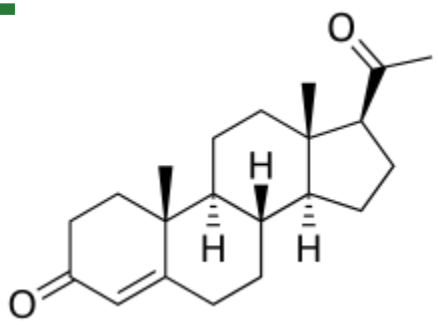
PROGESTERONE IN ASSISTED REPRODUCTION

Mina Jafarabadi- M.D.

Tehran University of Medical Sciences

Progestogens



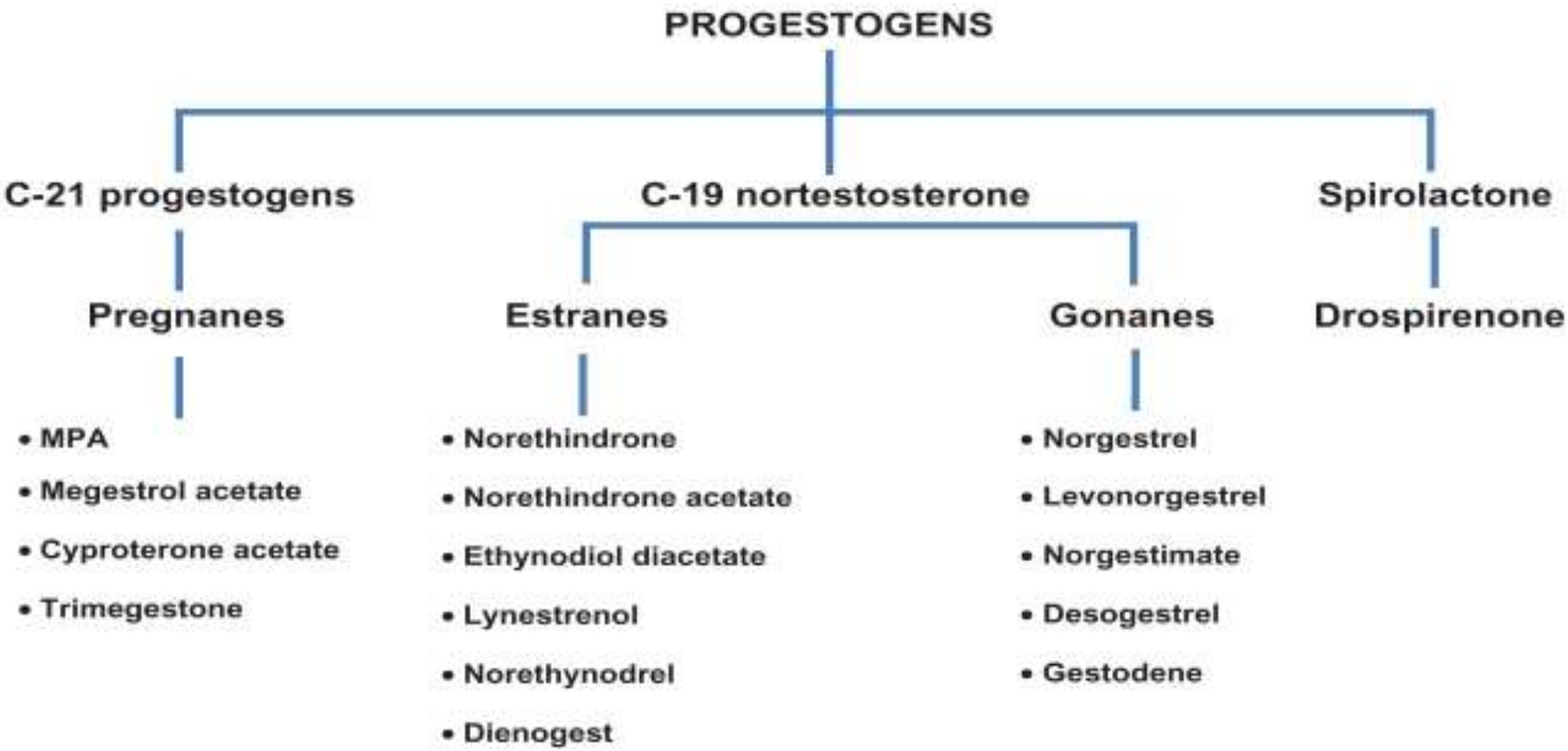
Progesterone (Prometrium, Utrogestan): **natural progestogen** produced in the body, or produced from a plant source but still chemically and structurally identical to human progesterone, and it is therefore referred to as **"bioidentical" or "natural".**

Progestin: Gestagen; Gestogen; **synthetic progestogen**
Progesterone receptor agonist

Grouping

- Progestins are sometimes grouped in "generations," which refer to how long they have been on the market.

