NEET SS

REPRODUCTIVE

Dr Ramesh P Dr Aravind Ramachandran

Contributing Editor

Dr Ramesh P is a highly proficient Obstetrician and Gynecologist with a remar...

REPRODUCTIVE PHYSIOLOGY

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3.  Ovarian Steroidogenesis and DSDs related to the Steroidogenic Pathway — 4.4 — 92 Min video
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DEVELOPMENT OF UTERUS AND OVARY

Active space

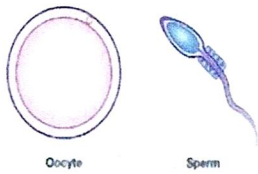
Embryogenesis

00:01:55

Fertilisation :

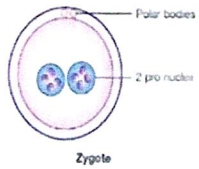
Oocyte :

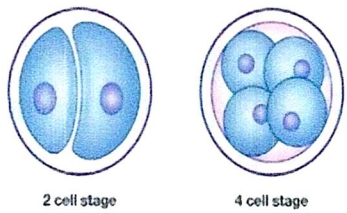
- Largest cell of the human body.
- Covered by zona pellucida : Role in sperm-oocyte interaction and prevention of fallopian tube implantation.
- Arrested in prophase of meiosis-I.
- Just before ovulation : meiosis I → meiosis II, release of 1st polar body.



Sperm-oocyte interaction :

- The acrosome (Tip of sperm) fuses with oocyte membrane.
- Sperm membrane disintegrates and its nucleus goes inside the oocyte.
- Earliest sign of fertilisation : 2 pronucleus.
- After fertilisation, 2nd polar body from oocyte is released.





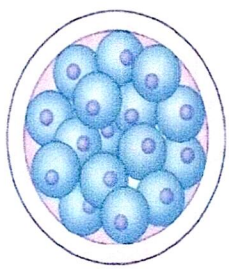
Embryo :

Day 1 after fertilisation (1 celled stage) : 2 pronucleus + 2 polar bodies.

Day 2 : 2-4 celled stage.

Day 3 : 8 celled stage.

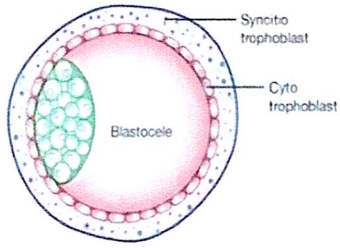
Day 4 : 16 celled stage (morula).



morula.

Morula (mulberry shape) :

- Enters the uterine cavity in a normal cycle.
- Covering : Zona pellucida.



Blastocyst.

Blastocyst :

- 256 celled stage.
- Fluid accumulation → Blastocele → Later forms the yolk sac.

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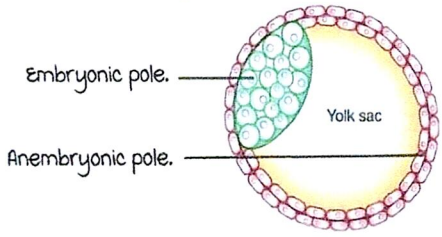
- Majority cells arrange at one embryonic pole : Embryoblasts.
- Cells at the margin : Trophoblasts.



Development of blastocyst.

Trophoblasts differentiate into :

1. Syncytiotrophoblasts : Acellular layer.
2. Cytotrophoblasts : Cellular layer.

Zona pelluca breaks → Embryo is released → Implantation.

Pre implantation genetic testing (PGT) :

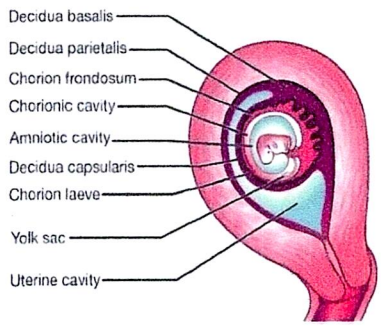
- Day 5 of embryo.
- Cells from trophoectoderm biopsied.
- Assessed for genetic analysis.
- Limitation : Mosaicism can be missed.

Implantation :

Blastocyt is implanted into decidua at the embryonic pole.

