Fertility drugs and how they work

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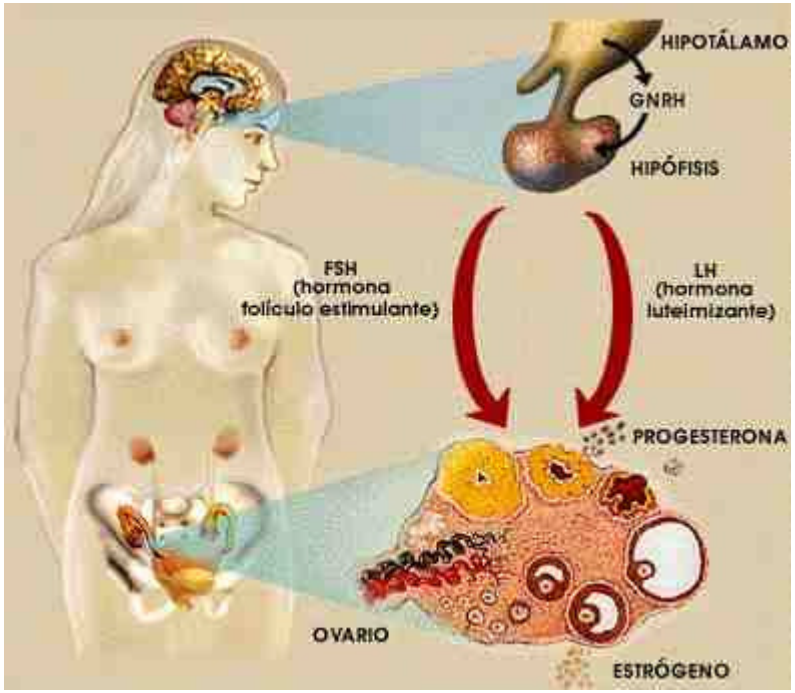
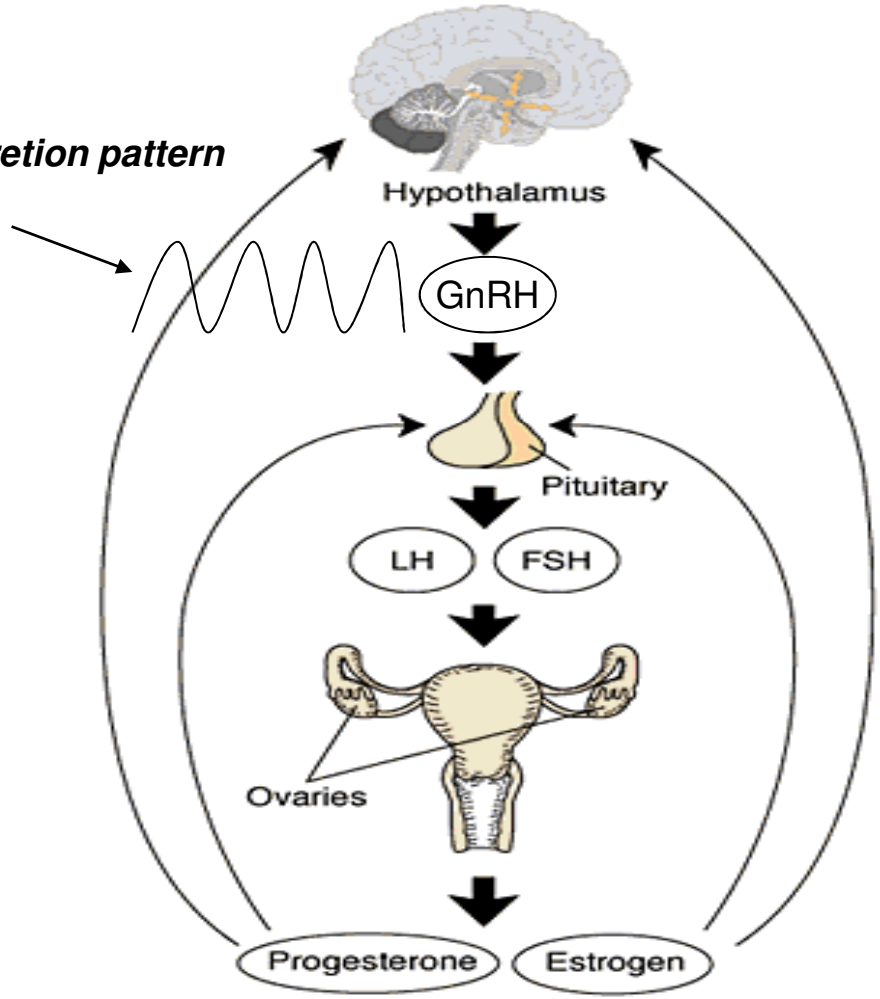
Drugs in infertility

