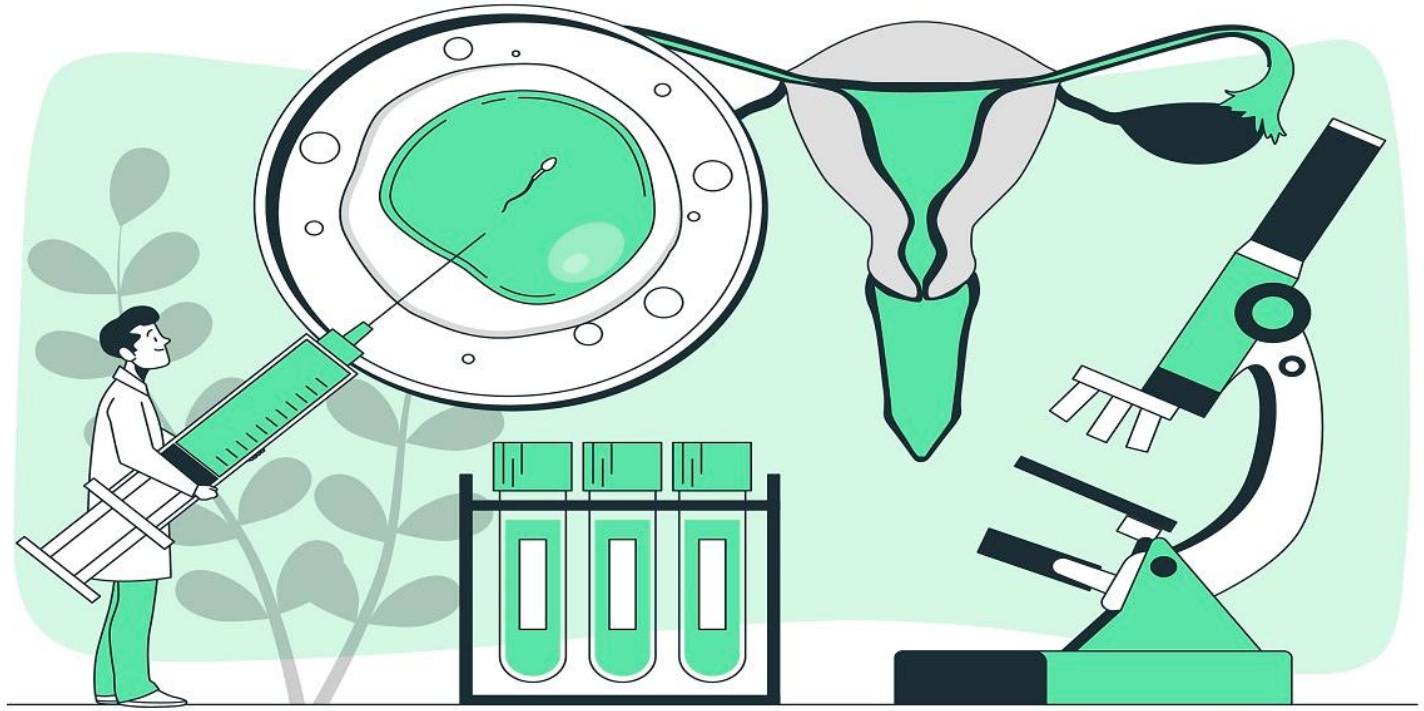

Drug Therapy in Assisted Reproductive Technology

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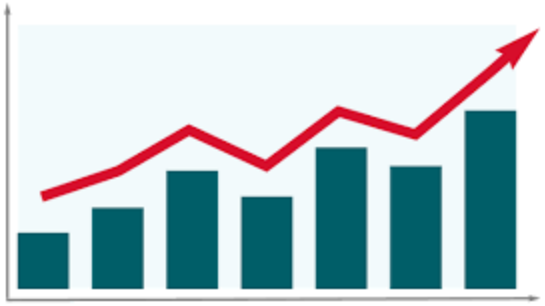
Overview and Indications

- A *variety of procedures* to address infertility factors **specific** to each couple.
- The use of ART is **trending upward**.



Description of Select Infertility Procedures

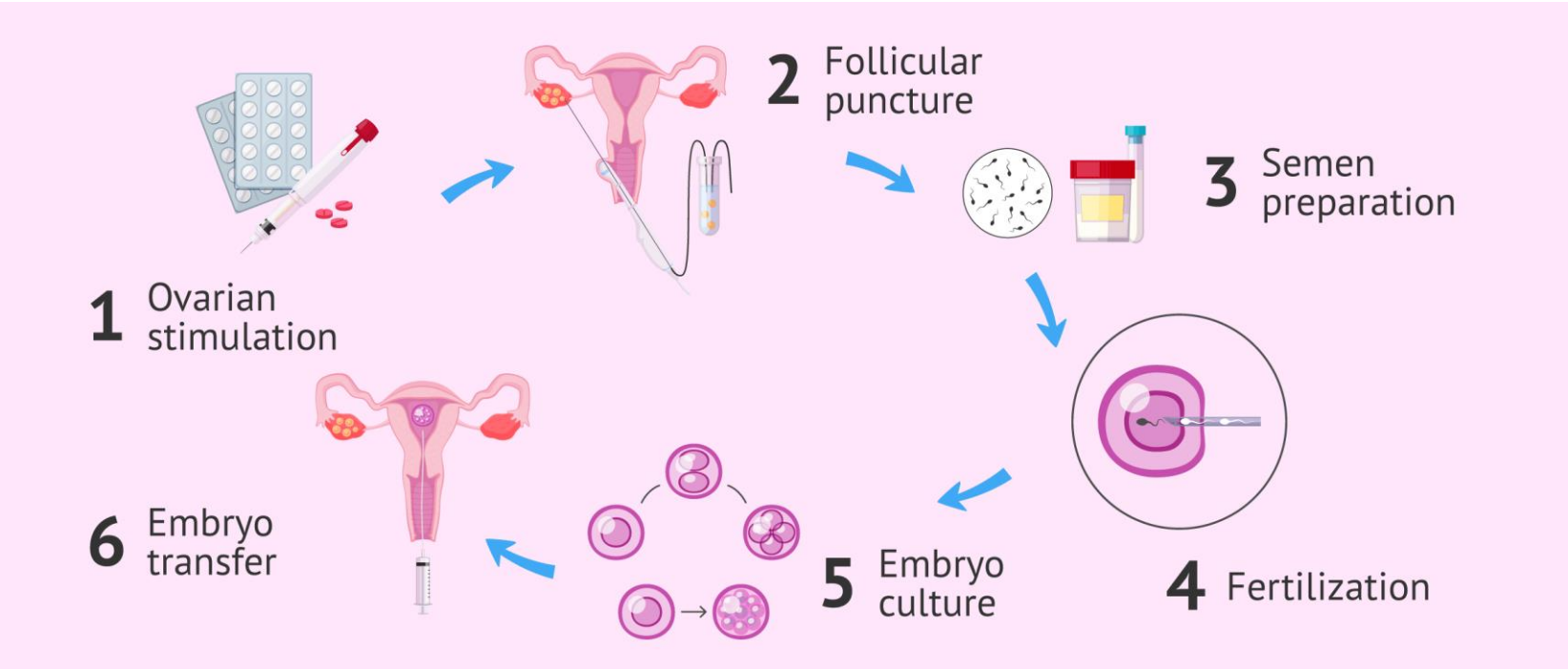
Classification	Procedure	Description
Insemination	Intrauterine, intracervical	Delivery of a prepared semen sample to the intended site (cervix, uterus) during ovulation
Assisted reproductive technology	Assisted hatching	Mechanical or chemical separation of the blastocyst from the zona pellucida (membrane surrounding the oocyte) during embryonic development in vitro
	Cryopreservation	Freezing and storage of biologic material (gametes, zygotes, embryos, blastocysts) for future ART cycles
	Gamete intrafallopian transfer	Laparoscopic transfer of the unfertilized oocytes and sperm to the fallopian tube for fertilization
	In vitro fertilization —embryo transfer	Transfer of one or more embryos resulting from in vitro fertilization into the uterus through the cervix
	Intracytoplasmic sperm injection	In vitro injection of the sperm into the oocyte
	Preimplantation genetic testing	Examination of oocytes or embryos for specific genetic abnormalities
	Zygote intrafallopian transfer	Laparoscopic transfer of the fertilized oocyte (zygote) into the fallopian tube

ART, assisted reproductive technology.