- To understand their effects is to group them by structure based on the hormone from which.h they were created


PROGESTOGENS
C-21 progestogens
C-19 nortestosterone
Spirolactone
Pregnanes
Estranes
Gonanes
Drospirenone
• MPA
• Megestrol acetate
• Cyproterone acetate
• Trimegestone
• Norethindrone
• Norethindrone acetate
• Ethynodiol diacetate
• Lynestrenol
• Norethynodrel
• Dienogest
• Norgestrel
• Levonorgestrel
• Norgestimate
• Desogestrel
• Gestodene

Endogenous progesterone

- Mostly produced by granulosa lutein cells
- Optimal role to allow for implantation
- Mudulation of maternal immune system
- Suppression of inflammatory response

natural progesterone

- Is rapidly metabolized after oral intake

- Ineffective in inducing a sufficient secretory transformation.

synthetic progesterone derivatives

The side-effects

- lipids
- the psyche

micronization of progesterone

- Micronization particle of <10 μm
- increases the available surface area of the drug
- enhances the aqueous dissolution rate and intestinal absorption of progesterone.
- Suspension in oil and packaging in a gelatin capsule further enhance the intestinal absorption
- even higher doses of oral micronized progesterone have failed to induce sufficient secretory transformation.

Dydrogesterone

-  Pharmaceutical-grade progesterone and dydrogesterone are produced from the same starting material, diosgenin, from the Dioscorea plant: wild-yam

- Exposure to ultraviolet light ‘bends’ precursor material into a curved retro-steroid structure

- A retroprogesterone, a stereoisomer of progesterone, + additional double-bond between carbon 6 and 7

Dydrogesterone

- high selectivity for the progesterone receptor minimizes unwanted effects

- Dydrogesterone versus oral micronized progesterone
  - Better oral bioavailability[1,2]
  - Requires a 10–20 times lower oral dose

- Selective for the progesterone receptor (and thus avoiding other receptor-related side effects)

- Vaginal micronized progesterone is also metabolized in the liver

- Oral micronized progesterone is associated with a risk of cholestasis in pregnancy

	Transformation dose mg/day p.o.	Ovulation suppression dose mg/day p.o.
progesterone	200- 300	300
Dydrogesterone	10- 20	>30
Medroxy progesterone	5- 10	10

i.m. application

disadvantages :

- pain at injection time

- swelling and redness and sterile abscess formation

- eosinophilic pneumonia

  an allergic reaction toward the oil vehicle

  life-threatening complication

Subcutaneous progesterone

An alternative for women who want to avoid

i.m. injections

as well as the vaginal route

Progesterone usage in ART

- Luteal phase support
- Blocking LH surge

Progestin-primed ovarian stimulation (PPOS)

- Mechanism:

  Progesterone reduces GnRH's pulsatility from the hypothalamus, thus inhibiting the LH release associated with increased estradiol levels.

- In 2015, Kuang first used Medroxyprogesterone acetate (MPA) for LH suppression in COS.

Progestin-primed ovarian stimulation (PPOS)

- Fixed regiment:

  started simultaneously with gonadotrophins and continued until the day of ovulation trigger

- Flexible regiment:

  started later in the cycle, based on leading follicle size or serum estradiol and/or LH levels

- Implies the freezing of all the embryos

PPOS

- In DOR /advanced age had a more robust effect than GnRH-ant:

  - Antagonists are usually applied on Day 5 of the stimulation, when the leading follicle reached 12-14 mm or when the serum estradiol > 200 pg/ml
  ➔ LH surge may occur before the antagonist application (especially in advanced age / DOR).

  - GnRH- ant works on GnRH receptor directly but the endogenous estrogen-induced GnRH release is still preserved. PPOS can hinder estrogen's positive feedback on the hypothalamus.

- advantage of low incidence of OHSS (mechanism:??).

Luteal Phase Support (LPS)

No gain from LPS

- Young women
- + normal ovarian reserve
- + normal BMI
- during natural cycle

Why do we need luteal phase support in ART?

- egg retrieval >> multiple corpora lutea >> high levels of steroids >> negative feedback >> lower LH levels >> in the early luteal phase>> premature luteolysis
- Triggering by hCG or GnRH-a >> P level elevates

- "luteal gap" between hCG trigger and endogenous hCG of pregnancy:
  in GnRH-a cycles: inhibition of LH can last 2-3 weeks after the end of treatment.

- In cycles with GnRH-a trigger:
  LH-FSH surge for final egg maturation is shorter than natural cycles ➔ shorter life span of CL : 5 days.
  GCs have lower level of LH receptors.
  GCs have down-regulated expression of anti-apoptotic genes.