Decidua (Endometrium during pregnancy) :

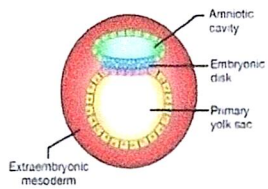
1. Decidua basalis : Related to embryonic pole.
2. Decidua capsularis : Encapsulating the embryo.
3. Decidua parietalis : Remaining part of decidua.



Decidua.

Chorion :

- Chorion frondosum : Related to decidua basalis.
- Chorion laeve : Surrounding chorion.

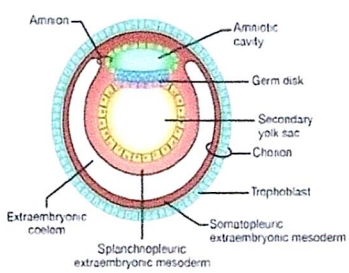


Note : Decidua basalis + chorion frondosum → Formation of placenta.

Extra embryonic mesoderm (EEM) :

Develops around the embryo.

Between the embryonic disc and trophoblast.



Extraembryonic mesoderm.

Fluid collected within the EEM divides it into 2 layers :

1. Somatopleuric EEM.
2. Splanchnopleuric EEM.

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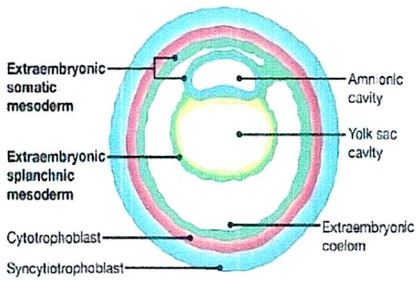
Extra embryonic coelom/chorionic cavity :

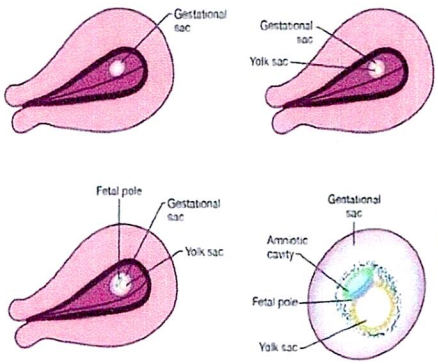
- Develops inside extra embryonic mesoderm splitting it into 2 except at connecting stalk.
- First fluid filled structure seen on ultrasound : Seen as gestational sac at 5 weeks of gestation.



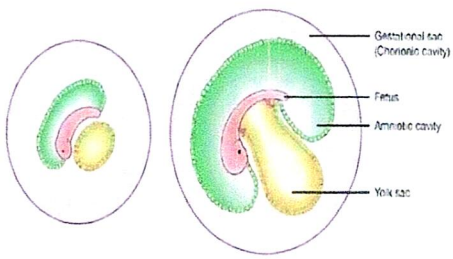
Extraembryonic coelom.

Implantation and embryonic disc : USG correlation.

- 5 weeks : Gestational sac from extra embryonic coelom.
- 5 weeks + 3/4 days : Yolk sac from blastocele.
- 6 weeks : Embryonic disc, cardiac activity.
- Decidua parietalis and capsularis : Double decidual sac sign.



USG evidence of pregnancy.



Formation of amniotic cavity.

Further embryo development, folding and amniotic fluid expansion :

Amniotic cavity :

- Between ectdoerm and trophoblasts.
- Enlarges and surrounds the embryo.
- Embryo is folded on itself.
- Yolk sac is compressed and seen as a small sac adjacent to fetal pole.

Yolk sac :

- Transformed structure of blastocele.
- Resorbed by 12 weeks.
- Normal diameter : 2-5 mm.
- Small yolk sac <3 mm, large yolk sac >6 mm.

---- Active space -----

Formation of placenta

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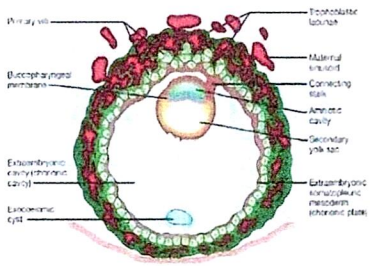
Connecting stalk :

- Fetal vessels reach the maternal vessels via the connecting stalk.
- Later, forms the umbilical cord.

Cytotrophoblasts, syncytiotrophoblasts, mesoderm : Form placenta.

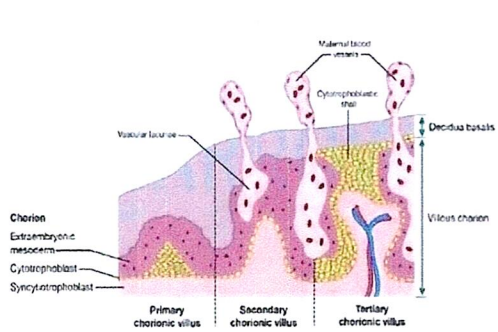


Connecting stalk.

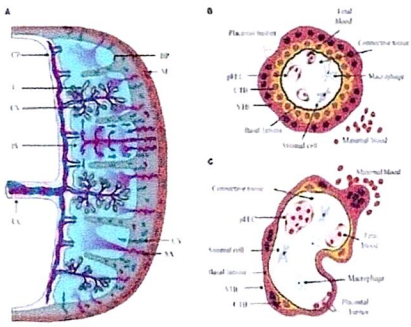
Villi :

Syncytio trophoblast erode into maternal vascular sinuses/lakes.

- Cytotrophoblast grow into syncytiotrophoblast : Primary villi (2 weeks).
- Mesoderm grows into the cytotrophoblast : Secondary villi (2 weeks).
- Blood vessels inside mesoderm : Tertiary villi (3 weeks).



Primary, secondary and tertiary villi.



Placental barrier.

Placental barrier :

Between maternal vascular sinuses/lakes and fetal blood inside vessels.

Formed by :

1. Syncytiotrophoblasts.
2. Cytotrophoblasts.
3. Basement membrane.
4. Endothelium of vessels.

Ultimately, the placental barrier thins out.

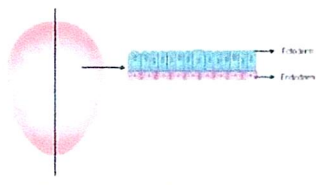
Further development of embryo

00:23:43

Development of embryonic disc :

2 layered embryonic disc at 2 weeks :

1. Epiblast/ectoderm.
2. Hypoblast/endoderm.



2 layered embryonic disc.

----- Active space ----

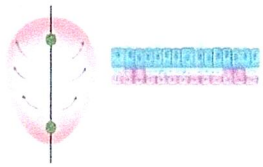
3 layered embryonic disc at 3 weeks :

Trilaminar disc.

Intra embryonic mesoderm (IEM) develops between ectoderm and endoderm.

Ectoderm and endoderm remains unseparated at 2 places :

- Procaudal plate.
- Cloacal plate.



3 layered embryonic disc.

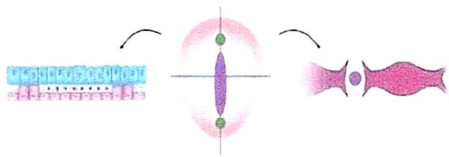
Notochord process formation :

Some ectodermal cells proliferate into IEM forming notochordal process.

It splits IEM into 2 halves.

Each half of IEM is divided into :

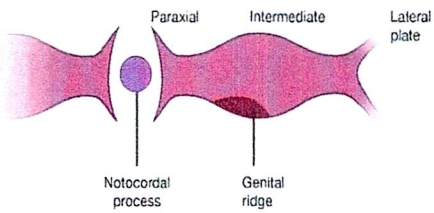
- Paraxial mesoderm.
- Intermediate mesoderm.
- Lateral plate mesoderm.



Notochord process formation.

Intermediate mesoderm :

- Cephalic end : Pronephros (Disintegrates).
- Middle : Mesonephros (Forms mesonephric/paramesonephric ducts and genital ridge).
- Caudal end : Metanephros.
- Medial part of intermediate mesoderm : Genital/gonadal ridge.



Parts of intermediate mesoderm.

Genital/gonadal ridge formation :

- Formed from medial most part of intermediate mesoderm.
- Later forms the gonads.
- Bipotential gonad till 6 weeks of gestation.
- After 6 weeks, differentiates into testis/ovary depending on presence/absence of Y chromosome.

Note : Genital tubercle forms the external genitalia (Scrotal sac/labia majora).

Paraxial mesoderm :

Forms the somites.

Somites can be used to determine embryonic age.

Somites divided into 3 parts :

-- Active space -----

- Sclerotome : Develops skeletal system.
- Myotome : Develops muscles.
- Dermatome : Develops dermis.

Development of paramesonephric ducts 00:32:47

Immediately lateral to the genital ridge, two duct systems extending from cranial to caudal end develop.

2 duct systems : Mesonephric and paramesonephric ducts.

Mesonephric and paramesonephric ducts.

Both ducts coexist and the final fate is decided by the gonads.

Testis :

- Secrete testosterone and antimullerian hormone (AMH).
- AMH hormone abolishes development of mullerian duct/paramesonephric duct.
- Promotes formation of wolffian/mesonephric duct.

Ovary :

- No testosterone, AMH is released.
- Paramesonephric duct develops.

Mullerian ducts :

Forms the female internal genitalia.

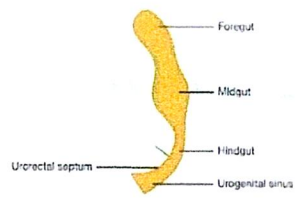
Caudal ends of mullerian ducts fuse in midline.

Tip of the fused ends is called mullerian tubercle.

Development of urogenital sinus from endoderm :

Endoderm develops into gut system : Foregut, midgut, hindgut.

Part of hindgut distal to allantois diverticulum : Primitive urogenital sinus.



Development of gut system.

Active space

Primitive urogenital sinus is divided by urogenital septum into :

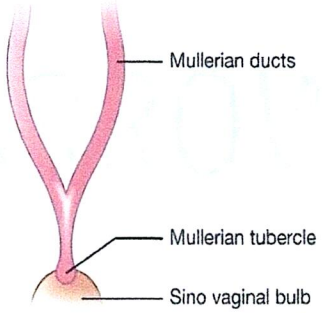
- Definitive urogenital sinus anteriorly : Forms part of urinary structures and urinary structures (Part of urethra, bladder except trigone).
- Anus/rectum posteriorly.

Part of urogenital sinus forming vagina : Sinovaginal bulb.

Tip of urorectal septum forms perineal body.

Mullerian tubercle opens into sinovaginal bulb :

- Fallopian tubes develop from the mullerian duct unfused part.
- Uterus, cervix and upper 2/3rd of vagina : Develop from the fused mullerian duct parts.
- Lower 1/3rd of vagina : Develops from sinovaginal bulb.
- Mesoderm around the sinovaginal bulb : Connective tissues and musculatures of the genital tract.
- The distally fused mullerian ducts then canalizes and the middle septum is resorbed from caudal part to cranial part at 20 weeks of gestation.



Mullerian ducts.

Mullerian duct anomalies :

No fusion of mullerian ducts : Didelphys uterus.

Partial fusion of mullerian ducts : Bicornuate uterus.

No resorption of septum : Septate uterus.

Development of only 1 mullerian duct : Unicornuate uterus.

No mullerian duct system development : Mullerian agenesis.

Associated anomalies with mullerian duct anomalies :

- 3% of renal anomalies.
- 12-15% of skeletal anomalies.

Development of urinary system

00:49:10

Ureteric bud :

- Diverticulum from mesonephric duct.
- Goes into the metanephros.
- Forms collecting system of urinary tract.
- Metanephros : Forms the kidneys.

- Active space -----

Development of bladder :

- mesonephric ducts open into urogenital sinus.
- Part of distal ends of mesonephric ducts resorbed → Trigone of bladder.
- Remaining part of bladder : From endoderm (urogenital sinus).

REPRODUCTIVE PHYSIOLOGY

Active space

Menstrual cycle

00:01:08

Duration : 28 days (24-35 days).

Controlling hormones :

- FSH : First 14 days.
- LH : Second 14 days.

Cells in the follicle :

- Granulosa cell : Under control of FSH.
- Theca cells : Under control of LH.

This is called the "2 cell 2 gonadotrophin theory".

Granulosa cells and theca cells are dependent on each other.