Source: Zegers-Hochschild F, Adamson GD, Dyer S, et al. The international glossary on infertility and fertility care, 2017. *Hum Reprod*. 2017;32(9):1786–1801.

Overview and Indications

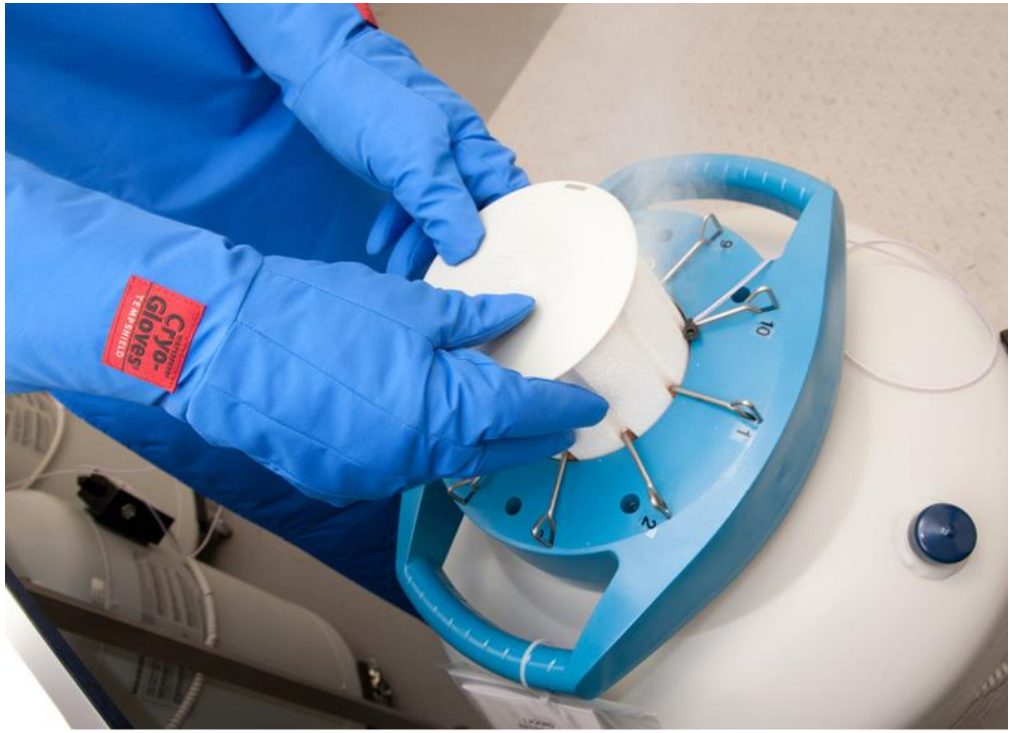
The primary ART is **IVF**, which involves retrieval of oocytes after ovarian stimulation (OS), fertilization in vitro, and transfer of the embryo(s) directly to the uterus through the cervix, bypassing the uterine tubes.



Overview and Indications

A variety of *ancillary procedures* can be used based upon each couple's history and clinical presentation:

- genetic screening
- cryopreservation of embryos
- donor sperm and/or oocytes



In Vitro Fertilization

The *basic steps* in an IVF protocol include OS, oocyte retrieval, fertilization, embryo culture, and embryo transfer.

Medications are primarily used during three main stages of IVF: OS, oocyte retrieval, and luteal phase support. Treatment **protocols vary widely** in the medications used, *dosing* regimens, and *timing* of administration.

