minor surgical procedure using an ultrasound-guided needle to retrieve multiple eggs

3. Fertilization: Laboratory fertilization via insemination or ICSI

4. Embryo Culture: Incubation of fertilized embryos to grow and divide

5. Embryo Transfer: Transfer of 1 or more embryos back into a woman's uterus

ICSI = intracytoplasmic sperm injection

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Who is IVF Ideal For?

- Historically used for women with blocked, damaged, or absent fallopian tubes
- Now, REs use IVF for many infertility causes
 - Endometriosis
 - Male factor infertility
 - Unexplained infertility
- Those with 3 or more failed IUI attempts
- ICSI is ideal when there is a likelihood of reduce fertilization
 - Poor semen quality
 - History of failed fertilization in another IVF cycle
 - Performed in about 60% of IVF cycles

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IVF Ovarian Stimulation Protocols

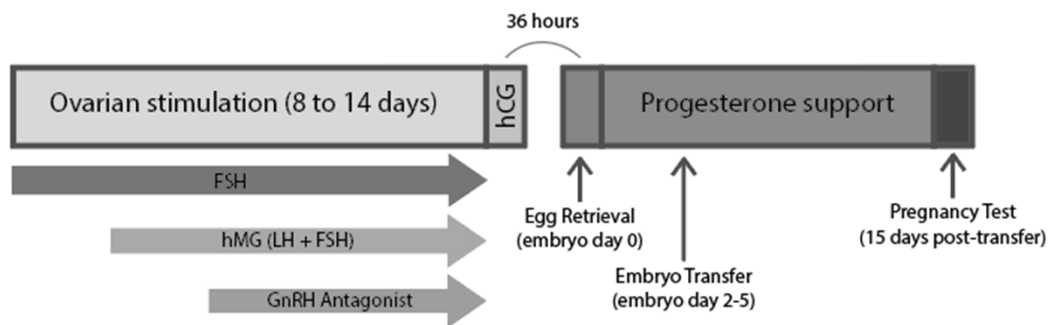
- No one-size-fits-all solution
- Ovarian stimulation protocols in the U.S. generally involve at least 3 drugs:
 1. FSH product to stimulate multiple eggs to develop
 2. GnRH agonist or antagonist to suppress premature LH surge and natural ovulation
 3. hCG to cause final egg maturation
- “Antagonist protocol” (also known as “short protocol”) is most common
 - Involves the fewest injections and is effective for most patients

Additional Resources:

1. Shrestha D, et al. Comparison of different stimulation protocols used in in vitro fertilization: a review. *Ann Transl Med.* 2015;3:137.
2. Pacchiarotti A, et al. Ovarian stimulation protocol in IVF: an up-to-date review of the literature. *Curr Pharm Biotechnol.* 2016;17:303-315.

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Antagonist IVF Stimulation Protocol



FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; LH, luteinizing hormone

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Supportive Therapies

- Blood thinners (e.g., aspirin, enoxaparin)
 - For patients with recurrent miscarriage caused by blood clotting problems
 - Antiphospholipid syndrome (APS)
 - Thrombophilias
- Estrogen support (oral, transdermal, and/or vaginal)
 - Helps to grow and maintain the endometrial lining and sustain pregnancy
 - Also a down-regulator to prevent natural spontaneous ovulation
 - Most common for donor-egg cycles or frozen embryo transfers
- Progesterone support (vaginal or intramuscular)
 - IVF medications can hinder the body's ability to make progesterone
 - Typically initiate the day of egg retrieval and continue through most of the first trimester

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Self-Administration Technique

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Subcutaneous Injection

1. Wash hands
2. Choose a spot to inject into the abdomen, top of the thigh, or back of the arm
3. Clean injection spot with alcohol swab and allow to air dry
4. Gently grasp a small fold of skin between thumb and index finger of nondominant hand
5. Insert entire needle at 45- to 90-degree angle into skin fold
6. Release pinched skin and inject medication in a slow, steady motion
7. When all medication is administered, pull needle straight out and apply gentle pressure with gauze
8. Dispose of needles in a Sharps container

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Intramuscular Injection

1. Wash hands
2. Choose a spot to inject into the hip, outer area of the mid-thigh, or deltoid muscle in the arm
3. Clean injection spot with alcohol swab and allow to air dry
4. Use thumb and index finger of nondominant hand to spread skin taut at injection site
5. Insert entire needle in quick, dart-like motion at 90-degree angle
6. Inject medication in a slow, steady motion
7. When all medication is administered, pull needle straight out and apply gentle pressure with gauze
8. Dispose of needles in a Sharps container

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Progesterone in Oil: Clinical Pearls

- Most patients feel this is the most cumbersome/bothersome
- Really large needle, inconvenient administration (often in buttocks)
- Warming the oil (under the armpit, etc. NOT in the microwave) before drawing out the dose thins it to reduce discomfort
- Applying a heating pad and gently massaging the area after injection can be helpful

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Final Notes

- **MYTH:** utilizing ART means you are guaranteed a baby
 - Only about 1/3 of IVF cycles with embryo transfer result in pregnancy
- Use of ART has doubled over the past decade
 - 306,197 ART cycles performed at 456 clinics in 2018
 - 131,115 embryo transfers
 - 57,989 resulted in live births
- Approximately 1.7% of all infants born in the U.S. every year are conceived using ART

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Questions?