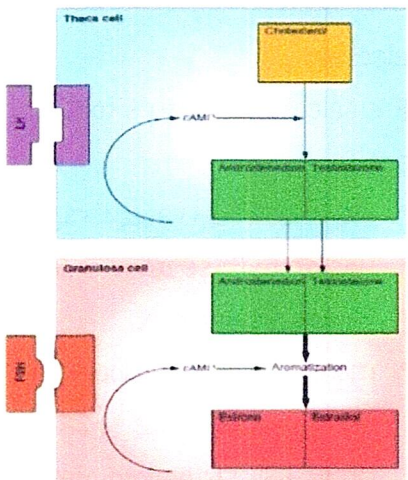
Production of estrogen :

Cholesterol → Pregnanalone → Progesterone

Progesterone → (Aromatase) → Androstenedione

Androstenedione → (P450 C17) → Estrogen

Granulosa cells lacks P40 C17 → Provided by theca cells.



Ovarian steroidogenesis.

Follicular phase :

Primordial germ cells :

- 7 to 8 billion in fetal life.
- 1 to 2 milllion at birth.
- 1000 at menopause.

1. Recruitment :
   - Process where a fixed fraction of primodial follicles are acted upon by FSH to develop in each cycle.
   - Influenced by intracrine & paracrine factors :
     Not by FSH, LH but possibly by GH & androgens.
2. Selection : Only one will get selected to grow prominently.

-- Active space -----

3. Dominance : Selected follicle will dominate and outgrow others.

Features of dominant follicle (DF) :

- Increased FSH receptors.
- Aromatase activity.
- Secretion of inhibin B.

Rescue & recruitment :

Duration of time to achieve preovulatory status : 85 days.

Majority of this time is independent of hormones until late stage.

Recruitment is achievement of readiness of follicle to respond to FSH selection.

Rescued at the beginning of the cycle from apoptosis.

Androgens/GH may have a role.

Selection :

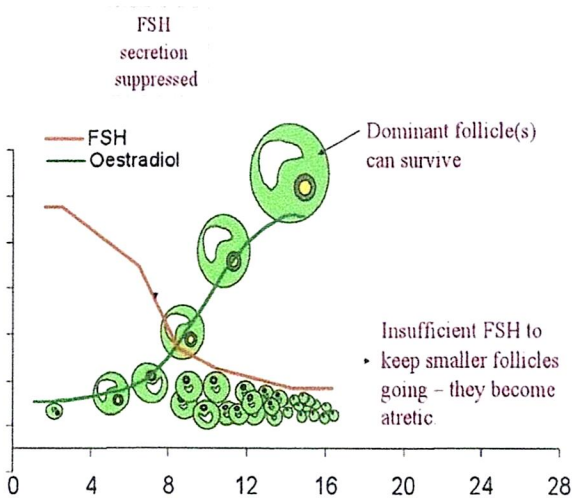
DF is selected by day 5 to 7.

Features :

- Increased FSH receptors.
- Has aromatase activity (Androgen → Estrogen).
- Inhibin B secretion.
- Monofollicular development :

  FSH levels fall (Due to E2 and Inhibin) but DF continues to grow.

  Other follicles go into atresia.



Summary of follicular phase.

Ovulation phase :

Estrogen effects :

- Negative feedback on FSH.

- Positive feedback on LH (Ea >200 pg/ml for >48 hrs).
  After maturation of HPO axis.
  Results in LH surge.

LH surge :

- Onset : 24 to 36 hrs before ovulation.
- Duration : 50 hours.
- Peak : 12 hours before ovulation.

FSH surge (Second peak) : D/t progesterone rise.

Leutinization : Cholesterol entry into cell.

Progesterone effects :

- Rising levels : Positive effect on pituitary.
- High levels : Negative effect on pituitary.

Structure of graafian follicle :

- Layers : Granulosa & theca cell layer.
- Oocyte surrounded by cumulus oophorus.
- Together called cumulus oocyte complex (COC).
- Filled with fluid.
- COC attached to the follicular wall (Freeing of COC mediated by FSH).

Note :

- Ovulation occurs 34 to 36 hrs after onset of LH surge.
- LH functions :
  a. LH surge lasts for 48 hrs leading to ovulation.
  b. Necessary for complete oocyte maturation.
  c. Supporting corpus luteum.
- Completion of metaphase I → Extrusion of first polar body → Secondary oocyte formation → Arrested in metaphase of 2nd meiotic division → Completes after fertilization.

