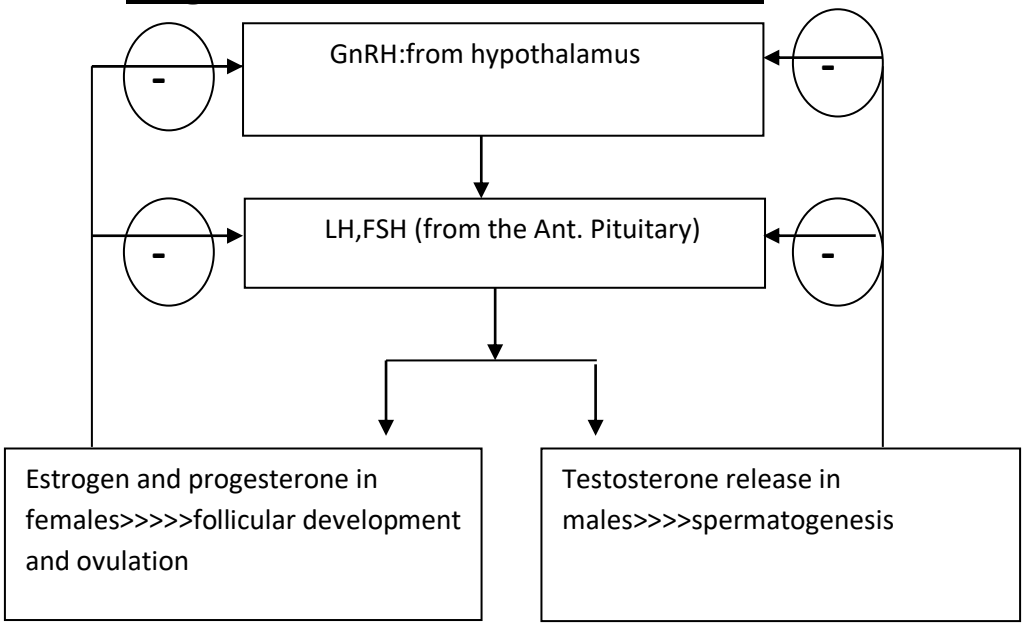
This summary includes all what's written in the slides, some notes are added from the record to make things clear, what's written in italics is added by the editor. Good luck all

GnRH (Gonadotropin Releasing Hormone; Gonadorelin)

- **A small peptide (decapeptide= 10 a.apeptide)**
- **Stimulates synthesis and release of two different complex glycoprotiens (LH & FSH)**
- **Has unique pattern of release from hypothalamus (***The physiologic actions of GnRH exhibit complex dose-response relationships that change dramatically from the fetal period through the end of puberty يعني إفرازه بيختلف باختلاف المراحل العمرية***)**

• Negative feedback mechanisms



Structure-activity relationship:

As said earlier it's a decapeptide and it's structure is very important for its function

Pro-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly

If the 1st three amino acids are manipulated we'll end up with a huge number of antagonists.

Pattern of release and MOA:

GnRH is either administrated in pulsatile or continuous mode, and we decide depending on the disease(to be discussed).

- Pulsatile (acts through Ca++ second messenger sustem) → increases↑ LH & FSH

- Large doses or continuous administration causes the down regulation of pituitary GnRH receptors)→ ↓ LH & FSH

• GnRH synthetic preparations:

Leuprolide acetate, Triptorelin, Goserelin, Histrelin,
Nafarelin, Busereline. (notice the relin suffix in all the agents)

Route of administration:

-Could be given S.C, I.M, I.V (so any type of injections)
-Mainly given S.C
-Ineffective orally
Available in intranasal, suppositories, subdermal implants and vaginal pessaries dosage forms (might be used as a Contraceptive?)

GnRH clinical uses:

a. Pulsatile administration (we said that it increases LH & FSH)
1- Diagnostic use (*To see if the gonadotrophes are responsive to GnRH, if LH doesn't increase after administration then the problem is either pituitary or hypothalamic*)
2- GnRH deficiency (Kallman's syndrome) *متلازمة يفشل فيها البدء أوإتمام البلوغ*
Treatment o of ♂ & ♀ hypogonadism; induction of ovulation (infertility), delayed puberty, amenorrhea, cryptorchidisim(*the absence of one or both testes from the scrotum*)
باختصار, أي مرض فيه نقص في الهرمون يؤدي إلى عيب في تكون المبيضين أو الخصيتين, أو الإباضة أو البلوغ.