- FET / donor oocytes
  Artificially prepared endometrium with estradiol and progesterone >> suppressed ovulation>> lack of corpus luteom

Luteal phase after GnRH-a triggering

The spontaneous LH surge:

- an ascending phase of approximately 4 h
- a peak plateau of 20 h
- a descending phase of 20 h

GnRHa-induced LH:

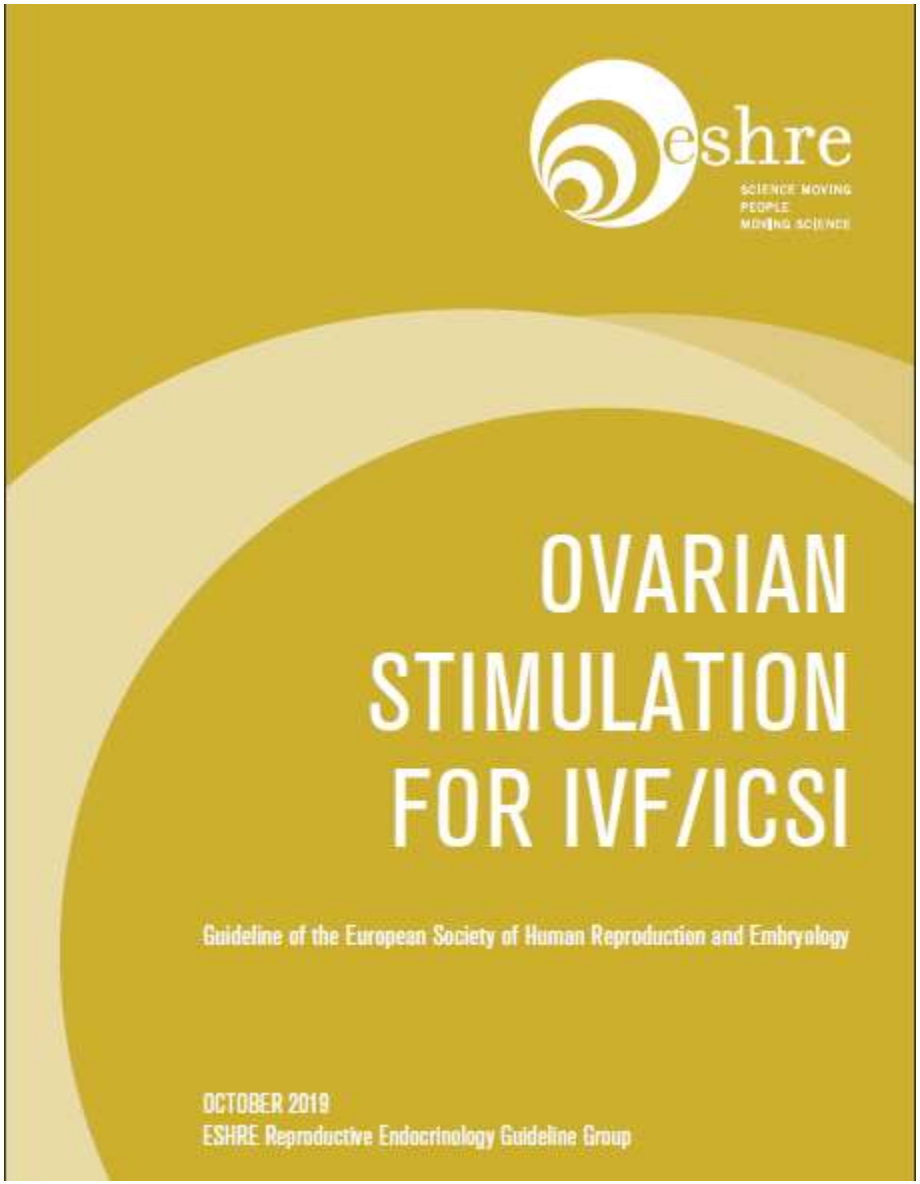
- shorter ascending phase of LH surge
- leads to a luteal phase with severe luteolysis

intensive luteal phase support is required (not later than 72 Hrs.) :

- i.m. progesterone injections
- hCG administration ➔ risk of OHSS (even with 250 IU every 3 days) .

LPS questions

- Timng
- Duration
- Rout



Cochrane Library

Cochrane Database of Systematic Reviews

Luteal phase support for assisted reproduction cycles (Review)

van der Linden M, Buckingham K, Farquhar C, Kremer JAM, Metwally M

van der Linden M, Buckingham K, Farquhar C, Kremer JAM, Metwally M.
Luteal phase support for assisted reproduction cycles.
Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD009154.
DOI: 10.1002/14651858.CD009154.pub3.

www.cochranelibrary.com

WILEY

GPP
GDG

- Good Practice Point (GPP), which is the recommended best practice based on the clinical experience of the Guidelines Development Group (GDG).

- The level of recommendation is rather low

Timing of initiation

start LPS during the window between the evening of the day of oocyte retrieval and day 3 post oocyte retrieval (GPP).

Duration

P for LPS should continue at least until the day of the pregnancy test (GPP).

The dosing of natural progesterone

Any non-oral routes for natural P can be used (GPP)

- 50 mg once daily for intramuscular progesterone
- 25 mg once daily for subcutaneous progesterone (prolutex)
- 90 mg once daily for vaginal progesterone gel
- 200 mg TDS for micronized vaginal progesterone in-oil capsules
- 100 mg TDS or BID for vag. P in starch supp (endometrin)
- 400 mg two times daily for vaginal pessary (cyclogest)

Dydrogesterone is probably recommended for luteal phase support (Conditional ⨁⨁⨁).

Personalized luteal phase support

- Neither the updated Cochrane meta-analysis on LPS, nor the ESHRE guidelines have included recommendations regarding patient monitoring during the luteal phase.