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

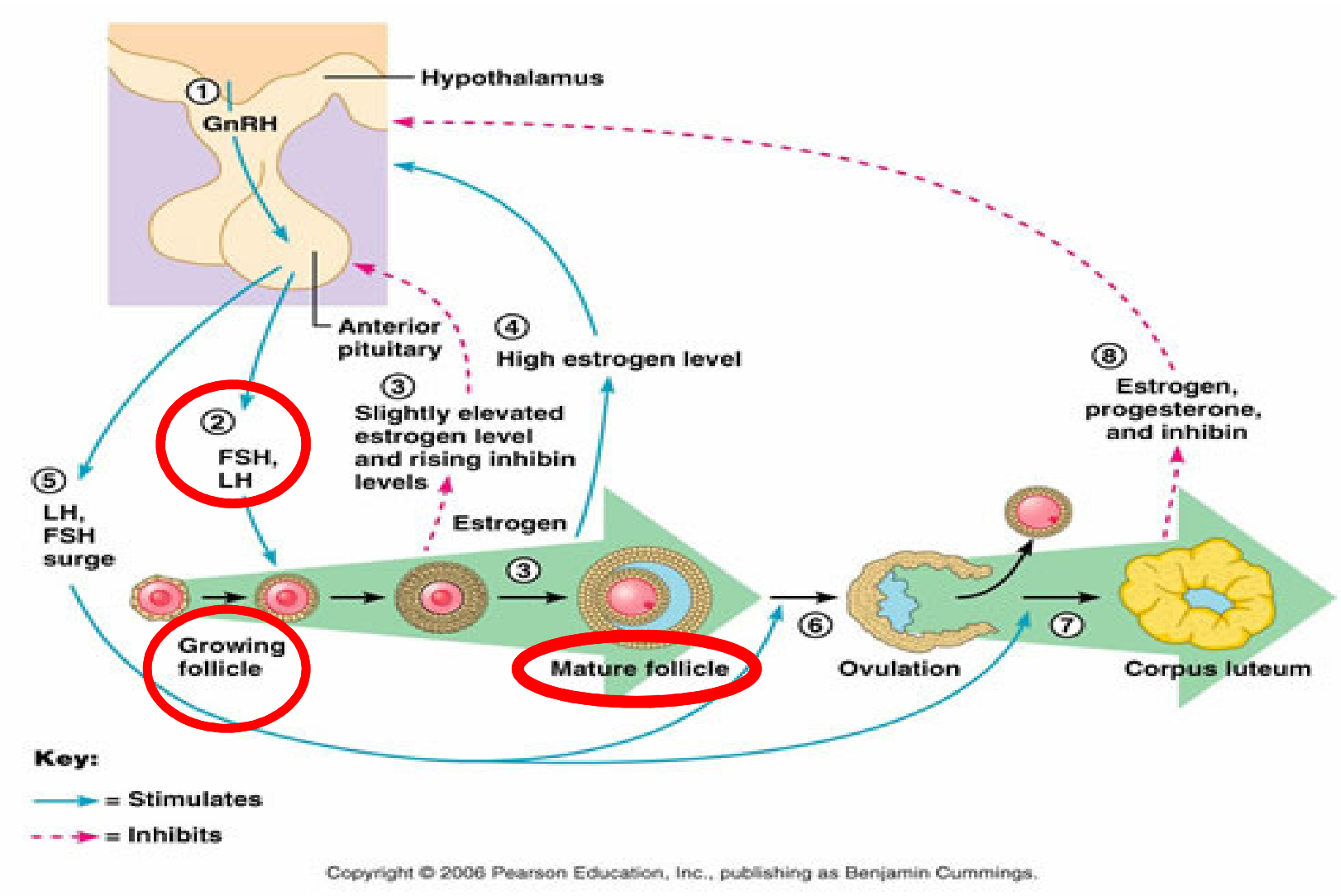
Hypothalamic-hypophysis cycle

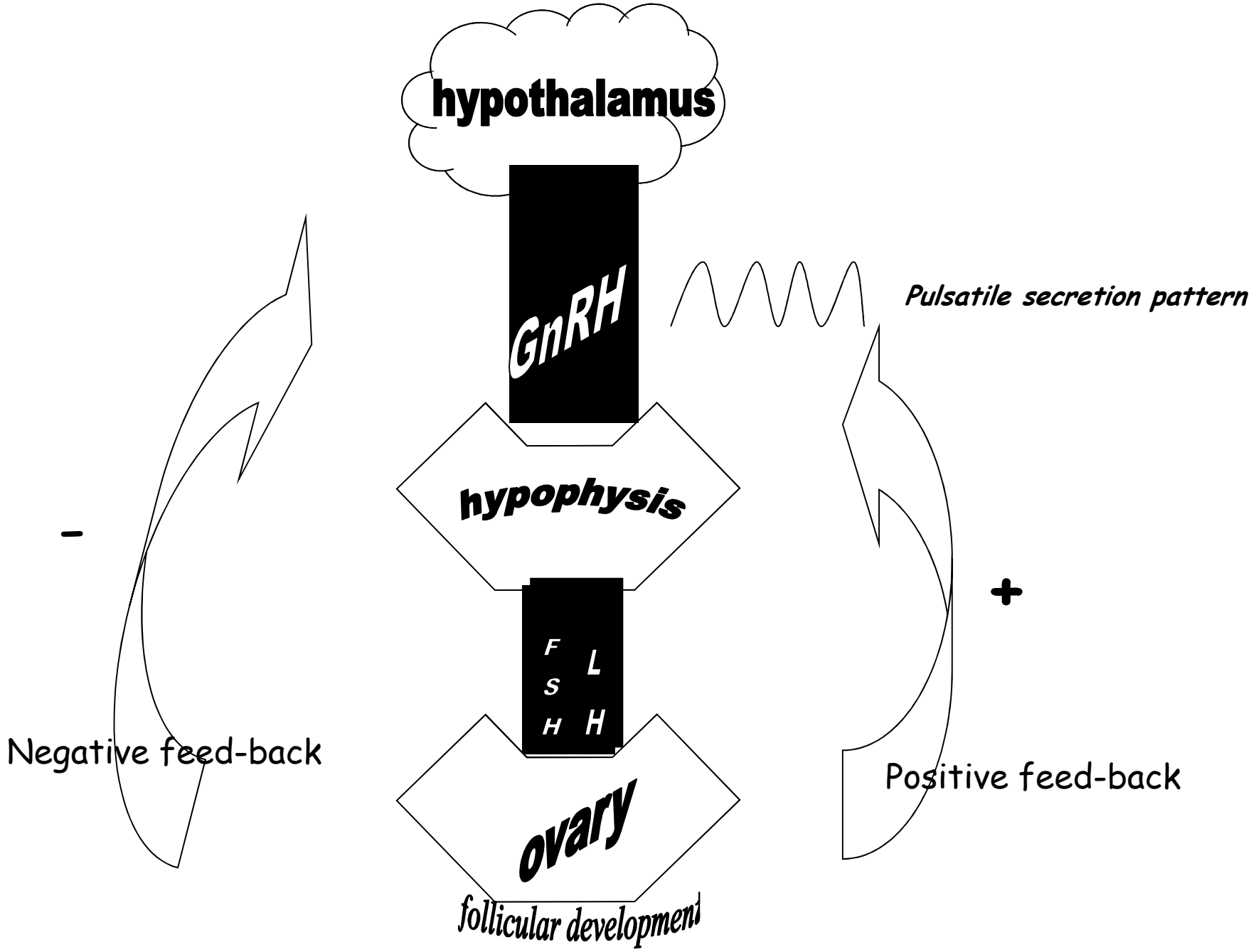


Pulsatile secretion pattern



Hypothalamus-hypophysis cycle




hypothalamus
GnRH
Pulsatile secretion pattern
hypophysis
–
+
F S H
L H
Negative feed-back
Positive feed-back
ovary
follicular development

¿Which problems are we going to treat?

Ovulatory disorders (W.H.O.)

- Group I : hypogonadotropic hypogonadism

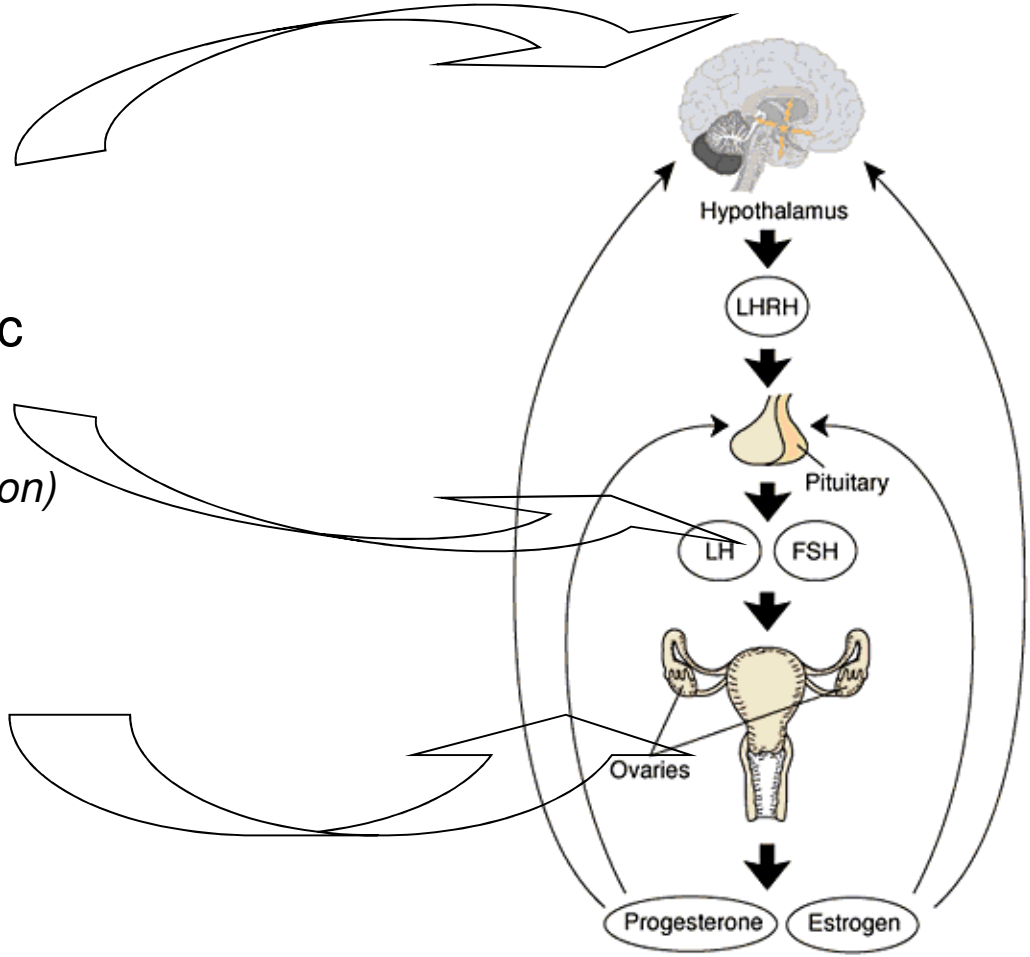
  (treatment:suply GnRH and/or FSH-LH)