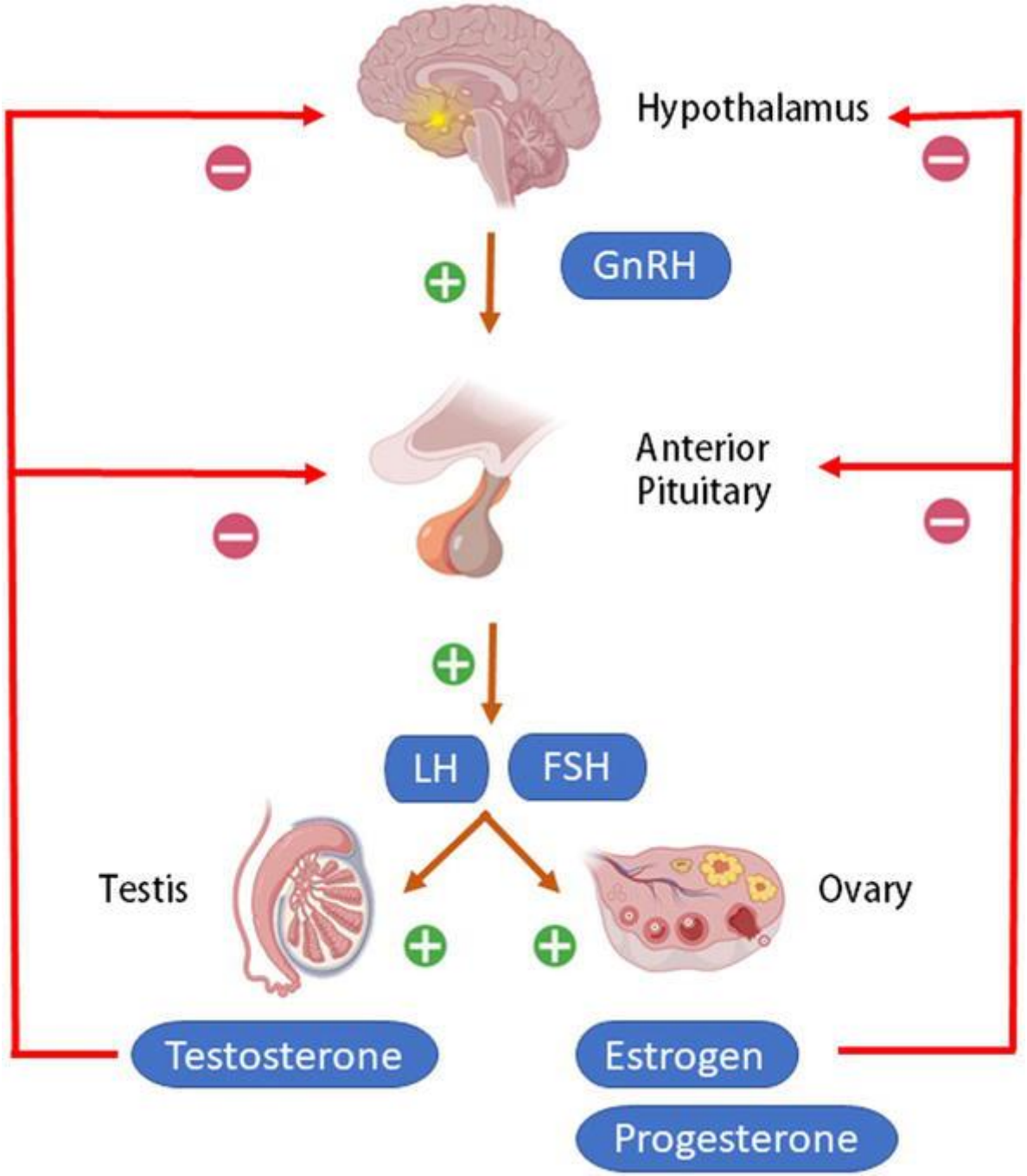
In Vitro Fertilization

Role of Medications in an In Vitro Fertilization Cycle

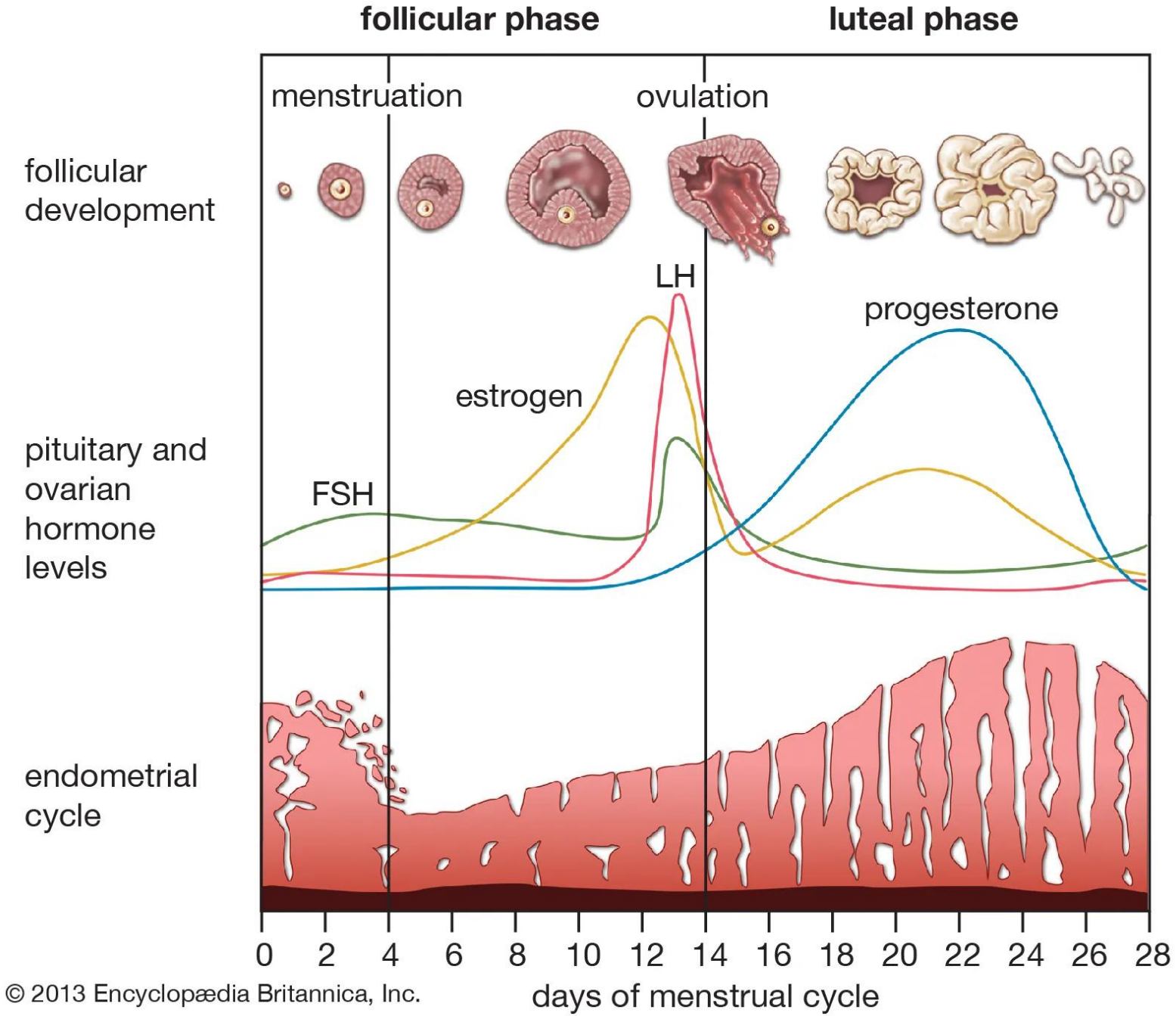
IVF Stage	Medications[a]	Role
Stage 1: ovarian stimulation	Oral contraceptives	Control the onset of menses and the start of controlled ovarian stimulation
	GnRH agonists or GnRH antagonists	Prevent a premature LH surge or disruption of controlled ovarian stimulation
	Gonadotropins (FSH or FSH plus LH)	Stimulate development of multiple ovarian follicles for oocyte retrieval
Stage 2: oocyte retrieval	hCG	Induce final follicular maturation to prepare for oocyte retrieval
Stage 3: luteal phase support	Progesterone	Maintain the endometrium for embryo transfer and implantation

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

[a]This list reflects the medications most commonly used during each stage. Alternate regimens vary widely by specialist.


Hypothalamus
GnRH
Anterior Pituitary
LH
FSH
Testis
Ovary
Testosterone
Estrogen
Progesterone

The menstrual cycle



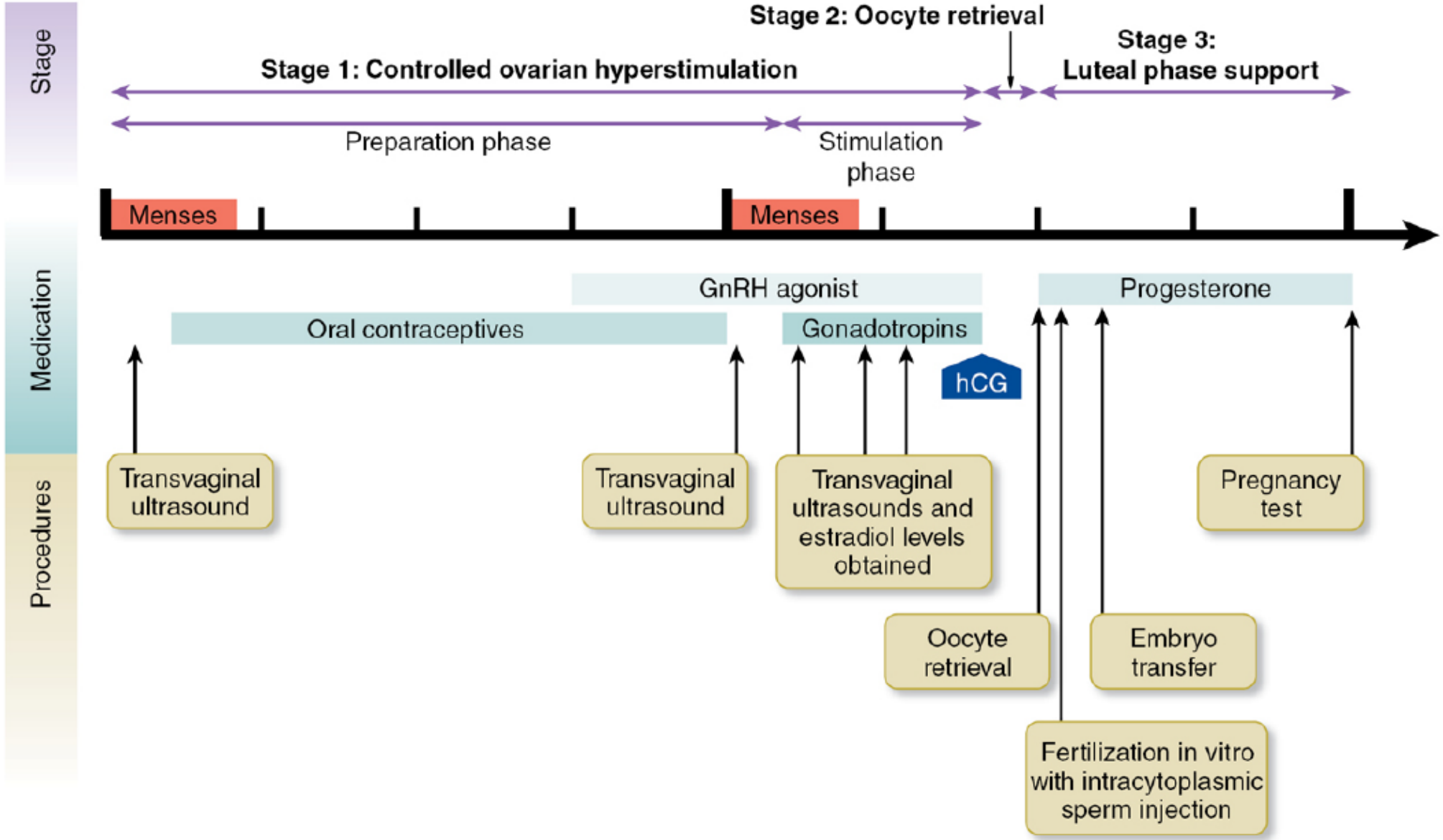
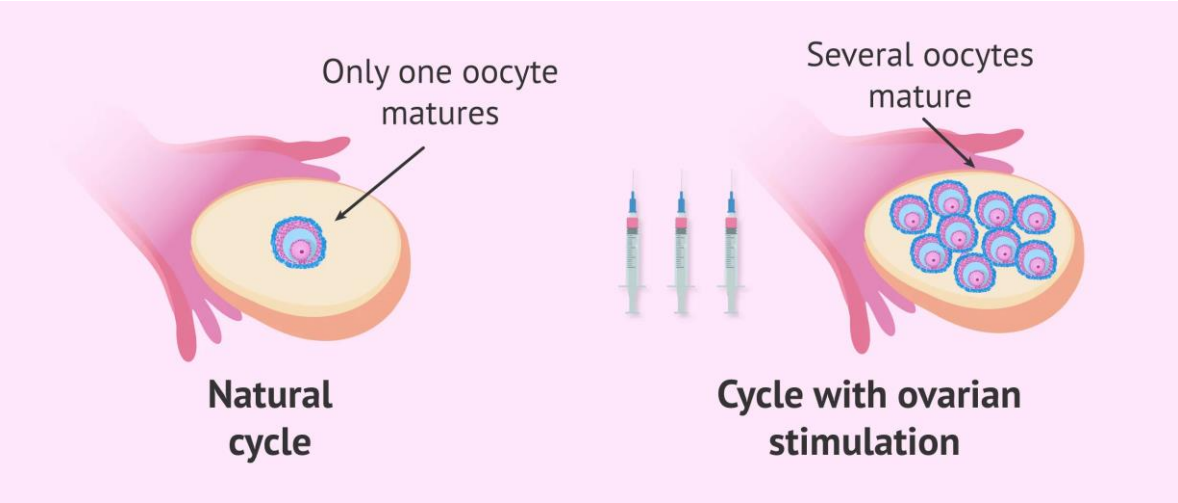


Figure 48-3 Sample in vitro fertilization protocol (Case 48-2). GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin.

Stage 1: Ovarian Stimulation

The *purpose* of OS for IVF is the **development of multiple follicles** for oocyte retrieval.

Although oocyte retrieval and fertilization can be performed during a *normal ovulatory cycle* without stimulation, it is **more common and many times necessary** to use this process.



Stage 1: Ovarian Stimulation

Oral Contraceptives

Many protocols start with the administration of oral contraceptives *control the timing* of the onset of the next menses **in order to plan** for initiating the OS regimen. This is particularly pertinent in females who have irregular or long menstrual cycles but may be used in those with regular menstrual cycles.

Stage 1: Ovarian Stimulation

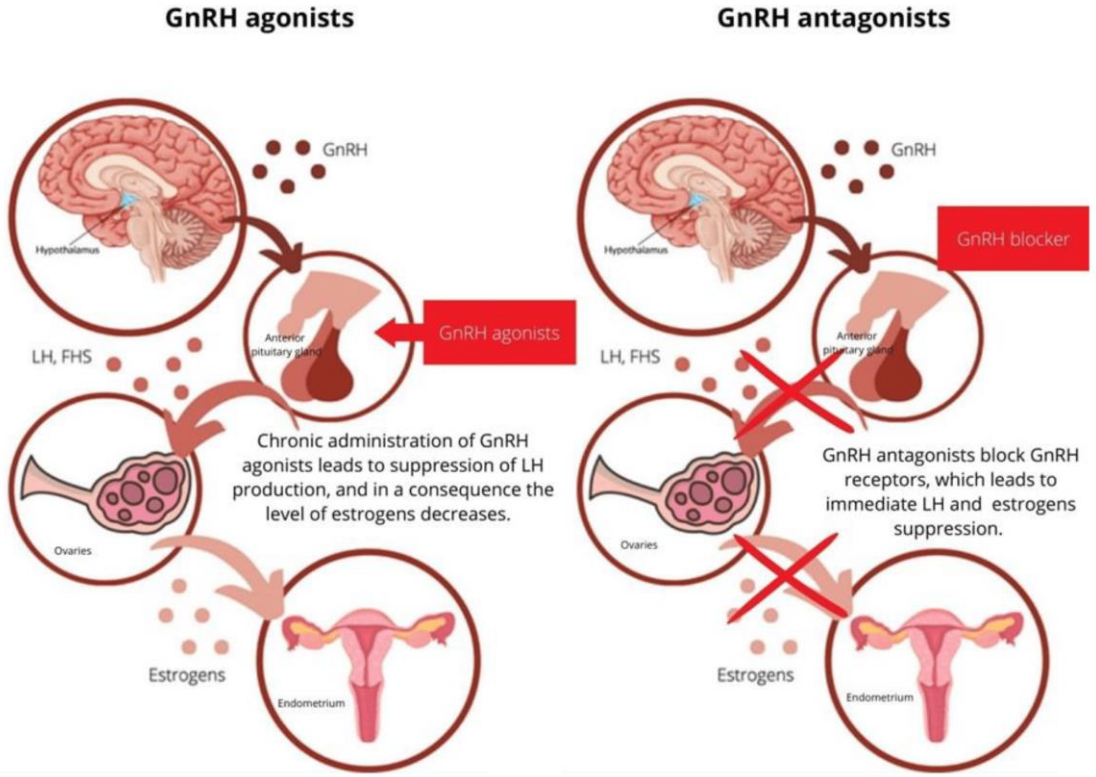
Gonadotropin-Releasing Hormone Analogs

- OS can be *interrupted* by an endogenous surge of LH that triggers ovulation prematurely.
- Most protocols use medications to *limit the influence* of any endogenous hormone levels as the cycle progresses.
- GnRH agonists have been used for this purpose for several decades.

Stage 1: Ovarian Stimulation

- Administration of a GnRH agonist initially increases pituitary gonadotropin release, often referred to as a "**flare**."

- Continued daily administration leads to *receptor downregulation* and reduced pituitary secretion of LH and FSH, allowing for direct administration of the gonadotropins by injection.

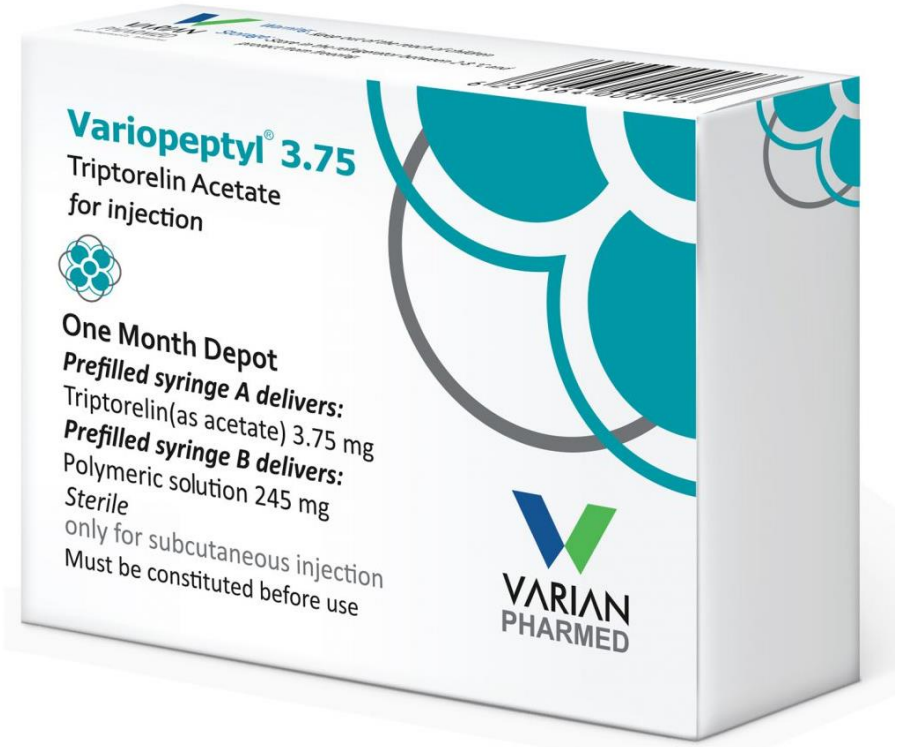


Stage 1: Ovarian Stimulation

Gonadotropin-Releasing Hormone Analogs for In Vitro Fertilization

Analog	Product Name	Strength/Dosage Form	Route of Administration
GnRH agonist	Nafarelin acetate (Synarel®)	2 mg/mL solution (200 µg/spray)	Intranasal
	Leuprolide acetate	1-mg/0.2-mL kit	SC
GnRH antagonist	Cetrorelix acetate[a] (Cetrotide®)	0.25-mg kit	SC
	Ganirelix acetate[a]	250-µg/0.5-mL syringe	SC