Agents causing ovulation :

1. Endogenous LH.
2. Exogenous LH (Large dose).
3. GnRH agonists.
4. hCG.

--- Active space -----

Mechanism of follicular rupture :

- Follicular pressure ↑ :
  Changes in composition of the antral fluid → ↑ Colloid osmotic pressure.
- Enzymatic rupture of the follicular wall :
  LH & FSH → Granulosa cells → Production of plasminogen activator → ↑ Plasmin → ↑ Fibrinolytic activity → Break down of follicular wall.
- LH → ↑ Prostaglandin E → ↑ Plasminogen activator → ↑ PG $F_{2\alpha}$ → Final common pathway (most accepted theory).

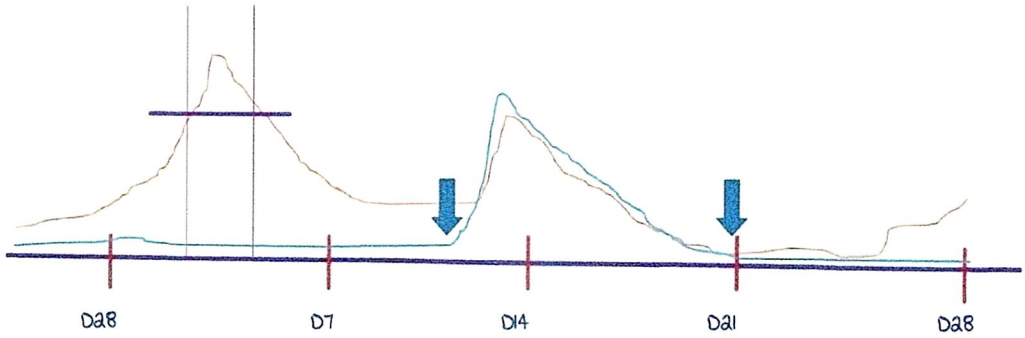
NSAIDS role in IVF/IUI : Prevent rupture of follicule to delay.

Luteal pnase :

Summary :

- Follicular rupture → Follicle becomes corpus luteum → Secretes progesterone under influence of LH → High levels inhibit LH.
- At D21 → Maximum levels of progesterone → Profound inhibition of LH.
- Corpus luteum supported by hCG instead of LH.
- No pregnancy → No hCG → Disintegration of corpus luteum.
- At D24 rising FSH → Recruitment of next cycle.
- Decreased progesterone d/t disintegration → Withdrawal bleeding on D28.

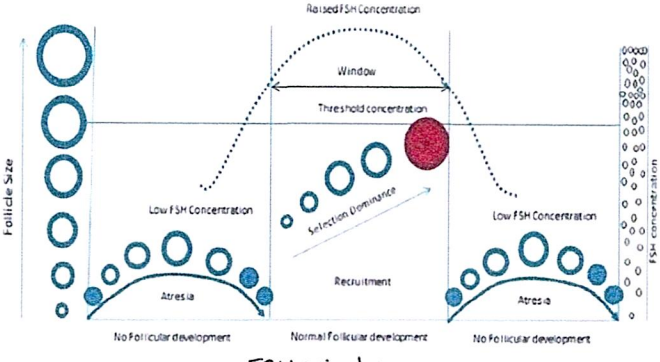
Luteal phase defect : Average values of progesterone on D20, 21, 22 less than 3.



Hormone dynamics.

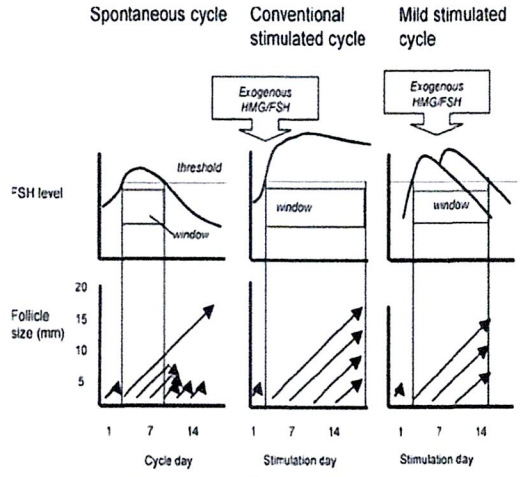
Concept of FSH window :

- Only follicles coming under FSH peak window can grow.
- Basis of ovarian stimulation : Expand the window either sides.



FSH window.