- Group II : normogonadotropic anovulation (Policystic ovarian syndrome- PCOS)

  (treatment: FSH/LH regulation)

- Type III: ovary disfunction

  (treatment: suply oocytes)



Fertility drugs

- ovulatory problems

  - hypogonadotropic hypogonadism (group I WHO)

  - normogonadotropic anovulation-PCOS (group II WHO)

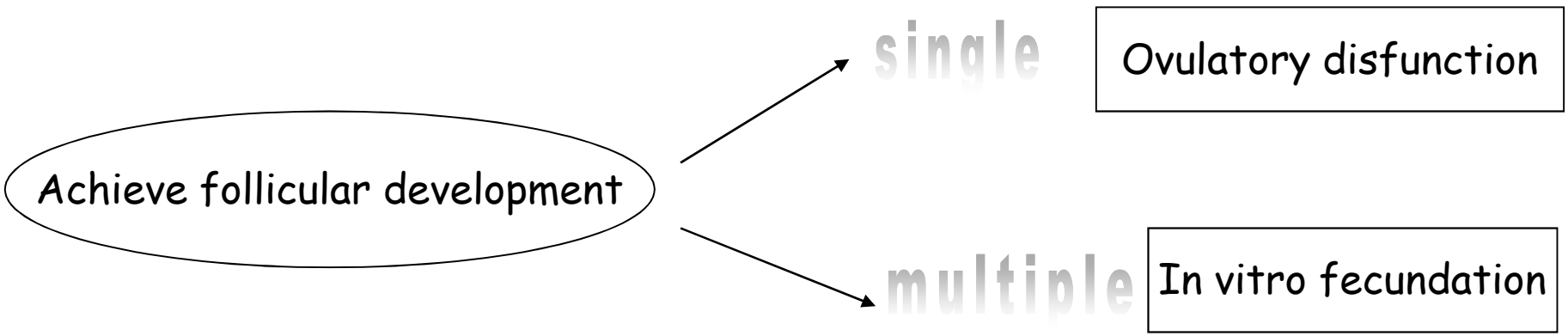
- Controlled ovarian hyperstimulation

  - artificial insemination

  - "in vitro" fecundation

Medication in assisted reproductive medicine

objective



1.- supress/modulate hypothalamus - hypophisis

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)*
  - *sildenafile citrate*
  - *insuline sensibilizating drugs (metformine, inositol)*
  - *sustained follicular stimulants (future)*

