

FEMALE INFERTILITY TREATMENTS (Part 1 of 2)

Definition: According to the World Health Organization (WHO), infertility is a “disease of the reproductive system defined by the failure to achieve clinical pregnancy after 12 months of regular, unprotected sexual intercourse” in women aged ≤35yrs. Infertility in women aged >35yrs is the inability to become pregnant after 6 months of unprotected intercourse. Both men and women can be infertile; important for both partners to be evaluated. Female infertility accounts for ~33% of infertility cases, which is more common in older women (>35yrs old) due to ovarian aging, gynecological diseases such as endometriosis, hormonal changes, and increased likelihood of spontaneous abortions (miscarriage).

Causes: Underlying causes of female infertility can be characterized as either ovulation disorders or tubal factors.

- Ovulation disorders: primary and secondary amenorrhea, low gonadotropin levels, estrogen deficiency, PCOS, hyperprolactinemic amenorrhea, premature ovarian failure, radiation, chemotherapy, or pelvic surgery.
- Tubal factors: most common is PID, especially when caused by *Chlamydia trachomatis* or *Neisseria gonorrhoea* infection. Others include endometriosis, compression from a mass such as fibroid, adhesions from pelvic surgery, or congenital abnormalities.

Treatments¹: Treatments include medications to suppress ovulation (GnRH agonists and antagonists), medications to stimulate follicle growth and maturation (gonadotropins, domiphen), hCG to trigger ovulation, and progesterone for endometrial support. Many of these treatment options are used in conjunction with ART, such as IVF and IUI, to regulate hormone levels and control ovulation.

ART step-wise approach: **Step 1:** Prestimulation treatment during cycle preceding ART cycle: oral contraceptives, then GnRH agonist/antagonist. **Step 2:** Ovarian stimulation with gonadotropins. **Step 3:** Monitor follicular development. **Step 4:** Final oocyte maturation with hCG administration. **Step 5:** Oocyte retrieval. **Step 6:** Sperm collection. **Step 7:** Embryology lab procedures. **Step 8:** Embryo transfer. **Step 9:** Cryopreservation of viable embryos. **Step 10:** Hormonal support of the endometrium with progesterone. **Step 11:** Pregnancy test. **Step 12:** Early pregnancy follow-up. This chart focuses on treatment options for female infertility. It includes both medications that are FDA-approved and off-label use.

Generic	Brand	Strength	Dosage Form	Dose	When to Start	Notes
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PRESTIMULATION TREATMENT

GnRH Agonists

leuprolide ²	—	5mg/mL	SC inj	0.5–1mg SC daily. Dose is halved during ovulation stimulation.	7 days before ovulation stimulation	<ul style="list-style-type: none"> • Continue until the day of hCG administration. • Administered with gonadotropins.
nafarelin acetate ³	Synarel	200mcg/spray	intranasal	<i>ART:</i> 400mcg twice daily as 1 spray into each nostril in AM and PM. <i>Endometriosis:</i> 400mcg daily as 1 spray in one nostril in AM and repeat in other nostril in PM. If menstruation continues after 2mos of therapy, increase to 800mcg daily as 1 spray into each nostril in AM and PM.	Cycle day 2	<ul style="list-style-type: none"> • <i>ART:</i> continue until the day of hCG administration. • <i>Endometriosis:</i> treat for 6mos; retreatment is not recommended.

GnRH Antagonists

cetorelix ³	Cetrotide	0.25mg	SC inj	0.25mg SC daily	Stimulation day 5 (morning or evening) or 6 (morning)	<ul style="list-style-type: none"> • Continue until the day of hCG administration. • Can be self-administered.
ganirelix acetate ³	—	250mcg/0.5mL	SC inj	250mcg SC daily	Cycle day 7 or 8 (mid to late follicular phase)	<ul style="list-style-type: none"> • Continue until the day of hCG administration. • Needle shield contains latex

OVARIAN STIMULATION

Gonadotropins

follitropin-alfa ³ (recombinant)	Gonal-F RFF Gonal-F RFF Pen	75 IU 300 IU, 450 IU, 900 IU	SC inj SC inj	<i>ART:</i> initially 150 IU SC daily in early follicular phase; usual max 10 days. <i>ART in women with suppressed endogenous gonadotropin levels:</i> <35yrs: initially 150 IU SC daily; ≥35yrs: initially 225 IU SC daily. All: adjust dose after 5 days based on response, then by up to 75–150 IU every 3–5 days; max 450 IU/day. <i>Induction of ovulation:</i> initially 75 IU SC daily for 14 days in the first cycle; then determine subsequent doses based on response; if indicated, may increase after the initial 14 days, then every 7 days in increments of up to 37.5 IU; usual max 300 IU/day for up to 35 days.	Cycle day 2 or 3 for ART	<ul style="list-style-type: none"> • Continue treatment until pre-ovulatory conditions are reached or adequate follicular development is evident, then administer hCG to induce final follicular maturation.
follitropin-beta ³ (recombinant)	Follistim-AQ	150 IU, 300 IU, 600 IU, 900 IU	SC inj	<i>Anovulatory women undergoing ovulation induction:</i> initially 50 IU SC daily for at least first 7 days; may increase by 25–50 IU at weekly intervals based on response. Max 250 IU/day. <i>Normal ovulatory women undergoing IVF or ICSI cycle:</i> initially 200 IU SC daily for at least first 7 days of treatment, then adjust based on response. Max 500 IU/day.	Cycle day 2 or 3 for ART	<ul style="list-style-type: none"> • Continue treatment until pre-ovulatory conditions are reached or adequate follicular development is evident, then administer 5,000–10,000 IU hCG to induce final oocyte maturation and ovulation.
menotropins (FSH, LH) ³	Menopur	75 IU FSH/75 IU LH	SC inj	Initially 225 IU SC daily for 5 days. Adjust dose based on response in increments of up to 150 IU at intervals of at least 2 days; max 450 IU daily; usual max 20 days.	Cycle day 2 or 3	<ul style="list-style-type: none"> • Continue treatment until adequate follicular development is evident, then administer hCG to induce final follicular maturation.