b. Continuous administration or large doses or the use of a GnRH superagonists: (as we said continuous use decreases LH and FSH)
so here we are suppressing the release of Gonadotropins.
- Cancer f the prostate & Cancer of the breast (in both we have excessive androgens)
- Endometriosis(*remember from pathology that endometriosis is the presence of an endometrium-like tissue outside the uterus and it's estrogen sensitive, and undergoes cyclic changes just like the uterus, and it's characterized by cyclic abdominal pain so to reduce the pain of your patient, you should reduce the cyclic changes by reducing estrogen and progesterone, so we give continuous GnRH to reduce LH&FSH and thus, estrogen and progesterone)*
- IVF *(when we want to hyperstimulate the ovaries for IVF, we suppress endogenous LH surge by giving GnRH agonist to prevent premature ovulation)*
- Precocious puberty *(appearance of 2ry sex characteristic before 7-8 in girls or 9 in boys)*
- Uterine fibroids or uterine leiomyomas,*(are benign, estrogen-sensitive, fibrous growths in the uterus that can cause menorrhagia, with associated anemia and pelvic pain)* polycystic ovarian syndrome (PCOS)(excessive androgen production)
- ?? Contraceptive

Side effects to GnRH:

1- Production of GnRH Abs → resistance to treatment

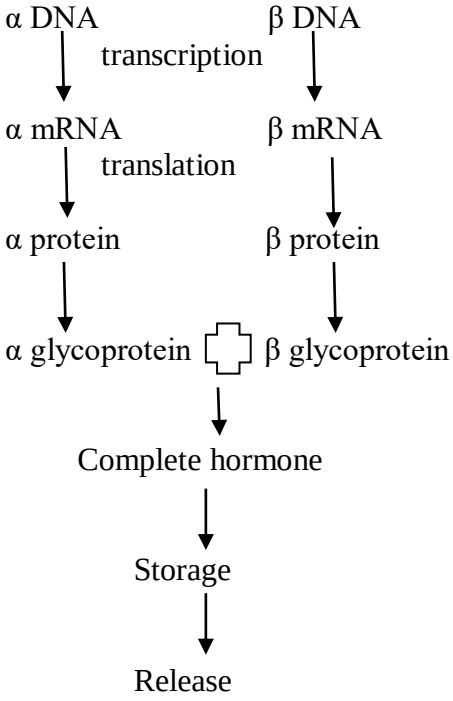
2- Headache and abdominal pain (**tolerance** develops to these side effects)
3- Sweating, facial flushing, hot flushes

4- Osteoporosis

• GnRH specific antagonist:

-(major side effect of all GnRH antagonists is histamine release)
-Ganirelix(the least associated with histamine release) ; given SC in IVF.

Gonadotropins: LH & FSH
Glycoproteins; under regulation by GnRH
-LH,FSH ,TSH &hCG all have alpha and beta subunits, the alpha subunit is similar in these hormones because all of them is encoded by the same gene, beta subunits are different because they are encoded by different genes, beta subunit is believed to produce the biological activity of the hormone.(both subunits are glycosylated).
-Both LH & FSH are glycosylated.



All of these processes are under the control of GnRH whether pulsatile or continuous

• **MOA of LH & FSH:**
- Surface receptors; cAMP 2nd messenger
- LH stimulates desmolase enzyme → ↑ steroidogenesis in gonads
- LH helps in the **descent of testes** during fetal life

• Source of LH & FSH:
- Natural human source. Human menopausal gonadotropins (HMG; Menotropin) (Mainly FSH)
- rDNA preparations (rβ-FSH)

• Human Chorionic Gonadotropin (hCG)
A product of the placenta ,Has similar pharmacological properties to LH
Obtained from the urine of pregnant ladies

• Clinical uses to gonadotropins:

- **Infertility** in ♂'s and ♀'s due to LH & FSH deficiency
- **I.V.F**
- Cryptorchidism (hCG; I.M)

• Side effects to gonadotropins:

1- Allergy
2- Ovarian hyperstimulation syndrome (fever; abdominal pain, ovarian enlargement, ascites, pleural effusion, arterial thrombosis, hemoperitoneum, shock...)(*can lead to death*)
3- Multiple births (*due to hyperstimulation*)
4- Production of specific antibodies
5- Precocious puberty and gynecomastia
6- ? Ovarian tumors
7- Failure of treatment (abortion)

- **If the problem is sexual function>>> Give estrogen or testosterone**
- **If the problem is infertility>> Give:**
  - **GnRH in pulses**
  - **LH, FSH, hCG**
  - **Estrogen (♀'s); testosterone (♂'s)**
  - **Bromocriptine (***dopamine agonist***)**
  - **Clomiphene citrate or Tamoxifen (estrogen antagonists) in ♀'s & ♂'s**

• Estrogen antagonists (Clomiphene citrate or Tamoxifen)
-are highly effective in inducing ovulation in ♀'s and restoring fertility in ♂'s
• Also E-antagonists are used with HMG and hCG to regulate ovulation in IVF

• MOA of estrogen antagonists as anti-infertility agents: