GnRH, LH, FSH
- **GnRH (Gonadotropin Releasing Hormone; Gonadorelin)** A decapeptide

  - Small, decapeptide from hypothalamus
  - Pulsatile pattern (each .5-1 hour) ... to anterior pituitary gland ... to membrane receptor calcium mediated effect to secrete FSH, LH (2 different hormones from 2 different cells) ... to blood stream ... to
  - *Ovaries in female (FSH ... follicular development, LH ... estrogen + progesterone secretion, ovulation)
  - *Testicles in male (FSH ... spermatogenesis, LH ... testosterone production)

- **E₂; Progesterone, follicle development & ovulation (♀)**

- **Testosterone; spermatogenesis (♂)**

So LH is essential for fertility in male and female
** Structure-activity relationship:

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

** Pattern of release and MOA:

- Pulsatile (Ca^{++} second messenger) $\rightarrow$ ↑ LH & FSH
- Large doses or continuous administration (downregulation of pituitary GnRH receptors) $\rightarrow$ ↓ LH & FSH
First 3 amino acids ...agonistic activity ...essential to produce GNRH activity .....(any chemical modification here will produce specific antagonist((drug that oppose the activity of GNRH )))

Amino acids (4-10) ...important for the binding characteristics of hormone to its receptors (any chemical modification here (ex. Gly at 6,10 positions ) will change the binding characteristics producing different agonists with different potencies ...here you can produce a super agonist )
GnRH synthetic preparations:

Leuprolide acetate, Triptorelin, Goserelin, Histrelin, Nafarelin, Busereline...

Could be given S.C, I.M, I.V
Mainly given S.C
Ineffective orally
Available in intranasal, suppositories, subdermal implants and vaginal pessaries dosage forms
GnRH clinical uses:

a. Pulsatile administration

- Diagnostic use

- GnRH deficiency (Kallman’s syndrome)

Rx of ♂ & ♀ hypogonadism; induction of ovulation (infertility), delayed puberty, amenorrhea, cryptorchidism...

Descending of testicles need LH (so…cryptorchidism treated by pulstile GNRH, HCG)
Prostate cancer:
In the past.....thy used to remove both testicles and suprarenals
But now.....no need for that, they manage it using a supra agonist or continues
administration of GNRH (this is the best management you can do because usually
prostate cancer discovered late in its course and metastases usually present at the time
of diagnosis

Breast cancer could be managed using hormonal therapy....how?
First you need to send biopsy of it to the lab to determine whether or not its rich in
estrogen and progesterone receptors....if rich..that's mean it will response to
hormonal therapy (this therapy differ depending on which hormone it depends on) ag.
If estrogen we give her anti-estrogen

Q: Breast cancer is managed by:
-estrogen
-anti-estrogen
-anti-androgen
-all of the above
Endometritis …endometrial tissue growth outside the uterus …in the peritoneum mainly
Look …we used GNRH for both delayed and precocious puberty (pulsatile and continues respectively )

Q: GNRH used for :
-precocious puberty
-delayed puberty

All of the above -

Q: major disadvantage of specific antagonists to GNRH is:
-IV only
-low efficacy

-histamine release

Q: قد يحضر سؤال واضعا فيه (osteoarthritis) مع ألم
This is wrong its aside effect
b. Continuous administration or large doses or the use of a GnRH superagonists: Strong agonist

- Ca prostate (androgen dependent); Ca breast

- Endometriosis

- IVF

- Precocious puberty

- Uterine fibroids or uterine leiomyomas (both are estrogen dependent), polycystic ovarian syndrome (PCOS) (associated with excess production of androgens)

- ?? Contraceptive

GnRH …..Usually we don’t use it permanently we use it as analog ???
- Side effects to GnRH:
  - Production of GnRH Abs $\rightarrow$ resistance to treatment
  - Headache and abdominal pain (tolerance develops to these side effects)
  - Sweating, facial flushing ...(both because of estrogen deficiency), hot flushes
  - Osteoporosis (special side effect)

- GnRH specific antagonist: (most of antagonists are associated with histamine release (allergy ,with exception of 2 which are used clinically (eg. Glucorilitaactitate (iv ,im , subcutaneous ....all effective except orally )

   Ganirelix (IVF)(has the least effect on histamine release ....especially used in IVF)
Gonadotropins: LH & FSH

Glycoproteins; under regulation by GnRH

LH      FSH      TSH      hCG

α

β
Both alpha and beta are Glycoprotein = polypeptide and sugar
*alpha and beta subunits are encode by 2 different genes
*Genes for alpha differ from genes of beta
*Genes of alpha in all these hormones are similar
*Genes of beta differ among all these hormones
(easily proved by a simple experiment …..separate all alpha subunits from their beta partners in all these hormone then make a recombination eg. Alpha of LH with beta of FSH w you will get FSH effect)
*So biological activity of the hormone is mainly due to beta subunit not alpha
But neither alpha nor beta is effective alone they must be bound to each other to produce the desirable effect of the hormone