(continued)

FEMALE INFERTILITY TREATMENTS (Part 2 of 2)

Generic	Brand	Strength	Dosage Form	Dose	When to Start	Notes
OVARIAN STIMULATION (continued)						
Selective Estrogen Receptor Modulator (SERM)						
domiphene citrate ³	—	50mg	tabs	50mg daily for 5 days; max 3 courses. If ovulation does not occur, may increase dose to 100mg daily during the 2nd course of therapy. Max 100mg/day for 5 days.	On or about cycle day 5	<ul style="list-style-type: none"> Not recommended for >6 cycles. Ovulation most often occurs 5-10 days after treatment.

FINAL OOCYTE MATURATION						
Human Chorionic Gonadotropin (hCG)						
chorionic gonadotropin (u-hCG) ³	—	5000Units/10mL, 10000Units/10mL	IM inj	<i>Ovulation induction:</i> 5,000–10,000 Units IM once.	1 day after the last dose of gonadotropins	<ul style="list-style-type: none"> Avoid pregnancy test <10 days after hCG inj as it can yield false positive result.
choriogonadotropin alfa (r-hCG) ³	Ovidrel	250mcg/0.5mL	SC inj	<i>ART or ovulation induction:</i> 250mcg SC once.	1 day after the last dose of follicle stimulating agent	<ul style="list-style-type: none"> May be self-administered by the patient. Avoid pregnancy test <10 days after hCG inj as it can yield false positive result.

ENDOMETRIAL SUPPORT						
Progesterones						
progesterone	—	50mg/mL	IM inj	<i>ART:</i> 50–100mg IM once daily ² . <i>Secondary amenorrhea:</i> 5–10mg IM daily for 6–8 days.	The day after oocyte retrieval in women undergoing ART	<ul style="list-style-type: none"> May be used to maintain pregnancy. Contains sesame oil; contraindicated in patients with sesame oil/seed allergy.
	Crinone	4% (45mg), 8% (90mg)	vaginal gel	<i>ART (supplementation):</i> 1 applicatorful of 90mg (8%) intravaginally once daily; <i>(replacement for ovarian failure):</i> 1 applicatorful of 90mg (8%) intravaginally twice daily. <i>Secondary amenorrhea:</i> 1 applicatorful of 45mg (4%) intravaginally every other day, up to 6 doses total. If failure occurs, may try 90mg (8%) every other day up to 6 doses total.	The day after oocyte retrieval in women undergoing ART	<ul style="list-style-type: none"> May be used to maintain pregnancy. If pregnancy occurs, treatment may be continued until placental autonomy is achieved, up to 10-12wks. Should not be used concurrently with other local intravaginal therapy.
	Endometrin	100mg	vaginal insert	<i>ART:</i> 100mg intravaginally 2–3 times daily for up to 10wks.	The day after oocyte retrieval in women undergoing ART	<ul style="list-style-type: none"> May be used to maintain pregnancy. Not recommended for use with other vaginal products.
	Prometrium	100mg, 200mg	caps	<i>Secondary amenorrhea:</i> 400mg daily at bedtime for 10 days.	The day after oocyte retrieval in women undergoing ART	<ul style="list-style-type: none"> Contains peanut oil; contraindicated in patients with peanut allergy. Food increases oral bioavailability.

NONPHARMACOLOGIC THERAPY						
<ul style="list-style-type: none"> Nutrition: dietary evaluation by a registered dietitian for patients with amenorrhea due to weight loss or extreme exercise Reduction in marijuana use⁴ Stress management from licensed healthcare provider⁵ Smoking cessation⁶ 						

NOTES						
<p>Key: ART = assisted reproductive technology; FSH = follicle stimulating hormone; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; IM = intramuscular; IU = international units; IUI = intrauterine insemination; IVF = in vitro fertilization; LH = luteinizing hormone; PCOS= polycystic ovary syndrome; PID = pelvic inflammatory disease; SC = subcutaneous.</p>						

<p>¹ To be used with timed intercourse or ART.</p> <p>² Not FDA-approved but has been successfully used in IVF for years (off-label use).</p> <p>³ Patient must not be pregnant at start of treatment.</p> <p>⁴ Marijuana inhibits GnRH secretion.</p> <p>⁵ Stress can cause hormone imbalances, leading to irregular menstrual cycles.</p> <p>⁶ Smoking reduces the germ cells in both men and women, reducing the number of gametes (eggs and sperm) that are produced.</p>						
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Please see drug monograph at www.eMPR.com and/or contact company for full drug labeling.

REFERENCES						
<p>Ordóñez ND. Infertility. In: O'Connell M, Smith JA. eds. Women's Health Across the Lifespan, 2e. McGraw Hill; 2019.</p> <p>World Health Organization. Sexual and reproductive health. https://www.who.int/reproductivehealth/topics/infertility/en/. Accessed November 2, 2021.</p> <p>A Patient's Guide to Assisted Reproductive Technology. <i>Society for Assisted Reproductive Technology</i>. https://www.sart.org/patients/a-patients-guide-to-assisted-reproductive-technology. Accessed November 3, 2021.</p>						