Fertility drugs and how they work

Víctor Martín González, M.D.
reproductive medicine unit
Clínica Quirón Valencia
Drugs in infertility

• Is impossible to understand how drugs work in fertility treatments without understanding the physiology of the hypothalamus- hypophysis- ovary
Hypothalamic-hypophysis cycle

Pulsatile secretion pattern

Hypothalamus → GnRH → Pituitary → LH, FSH → Ovaries → Progesterone, Estrogen

FSH (hormona fótilculo estimulante) → Ovario → Estrógeno

LH (hormona luteinizante) → Ovario → Progesterona
Hypothalamus-hypophysis cycle
Pulsatile secretion pattern

Negative feed-back

Positive feed-back

hypothesis

GnRH

ovary

follicular development

hypothalamus

Pulsatile secretion pattern
¿Which problems are we going to treat?
Ovulatory disorders (W.H.O.)

- **Group I**: hypogonadotropic hypogonadism
  
  *treatment: supply GnRH and/or FSH-LH*

- **Group II**: normogonadotropic anovulation (Policystic ovarian syndrome - PCOS)
  
  *treatment: FSH/LH regulation*

- **Type III**: ovary disfunction
  
  *treatment: supply oocytes*
Fertility drugs

• ovulatory problems
  - hypogonadotropin hypogonadism (group I WHO)
  - normogonadotropin anovulation-PCOS (group II WHO)

• Controlled ovarian hyperstimulation
  - artificial insemination
  - “in vitro” fecundation
Medication in assisted reproductive medicine

**objective**

- **Achieve follicular development**
  - single
    - Ovulatory disfunction
  - multiple
    - In vitro fecundation
1. supress/modulate hypothalamus - hypophosis

2. stimulate follicular development

3. produce ovulation/recover oocytes
Fertility drugs

- **Controlled ovarian stimulation**
  - clomiphene citrate
  - gonadotropins (urinary, recombinant)

- **Ovulation triggerers**
  - HCG (urinary, recombinant)
  - GnRH agonistic analogs

- **Hypothalamic-hypophisis suppression**
  - GnRH agonistic analogs
  - GnRH antagonistic analogs

- **Luteal phase support**
  - HCG
  - progesterone

- **Others**
  - estrogens
  - aromatase inhibitors (letrozol)
  - sildenafil citrate
  - insuline sensibilizing drugs (metformine, inositol)
  - sustained follicular stimulants (future)
Hypothalamus-hypophisis suppression

- GnRH agonistic analogs
- GnRH antagonistic analogs

These drugs produce abolishment of endogenous gonadotropine secretion, thus, allowing ovarian stimulation with exogenous gonadotropines).

They prevent from a premature/incontrolled LH surge responsible for failures in the process of controlled ovarian induction.
GnRH agonistic analogs

Its administration produces continuous activity of GnRH, disappearing the pulsatile secretion rhythm of GnRH, the pituitary gland becomes non sensitive to this type of GnRH secretion and ceases producing gonadotropines.
GnRH antagonistic analogs

they produce the blockage of pituitary GnRH receptors, so the endogenous GnRH can not stimulate this gland to produce gonadotropines
GnRH agonistic analogs

- As seen before, they produce an initial flare-up effect, blocking hypothalamus activity days after their administration.
- Consequently, they need to be administered days before the beginning of the ovary stimulation with gonadotropines (usually during mid-luteal phase)
GnRH agonistic analogs

**Triptoreline**
- decapeptyl (Ipsen Farma) (vials 0.1mg, subcutaneous, daily administration)
- decapeptyl depot (vials 3.75 mg intramuscular, monthly administration)
- gonapeptyl depot (Ferring) (vial 3.75 mg, subcutaneous intramuscular, monthly administration)

**Leuproreline**
- procrin (Abbott) (vial with 2.8ml, dose of 1mg/0.2 ml, subcutaneous, daily administration with doses of 0.1ml)
- procrin depot (vial 7.5 mg, intramuscular, monthly administration)

**Nafareline**
- Synarel nebulizer spray (Seid) (8 ml, 200μgr each nebulization, usually 400μgr twice a day, 2 nebulizations in the morning, two in the evening)
GnRH antagonistic analogs

- No flare-up effect
- Immediate initiation of activity
- Immediate cease of activity when withdrawal
- Administration later in the cycle compared with agonistic analogs.
- Stop administration the day of HCG.
- Subcutaneous administration
GnRH antagonistic analogs

- **French protocol**
  - administration of a single dose of 3 mg once the follicles are ≥14 mm size, if HCG is not administered in 72 hours, repeat dose of 3 mg.

- **Lübeck protocol (German)**
  - administration of a daily dose of 0.25 mg starting day 6° of the stimulation

- **Mixed protocol**
  - administration of a daily dose of 0.25 mg once the follicles are ≥14 mm size
GnRH antagonistic analogs

• **Ganirelix (3th generation)**  
  orgalutran (MSD)  
  prefilled syringe of 0.25 mg

• **Cetrorelix (3th generation)**  
  cetrotide (Serono)  
  prefilled syringe of 0.25 mg and 3 mg
Clomiphene citrate

**Mechanism of action**

reduction in the negative feed-back of endogenous estrogens owing to prolonged depletion of hypothalamic and pituitary estrogen receptors. Hypothalamus “thinks” there are no estrogens, thus produces GnRH leading to great stimulaton of pituitary gland, gonadotropines and ovary estimulation.

**Indication**

normogonadotropic anovulation (Group II WHO) - policystic ovarian syndrome-
Clomiphene citrate

• Posology

  50 mg/day, oral intake, 5 days; from 3º-7º day of cycle (possible 25 or 12.5 in hyperresponders or initiate 5º day of cycle)
  
  increase dose in 50 mg each time if no ovulation is achieved
  
  maximal permissible dose of 150-200mg/day

• Side effects

  hot flushes, nausea, blurry vision, gastrointestinal discomfort, ovarian hyperstimulation syndrome (OHSS), multiple gestation.
Clomiphene citrate

• Ovulatory succeed of 75% if optimal selection of patients is achieved.
• Change strategy of treatment if no pregnancy after 3-6 ovulatory cycles.
• Sonography control of follicle development prevent from multiple gestation and OHSS (preovulatory follicles present after 5°-7° day of ending medication)
gonadotropines

• Mechanism of action

Multiple follicular development due to direct stimulation on ovarian follicles, increasing the number of follicular recruitment depending on the administered dose.
gonadotropines

- **Urinary**

  Obtained from postmenopausal urine after purification methods.
  Postmenopausal urine is rich in HMG-human menopausal gonadotropine-
  (FSH-LH activity)
  Postmenopausal urine is rich in non useful proteins (allergic reactions,
  hypersensibility)
  Methods of purification eliminate these undesirable proteins.
  Methods of purification can reduce to only vestigial the LH activity.

- **Recombinants**

  recombinant DNA technology in chinese hamster ovary cells

  produce substances with pure FSH activity, >99%

  free from urinary proteins and LH activity
gonadotropines

• **Urinary**
  
  purified (menotropins)
  
  (FSH-LH activity)
  
  highly purified
  
  (menotropins)
  
  (FSH and LH activity)
  
  (urofollitropins)
  
  (FSH activity)

• **Recombinants**

  follitropin $\alpha - \beta$
  
  (pure FSH activity)

  luteotropine
  
  (pure LH activity)
Urinary gonadotropins

- Produced from the purification of postmenopausal urine, obtaining HMG (end 40’s-beginning 50’s)
- Initially obtained from pigs and sheeps pituitary extract and then from corpses pituitary and mares urine.
- Nowadays the methods of purification produce substances practically free from non desireable urinary proteins.
- In urofollitropine, LH activity is reduced almost to nothing.
Recombinant gonadotropines

• Insertion of the gene of $\alpha$ and $\beta$ chain of FSH in Chinese hamster ovarian cells
gonadotropines

• Posology:

  Last generation products are subcutaneously administered.
  
  Daily administration starting day 2°-3° of cycle.
  
  Doses vary with the patient and type of protocol.
gonadotropines

• Doses

  a) single ovulation induction (i.e. artificial insemination)

      37.5 IU to 75 IU / day

  b) Multiple follicular development (IVF)

      b.1) <35 year old, corporal mass index < 25, good ovarian reserve, hyperresponders, antecedent of OHSS, PCOS

      75 IU to 150 IU / day

      b.2) >35 years old, corporal mass index > 25, poor ovarian reserve, basal FSH > 12 IU/ml, antecedent of poor response

      150 IU to 375 IU / day
gonadotropines

• Side effects:

  local injection hypersensibility reactions
  abdominal discomfort
  breast soreness
  Ovarian hyperstimulation syndrome (OHSS)
  Multiple gestation
Commercial trademarks

- **Urinary**
  
  **Purified menotropine**
  
  HMG-lepori, Pergonal, Menogon, Humegon
  
  75 IU vials
  
  fsh/lh (1:1) activity
  
  Intramuscular injection
  
  **Highly purified menotropine**
  
  Menopur (FERRING)
  
  75 IU vials
  
  fsh/lh (1:1) activity
  
  Subcutaneous administration
  
  **Highly purified urofollitropine**
  
  Bravelle (FERRING)
  
  75 IU vials
  
  fsh activity
  
  Subcutaneous administration
  
  Fostipur (Angelini)
  
  75 and 150 IU vials
  
  fsh activity
  
  Subcutaneous administration

- **Recombinant**
  
  Puregon (β follitropine)
  
  MSD
  
  FSH activity, subcutaneous
  
  50, 100, 150, 200 IU vials
  
  Puregon-Pen
  
  300, 600, 900 IU
  
  Gonal-F (α follitropine)
  
  Merck-SERONO
  
  FSH activity, subcutaneous
  
  75, 1050 IU vials
  
  Prefilled pen
  
  300, 450, 900 IU
  
  Pergoveris
  
  Merck-SERONO
  
  Vial with 150 IU FSH activity plus 75 IU LH activity
  
  Subcutaneous administration
  
  Luveris
  
  Merck-SERONO
  
  Vial with 75 IU LH activity
  
  Subcutaneous
Drugs for triggering ovulation

- HCG
  - urinary
  - recombinant

- GnRH agonistic analogs
Triggering ovulation

- **HCG (urinary/recombinant)**

  HCG has LH-like activity, its administration simulate the physiological mid-cycle LH surge, thus triggering the ovulation.

  Ovulation also includes the final process of maturing the oocyte.

  Single dose administration, once the follicles are 18-20 mm size, intramuscular/subcutaneous, triggers ovulation approximately 36h. after administration.
Triggering ovulation

- **Urinary HCG**
  - intramuscular administration
  - 5000-10000 IU dose depending on the number of oocytes developed.
    - 5000 IU in intrauterine insemination (1-3 follicles)
    - 7500-10000 IU in IVF (>3 follicles)

- **Recombinant HCG**
  - subcutaneous administration
  - registered trademark: Ovitrelle (Merck-Serono)
  - dose 250 µgr. (equivalent to 6500 IU of urinary HCG)
  - administered in IVF treatments
Triggering ovulation

- **GnRH agonistic analogs**

After subcutaneous administration of bolus of GnRH agonistic analog, an important and early gonadotropine secretion is produced (flare-up), soon after, the activity of hypothalamus is blocked.

This early and great gonadotropine secretion allows an FSH-LH surge that induces ovulation.
Triggering ovulation

• **GnRH agonistic analogs**

  Only feasible if the hypothalamus is not previously blocked by the administration of a GnRH agonistic analog, which means, only possible in cycles with GnRH antagonistic analogs.

  A single bolus dose is administered subcutaneously once the follicles are 18-20 mm size:

  \[
  \begin{align*}
  & \text{leuprolide} \quad 0.5 \text{ mg} \\
  & \text{triptorelin} \quad 0.2 \text{ mg}
  \end{align*}
  \]
Luteal phase support

• Drugs used to supply progesterone produced by corpus luteum after ovulation, or to supply function of corpus luteum when is not working (i.e. : receptors in oocyte donation cycles, substitution cycles in embryo donation)
Luteal phase support

• HCG

intramuscular administration

2500 IU every 3 days, 3 doses, starting next day to oocyte retrieval

Not recommended if high risk of ovary hyperstimulation syndrome
progesterone

- **Natural progesterone**
  oral /vaginal administration
dose: 400 mg/day (insemination)
  600-800 mg/day (IVF)
presentation: 100 and 200 mg pills
common side effect: drowsiness (< vaginal)

- **Progesterone cream**
  vaginal administration
  posology in IVF: 90 mg/ day (1 application)
presentation: vaginal cream
Other drugs

- Sildenafil citrate
- Letrozol
- Inositol
- Sustained follicular stimulants
- Estrogens
estrogens

- Improvement of endometrial thickness when <6-7 mm.
- Achieve endometrial thickness when ovary is not working (substitution cycles, i.e. oocyte donation)
estrogens

- Estradiol valerianate
  oral (tablets)
    progynova 1 and 2 mgr.
  transdermal (patches)
    progynova patch (25,50,100 µgr)
    evopad (25,50,75,100 µgr)
    dermestril (25,50,75,100 µgr)
    estradot (25,37.5,50,75,100 µgr)
    estraderm (25,50,75,100 µgr)

- Micronized estradiol
  vaginal (tablets, cream)
estrogens

• Posology:

  a) improve endometrial thickness
     2,4,6 mg /day, orally
     1-2 patches/48-72 h.

  b) substitution cycles
     2,4,6,8 mg / day, orally
     1-2 patches /48-72 h.
Sildenafil citrate

- registered trademark: “viagra”
- Produce vasodilatation of vascular involuntary muscle
- Used to increase uterus and ovary vascular flow, improving endometrial thickness and ovarian response to gonadotropines
- Posology: 50 mg/12h. Vaginal, for 5 to 6 days, at the beginning of ovary stimulation
letrozol

- Produce aromatase inhibition (enzyme that convert androgens to estrogens in periferic tissues)
- therefore, enhance the hypothalamic activity. The hypothalamus “thinks” there is lack of estrogens.
- Used as coadjuvant of gonadotropines, mainly in low responders.
- posology: 2.5-5 mg/day, oral, between 3°-7° day of cycle.
- Side effects: hot flushes, nausea, fatigue
- Strong controversy because of supposed teratogenic effects
- Registered trademark: “femara”
inositol

- Group B vitamin
- Vegetal origin
- Several isomeric forms, mioinositol is the used one
- Produce regulation of cellular functions relying on certain hormones.
inositol

- Application in reproductive medicine:
  
  - Takes part on the proper development and maturation of oocyte
  - Improves the hormonal disorders in polycystic ovarian syndrome (PCOS) by improving insulin resistance.
  - It seems to improve the quality of oocyte in IVF cycles
  - Induction of ovulation in anovulatory patients with PCOS, due to its activity improving insulin resistance and hyperandrogenism.
inositol

- Registered trademark: ovusitol (Italfarmaco)
- Dose in powder with 2 gr. of mioinositol + 200 µgr. of folic acid
- Posology: 2 daily doses, during the treatment with other drugs or alone as initial approach in patients with PCOS
- Same effect in PCOS that metformine, but with much less gastrointestinal side effects.
Sustained follicular stimulants

- Initiate and sustain multiple follicular development
- Recombinant FSH: corifollitropine α
- Recombinant DNA technology in chinese hamster ovary cells
- A single subcutaneous injection the first day of stimulation sustain multiple follicular growth for an entire week
- It has the same pharmacodynamic profile as recombinant FSH but with a markedly prolonged duration of FSH activity
- Approved for use with GnRH antagonistic analogs protocols only.
Sustained follicular stimulants

- Presentation: prefilled syringe with 100 and 150 µgr of corifollitropine α

- Posology:
  \[
  \begin{align*}
  \text{patients } < 60 \text{ kg} & : \text{ single dose of } 100 \, \mu\text{gr} \\
  \text{patients } > 60 \text{ kg} & : \text{ single dose of } 150 \, \mu\text{gr}
  \end{align*}
  \]

- Recently approved for human use in Europe, not yet in USA

- Registered trademark in Germany (not commercialized in Spain yet): ELONVA (MSD)
The author certifies no commercial relationship or sponsorship with any of the laboratories mentioned in this presentation
thank you