Alpha and beta …transcription ,translation , glycosilation ,combination all these are possible sites for the action of GNRH …..could enhance all these process if pulsatile or inhibit it if continues (but the first process to be affected is the release because it’s immediate effect will result here..............................but stimulation of synthesis need time „„„so if you gave a drug to inhibit the synthesis , the action of this drug star after the depletion of the stored amount of the hormone (((((but the GNRH antagonists have direct effect)))))
α DNA → α mRNA → α protein → α glycoprotein

β DNA → β mRNA → β protein → β glycoprotein

Complete hormone

Storage

Release
**MOA of LH & FSH:**

- **Surface receptors (on ovaries or testicles); cAMP 2nd messenger**

- **LH stimulates desmolase enzyme** (convert cholesterol to pregnanolone (first step in the synthesis of different steroids) → ↑ 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)**
HMG….extracted from the urine of menopausal females (in these females there is no ovaries function so no progesterone or estrogen to make a negative feedback inhibition on LH,FS so they are secreted tremendously by active secretory mechanism of the urine ….this mechanism called HMG ..it has a ratio of 1:1 LH:FSH but because LH is less stable than FSH (very quickly metabolized by liver so when they administered its mainly appear as FSH

So we use HCG …more stable than LH and has the same effect (ovulation ,production of estrogen +progesterone )
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)
- Allergy
- Ovarian hyperstimulation syndrome (dangerous; usually fatal) (fever; abdominal pain, ovarian enlargement, ascites, pleural effusion, arterial thrombosis, hemoperitoneum, shock...)
- Multiple births
- Production of specific antibodies
- Precocious puberty and gynecomastia
- ? Ovarian tumors
- Failure of Rx (abortion)
*** If the problem is sexual function
Give estrogen or testosterone

*** If the problem is infertility:

- GnRH in pulses
- LH, FSH, hCG
- Estrogen (♀’s); testosterone (♂’s)
- Bromocriptine (in case of hyperprolactenemia)
- Clomiphene citrate or Tamoxifen (estrogen antagonists) in ♀’s & ♂’s (estrogen responsible for negative feedback of testosterone on GNRH)
Regardless we is the problem along the axis …problems of sexual functions……
In the past) used to be treated with testosterone administration
But now) inside of that we use Viagra (solved most of the impotency problems in
males ,very safe even in hypertension or diabetes …except in case of administration
nitrate with it )
*if a female has problem with ovulation caused by GNRH deficiency with normal
LH,FSH….here administration of estrogen and progesterone will cause infertility to
that female
*if the problem in ovulation or spermatogenesis was because of estrogen or
progesterone and the rest of the axis is normal here taking these hormones will solve
the problem

prolactin is amajor cause of infertility in both males and females
bromocriptin تحل المشكلة باستخدام FSH,LH زيادته تمنع إنتاج
*intrafalopiamn insemination …take the sperms from the male and inject it directly to the female fallopian tube (if the problem was in reaching to the sperm to tubes)

*If all the previous solutions did not work we use IVF (here we make a zygote then insirte it to the uterus
To mak this we need from the female to produce more than the normal amount of ovaries in that mounth (max =2)

………..we do this by

1-supressing the normal axis and the drug of choice here is GNRH super agonist or continues administration
(with the super agonist we will have an initial raise in FSH,LH but a suppression after that
With the continues administration suppression from the beginning ….so this is better )
2-then ,we need to over stimulate the ovaries …by using

- a large doses of LH,FSH(in form of HMG )…but take care not to have OHS
- HCG (why?...because HMG is mainly FSH
- Anti-estrogen
- Bromocriptin
Now the lady produced 4-7 ova
Retrieve then by an intra-vaginal procedures
Take the sperms from the husband
Put both in pitridish or inject the sperm directly inside the ova (here sex can be determines)
Then put the zygote in the uterus

?! why we suppressed the axis not giving FSH ,LH directly from the beginning?
Because the incidence of OHS (ovarian hyper stimulation syndrome ) is more if you give FSH,LH with a normal axis

IVM: a new technique (in vitro maturation )
Here the ladies don’t have to take hormones …..we just take immature follicles ,treat them with hormones to make them mature
The success rate here is the same as IVF
- E-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:

\[ \text{E}_2 \rightarrow \text{LH; FSH} \rightarrow \text{GnRH} \rightarrow \text{X} \rightleftharpoons \text{X} \rightarrow \text{E}_2 \]

\[ \text{E}_2 ; \text{Progesterone (♀)} \]

\[ \text{Testosterone (♂)} \]