Hypothalamus-hypophisis suppression

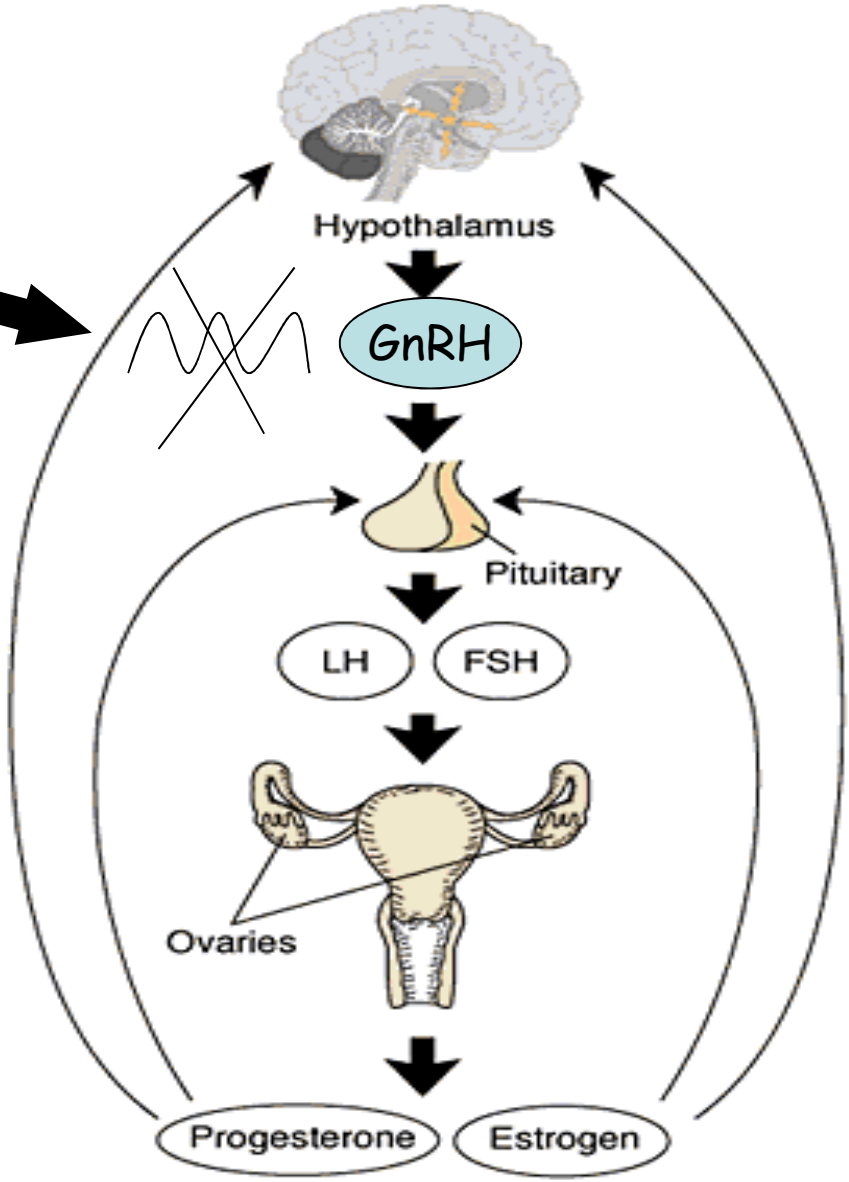
- GnRH agonistic analogs
- GnRH antagonistic analogs

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

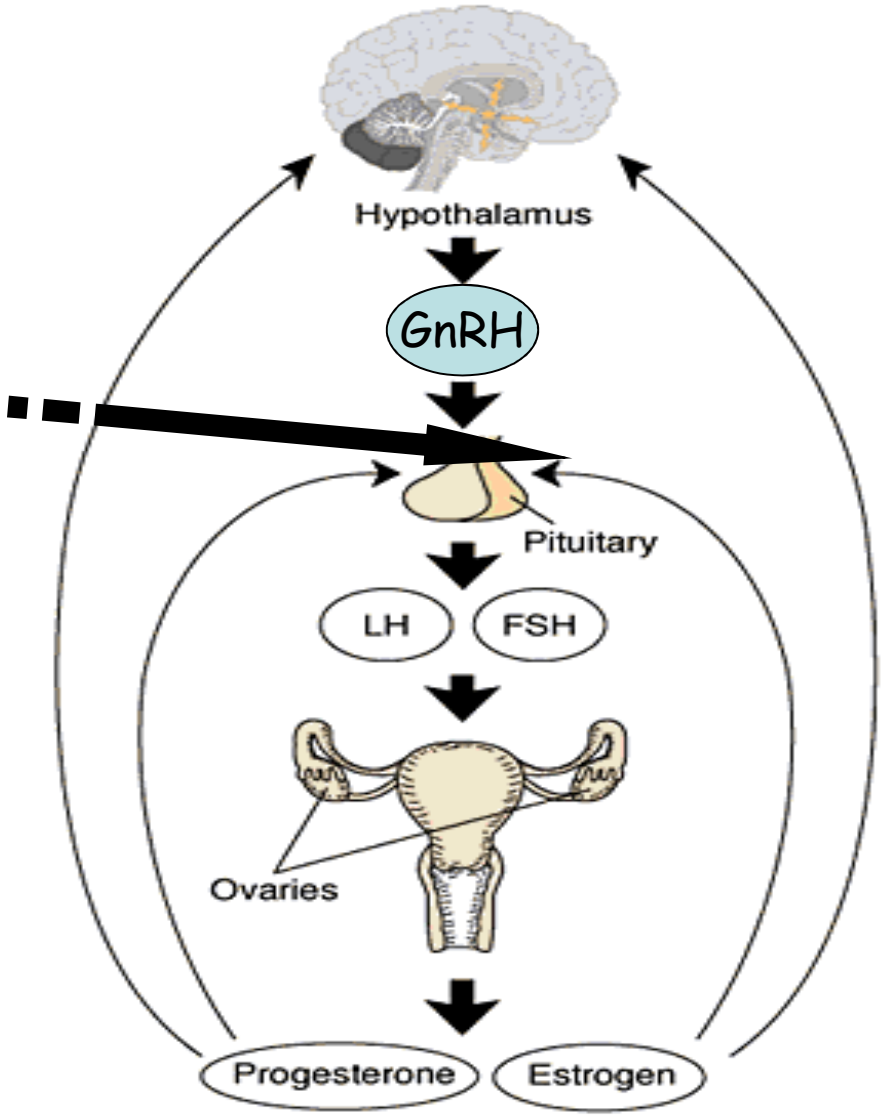
GnRH agonistic analogs

Its administration produces ***continuous activity of GnRH,disappearing the pulsatile secretion rythm of GnRH,*** the pituitary gland becames 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 syringue of 0.25 mg

- Cetrorelix (3th generation)
  cetrotide (Serono)
  prefilled syringue of 0.25 mg and 3 mg

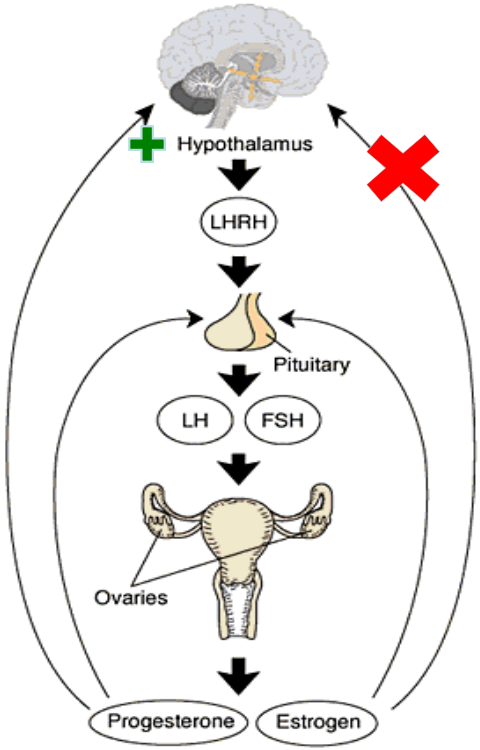
Clomiphene citrate

- 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 estimulation 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 3°-7° day of cycle (possible 25 ó 12.5 in hyperresponders or initiate 5° 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 succed 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 gonadotropines

- 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 α and β chain of FSH in chinese hamster ovarian cells

gonadotropines

- Posology:

Last generation products are subcutaneouslly 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-pen300,600,900 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 75IU 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 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)