Stage 1: Ovarian Stimulation



Stage 1: Ovarian Stimulation

Stage 1: Ovarian Stimulation

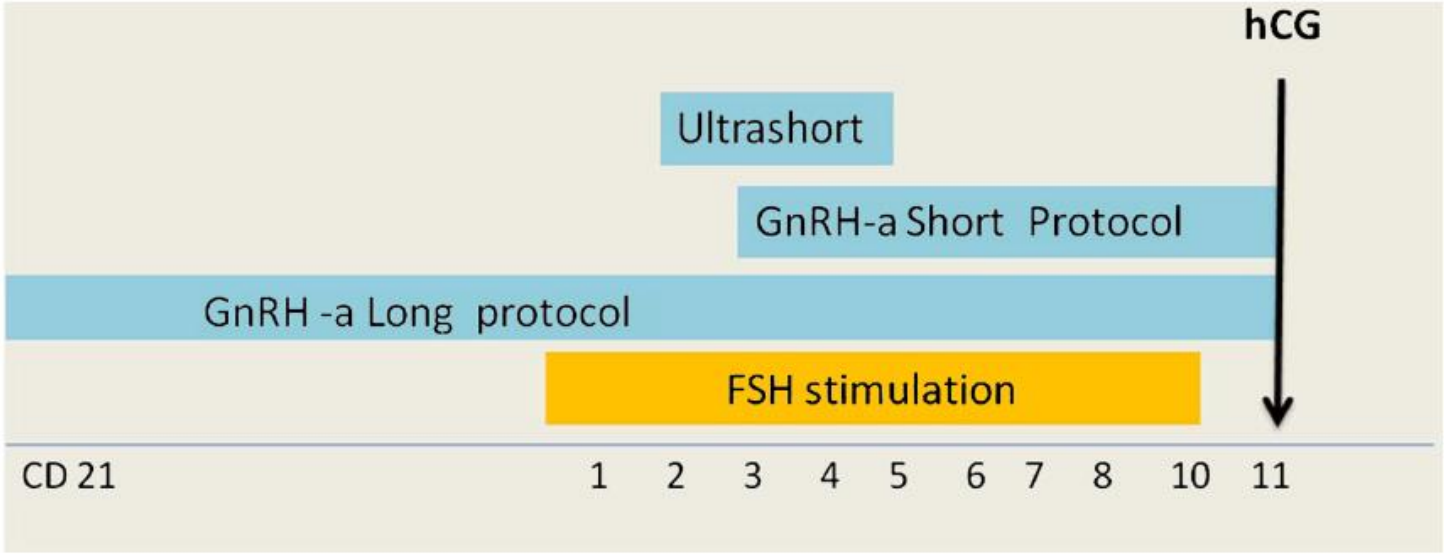
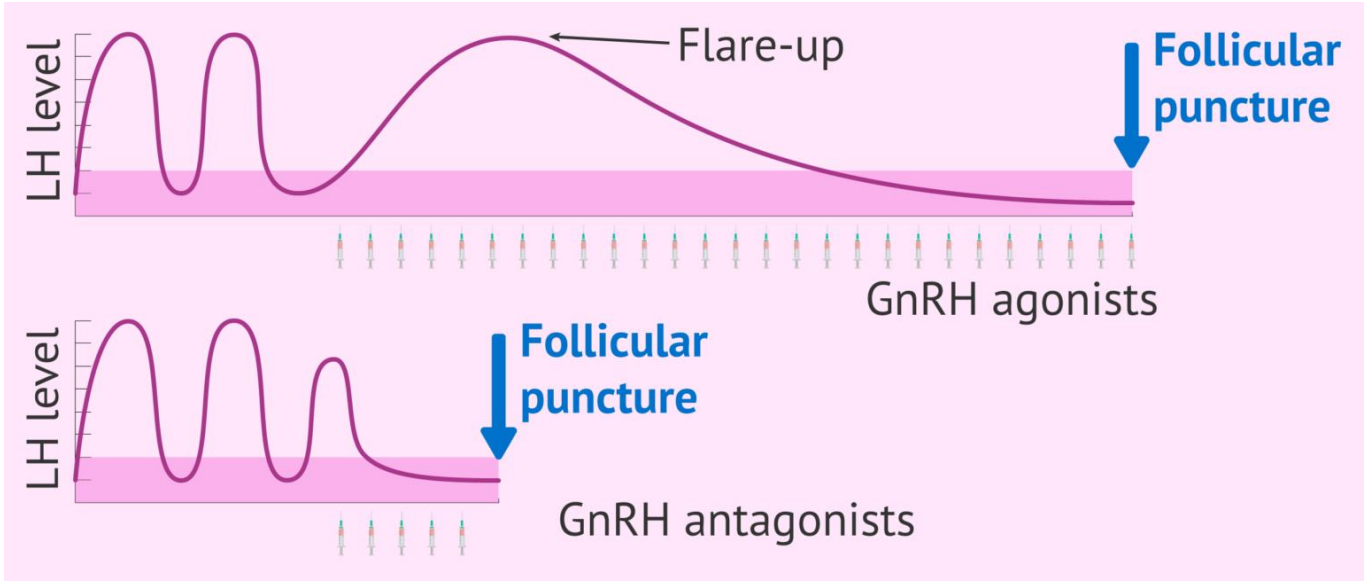


Figure 1 GnRH agonist protocols. Long Protocol: GnRH agonist 0.1 mg starting in follicular phase or luteal phase (Cycle Day 21) of the previuos cycle until hCG administration . Short Protocol: GnRH agonist 0.1 mg starting on day 1 or 3 of stimulation until hCG administration. Ultrashort Protocol: GnRH agonist 0.1 mg administered on day 2–4 of stimulation.

Stage 1: Ovarian Stimulation

The administration of GnRH analogs in the **long protocol** is associated with *hot flashes, headaches, and sleep disturbances* due to hypoestrogenic effects.

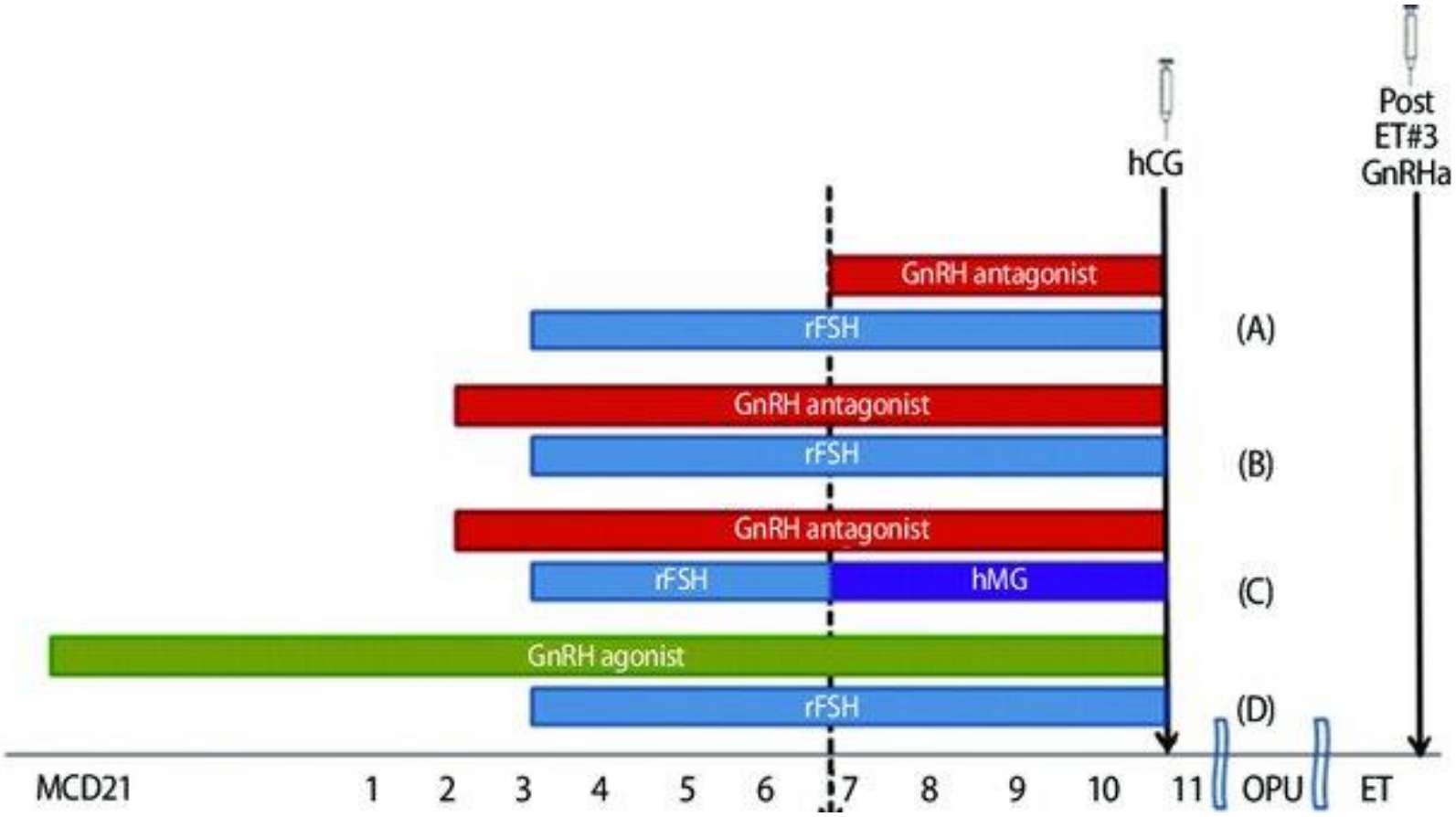
Local reactions at the injection site and nasal and throat irritation are adverse effects expected with the subcutaneous and intranasal routes of administration, respectively.



Stage 1: Ovarian Stimulation

Alternatively, the *immediate suppression* of gonadotropin secretion using **GnRH antagonists** such as cetrorelix and ganirelix allows for a shorter duration of administration and improved convenience and is associated with a **lower risk** for ovarian hyperstimulation syndrome (**OHSS**).

Stage 1: Ovarian Stimulation



Stage 1: Ovarian Stimulation

The **GnRH antagonists** are administered after the gonadotropin-induced follicular development is established, as either a *higher dose single injection* or a *lower dose daily injection* that is continued until ovulation is triggered.

Ganirelix is administered as a daily *250-µg subcutaneous injection*, and cetrorelix is either a *daily* subcutaneous injection of *0.25 mg* or a *single 3-mg dose*. The timing of initiation is either "fixed" on a particular day of stimulation or "flexible" based on follicular development. Available data suggest that there is **no difference in pregnancy and live birth rates** between GnRH agonist and antagonist protocols.

Stage 1: Ovarian Stimulation

Gonadotropins

The exogenous administration of **FSH** either *alone* or in *combination with LH* is intended to mimic the natural process of follicular recruitment and maturation.

Stage 1: Ovarian Stimulation

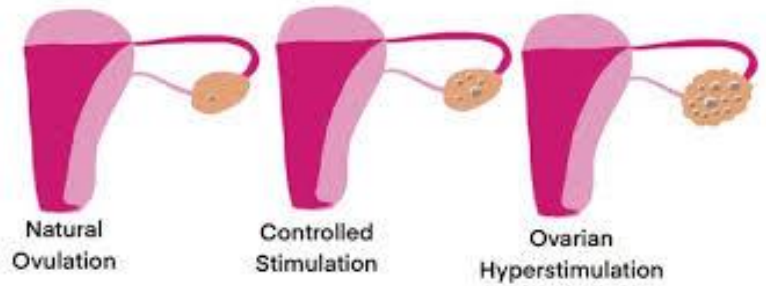
Dosage regimens for the gonadotropins are intended to promote **multiple follicles** for oocyte retrieval and vary widely among clinics. A common *starting dose* in fixed-dose protocols is **150 to 225 IU** daily, with further *dose adjustments* made *based on the status of the developing follicles*.

Treatment may continue for **7 to 12 days**, although *longer courses* may be necessary depending on follicular response. If subsequent cycles are needed, the initial treatment doses are chosen based on the stimulation achieved in the *first cycle*.

Stage 1: Ovarian Stimulation

The goal of gonadotropin therapy is to guide the development of multiple follicles for oocyte retrieval **without** increasing the risk for **OHSS**, a rare but serious complication of OS. In its *most severe form*, this syndrome is characterized by increased systemic vascular permeability that can result in ovarian rupture, thromboembolism, renal failure, and acute respiratory distress syndrome.

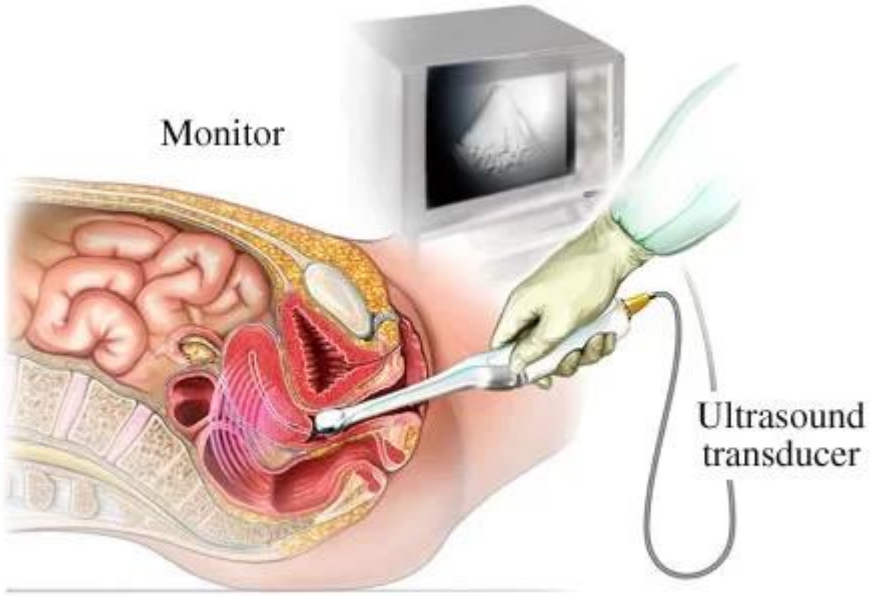
	Increase of estradiol and progesterone	Larger ovaries	Larger belly	Damaged liver	Damaged kidney	Thrombotic processes
Mild	✓	✓ Mild				
Moderate	✓	✓	✓			
Severe	✓	✓	✓	✓	✓	✓



Stage 1: Ovarian Stimulation

Routine monitoring of *ovarian follicular development* allows the clinician to maximize efficacy and reduce the risk for overstimulation. Typical monitoring includes vaginal ultrasounds with or without serum estradiol measurements performed every 1 to 3 days during the OS phase.

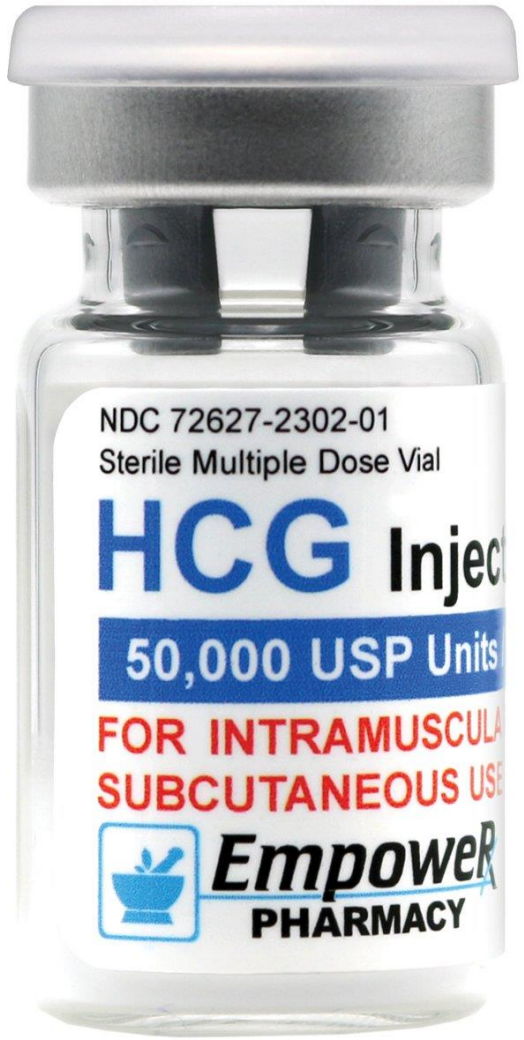
The monitoring *frequency increases* as the follicular development advances, and the gonadotropin **doses** may be reduced or increased depending on the number and size of the follicles. If *hyperresponse* is evident, the cycle may be **canceled** before oocyte retrieval.



Stage 2: Oocyte Retrieval

Chorionic gonadotropin is administered in preparation for **oocyte retrieval** to simulate the effect of the *physiologic LH surge* on final oocyte maturation.

The oocyte retrieval must be **carefully timed** to coincide with the completion of the oocyte maturation process, just before ovulation.



Stage 2: Oocyte Retrieval

Many clinics schedule oocyte retrieval between **24 and 36 hours** after chorionic gonadotropin is injected. Chorionic gonadotropin is available from *urinary* or *recombinant* sources.

The urinary hCG product is administered as a single intramuscular injection of **5000 to 10,000 IU**. The dose of the recombinant product is 250 μg injected subcutaneously.

Stage 3: Luteal Phase Support

Supplemental progesterone is administered *immediately after oocyte retrieval* to provide additional "luteal phase support" during IVF.

The *luteal phase* of the menstrual cycle is dominated by progesterone released by the *corpus luteum* that prepares the endometrium for implantation of the fertilized ovum.

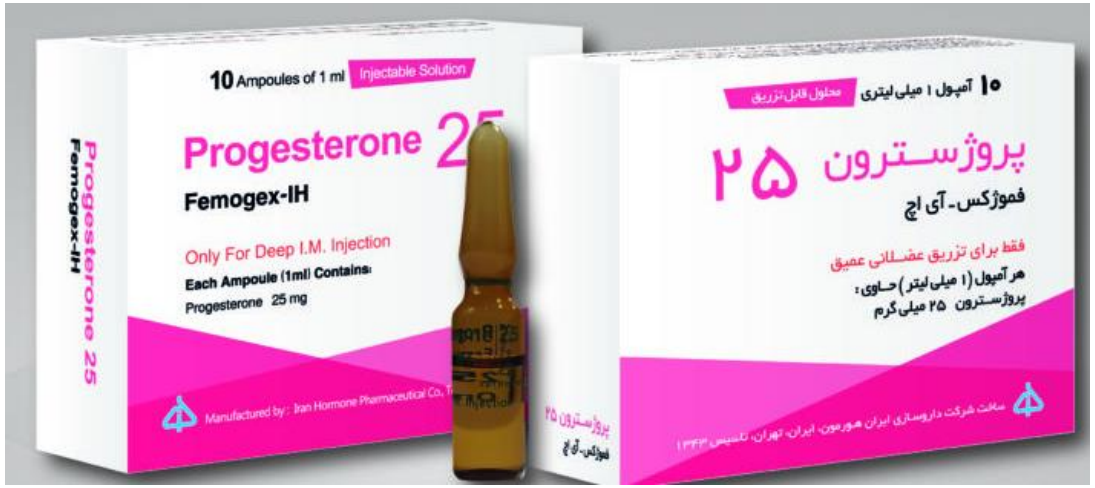
Stage 3: Luteal Phase Support

The disruption of follicles during the oocyte-retrieval process **delays** the production of **progesterone**, necessitating supplementation. In addition, cycles that utilize a GnRH agonist may be complicated by residual *inhibition of pituitary LH secretion* and progesterone production into the luteal phase.

The use of hCG, GnRH agonists, and estradiol for luteal phase support has been investigated; however, progesterone is the most common.

Stage 3: Luteal Phase Support

Progesterone is available in oral, vaginal, or injectable formulations. *Intramuscular* injection of progesterone in oil in a **daily dose of 50 mg** was the first method used for supplementation and continues to be widely used. However, alternatives to progesterone in oil have been sought because of frequent reports of *rash* and *discomfort* at the injection site.



Stage 3: Luteal Phase Support

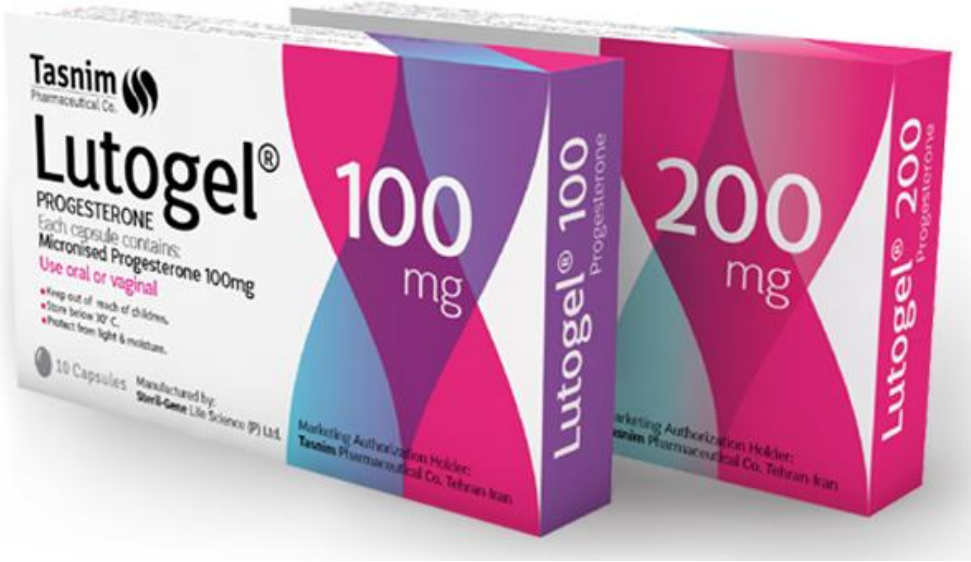
Commercially Available Progesterone Products Used in Assisted Reproductive Technology

Product Name	Strength/Dosage Form	Route of Administration
Crinone®	8% vaginal gel[a]	Vaginal
Endometrin®	100-mg vaginal insert[a]	Vaginal
FIRST®-Progesterone VGS	100-, 200-mg vaginal suppository (compounding kit)	Vaginal
Progesterone®	50 mg/mL (oil)	Intramuscular
Prometrium®/micronized progesterone	100-, 200-mg capsule	Oral

[a]FDA labeled for luteal phase support.