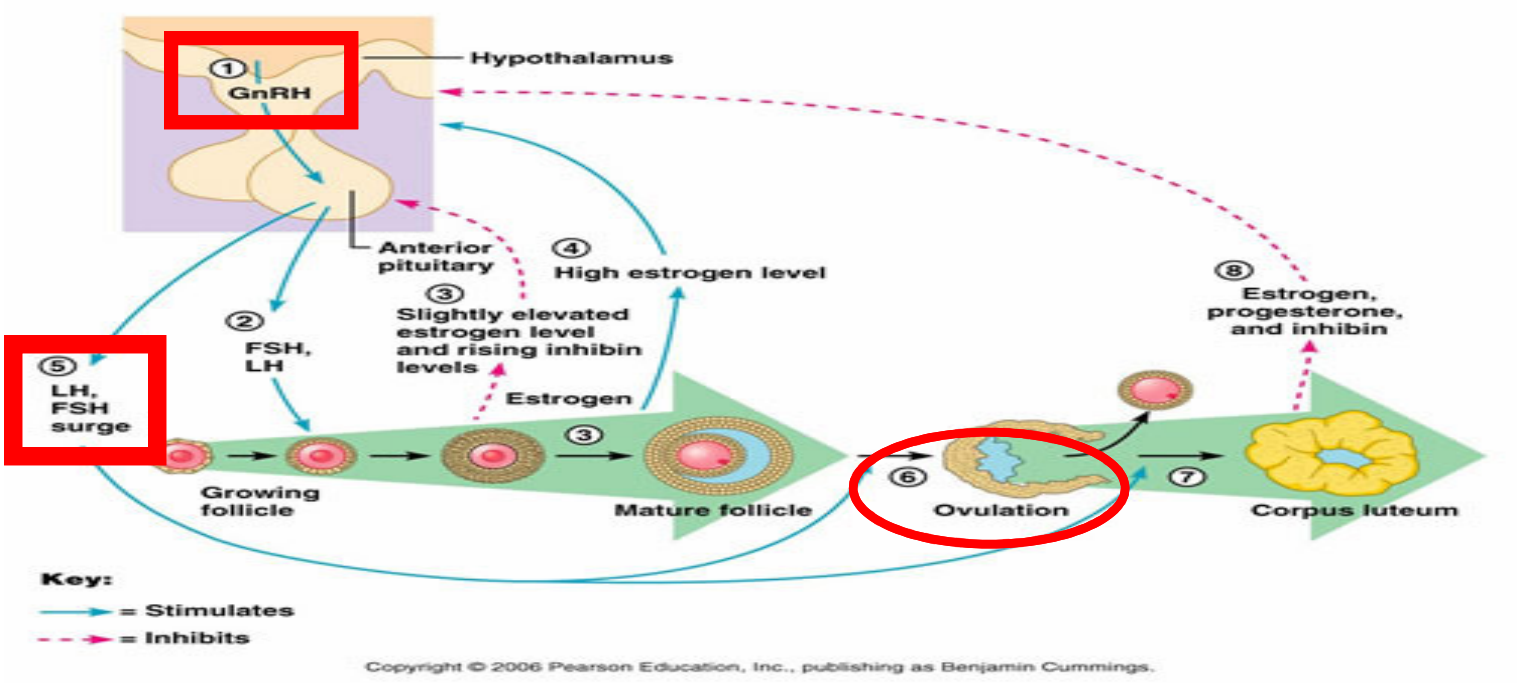
  administered in IVF treatments

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, wich means, only possible in cycles with GnRH antagonistic analogs.

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

leuprolide 0.5 mg
triptorelin 0.2 mg

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

- Sildenafile 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.

Sildenafile 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 beggining 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 supossed teratogenic effects
- Registered trademark: "femara"

inositol

- Group B vitamine
- 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 policystic ovarian syndrome (PCOS) by improving insuline resistance.

it seems to improve the quality of oocyte in IVF cycles

induction of ovulation in anovulatory patiens with PCOS,due to its activity improving insuline 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 prolongued duration of FSH activity
- Approved for use with GnRH antagonistic analogs protocols only.

Sustained follicular stimulants

- Presentation: prefilled syringue with 100 and 150 μgr of corifollitropine α
- Posology:
  - patients <60 kg : single dose of 100 μgr
  - patients >60 kg : single dose of 150 μgr
- Recently approved for human use in Europe, not yet in USA
- Registered trademark in Germany (not commercialized in Spain yet): ELONVA (MSD)

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thank you