Source: Data from Facts & Comparisons eAnswers. Accessed September 23, 2022. https://fco.factsandcomparisons.com/lco/action/home


actavis
Cyclogest
200 mg
400 mg
Progesterone
Ordered by ACTOVER
IRC: 1228025952
15 Pessaries

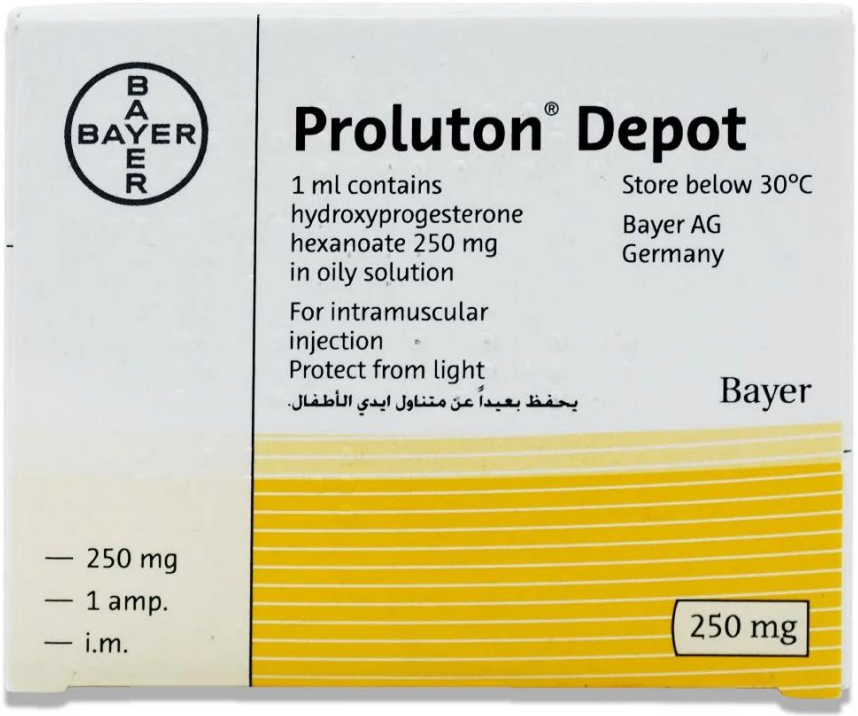

Tasnim
Pharmaceutical Co.
Lutogel®
PROGESTERONE
Each capsule contains:
Micronised Progesterone 100mg
Use oral or vaginal
10 Capsules
100 mg
200 mg
Lutogel® 100
Lutogel® 200
Progesterone


Endometrin 100mg
Vaginal tablets
Progesterone
اندومیترین 100ملغم
اقراص مهبلية
Endometrin
Progesterone
100mg
21
Units


vasclor
Progesterone
8% β/β
Κολπική γέλη 22,5g + 15 εφαρμοστές
verisfield

Stage 3: Luteal Phase Support

What about hydroxyprogesterone caproate?



Stage 3: Luteal Phase Support

Author/Year	Arms	Results
Funda Satir, 2013	intramuscular (IM) 17-α-hydroxyprogesterone caproate (17-HPC) (n=632) and intravaginal (IV) progesterone gel (n=320)	Higher pregnancy rates with intravaginal progesterone, but irrelevant in terms of ongoing pregnancy outcomes.
Srividya Seshadri, 2022	intramuscular (IM) 17 alpha-hydroxyprogesterone caproate and natural intramuscular progesterone	Live birth rates were significantly higher in women who received artificial progesterone compared to women who received natural progesterone.
Vittorio Unfer, 2004	A total of 320 patients): 17 alpha - hydroxyprogesterone caproate (17-HPC) (341 mg every 3 days)administered intramuscularly and intra-vaginal progesterone in gel (90 mg daily)	17-HPC administered every 3 days appears to be more effective in providing luteal support.
L Costabile, 2001	A total of 300 cycles: i.m. P (50 mg daily) and 17alpha-hydroxyprogesterone caproate (341 mg every 3 days)	No difference was found in the main outcome parameters considered.

Stage 3: Luteal Phase Support

Vaginal progesterone preparations have gained popularity for luteal phase support owing to **ease of administration** and avoidance of injection-site reactions.

The 8% progesterone vaginal gel and the 100-mg vaginal insert are the only commercially available **FDA-labeled** preparations for use in ART procedures. The gel is administered as one 90-mg applicator once or twice daily. The dose of the vaginal insert is 100 mg either twice a day (every 12 hours) or three times a day (every 8 hours).

Stage 3: Luteal Phase Support

The *vaginal* preparations may cause local irritation and vaginal discharge, although the vaginal **gel** is generally associated with *less discharge* than the inserts or suppositories. Clinical studies suggest **no difference in pregnancy rates** between *vaginal* and *intramuscular* formulations, so clinician and patient preferences often dictate the selection.

Oral formulations are **not recommended** for the purpose of luteal phase support with ART because of lower absorption and reduced pregnancy rates.

Stage 3: Luteal Phase Support

Embryo Transfer

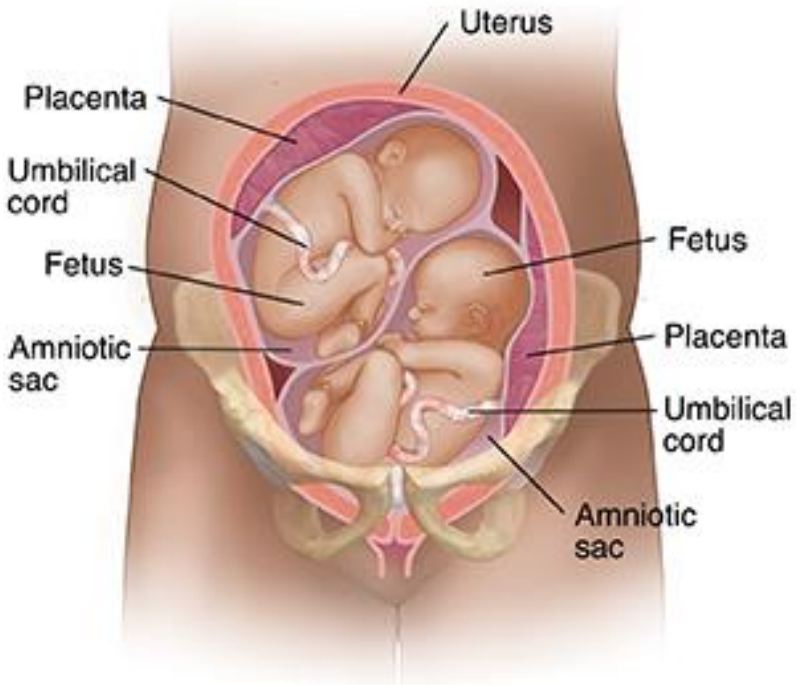
After fertilization, the *timing* of the embryo transfer into the uterus depends on the stage of development.

Cleavage-stage embryos are transferred 2 to 3 days postfertilization, whereas embryos in the blastocyst stage are transferred at day 5 or 6. The **number of embryos** placed during this process must balance the risks of a *multiple gestation* pregnancy with the *likelihood of successful implantation*.

Stage 3: Luteal Phase Support

Multiple gestation pregnancies are associated with **increased maternal and neonatal morbidity**. The **mother** is at risk for *complications* such as premature labor, pregnancy-induced hypertension, and gestational diabetes. Preterm labor occurs in ~15% of single gestation pregnancies compared with 75% of triplet pregnancies.

The **neonates** are more likely to experience fetal growth restriction and require intensive care for pulmonary, gastrointestinal, and neurologic complications.



Role of Supplements in Female Infertility

The results form SR&MAs:

- *Panagiota Florou (2020):* CoQ10 may increase clinical pregnancy rate without an effect on live birth rate and miscarriage rate.

- *Chiara Di Tucci (2020):* Alpha lipoic acid has positive effects in multiple processes from oocyte maturation to fertilization, embryo development and reproductive outcomes.

- *Marian G Showell (2017):* Very low-quality evidence to show that taking an antioxidant (NAC, melatonin, L-arginine, inositol, carnitine, selenium, vitamin E, vitamin B-complex, vitamin C, calcium-D, CoQ10, pentoxifylline, omega 3) may provide benefit for subfertile women.