----- Active space ----



Concept of FSH window.

- Ovarian induction : Aim to induce atleast one ovum.
- Ovarian stimulation : Aim to increase the number of ovum.

LH window and ceiling :

- LH ceiling : <5 IU/L.
- LH threshold : >1.2 IU/L.
- LH window : Optimal follicular development.
- Low LH levels :
  - Impaired follicular growth.
  - Impaired oocyte maturation.
  - Inadequate androgen and oestrogen synthesis.
- High LH levels :
  - Follicular atresia.
  - Oocyte development compromised.
  - Suppression of granulosa cell proliferation.
  - Premature luteinization.

Summary of all events in mentsrual cycle :

Days	Hormonal events	Ovarian events	Endometrial events
1 to 4	$\uparrow E_a$ (Estradiol) & P → Release of FSH & LH (-).	Recruitment.	Sloughing of endometrium.
5 to 7	$E_a\uparrow$ (From follicles).	Selection.	Proliferation.
8 to 12	$\uparrow E_a$ & inhibin → (-) FSH.	Dominance.	Growth of glands & stroma.
13 to 15	$\uparrow E_a$ → LH surge.	Ovulation.	Proliferative → Secretory.
15 to 25	E2 & P → (-) FSH & LH↓↓	CL formation.	Secretory.
25 to 28	↓E2 & P → no -ve effect → ↑FSH.	Luteolysis.	P withdrawal → Sloughing.

GnRH physiology

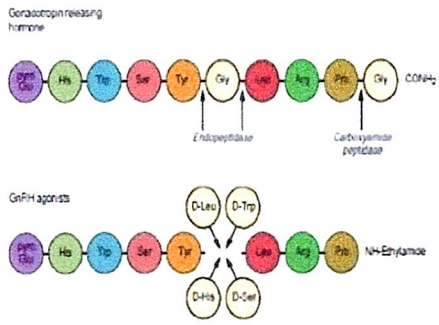
00:55:00

Features :

- Action : Stimulates production of FSH & LH.
- It is a nona/deca-peptide.
- Short t 1/2 of 5 to 6 mins (Rapid hydrolysis due to weak bonds 5 to 6 and 6 to 7).
- At 6th position : Glycine is present (main cause of weakness of GnRH).

GnRH agonist :

- Substitution of 6th positon glycine.
  a. With Leucine : Leuprolein.
  b. With Serine : Goserelin or buserelin.
- Has increased affinity.
- Has increased t 1/2.



GnRH agonist

GnRH antagonist :

- Multiple aminoacid substitutions (1,2,3 mainly).
- Morphologic similarity.
- No intrinsic activity.
- Competitive antagonist.
- Eg : Cetrorelix, Ganirelix.

Individual molecules.	
Leuprolide.	Leucine at 6.
Buserelin.	Serine at 6.
Naferelin.	Naphthylamine at 6.
Histerelin.	Histidine at 6.
Goserelin.	Serine at 6, Aza-Gly at 10.
Triptorelin, Deslorelin.	D and L tryptamine.
Antagonists.	
Abarelix, Cetrorelix, Ganirelix, Antarelix.	

----- Active space ----

GnRH action on pituitary :

Pulsatile secretion.

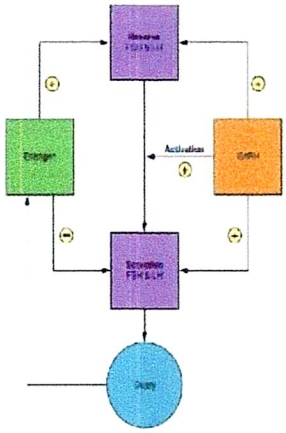
Pulse frequency :

- Once in 1 hour.
- Can be increased or decreased.
- High frequency : Preferential synthesis & secretion of LH.
- Low frequency, high amplitude : Preferential synthesis & secretion of FSH.
- Regulated by E2 and progesterone.

Gonadotrope : For both FSH and LH.

Actions of GnRH :

1. Release/flare : Immediate event.
2. Storage/priming : For further release.
3. Activation of stored pool for release.



Actions of GnRH

Note :

- FSH and LH exist partly as subunits and partly as stored pool.
- β subunit synthesis is the rate limiting step.

Key concepts :

- Low E2 level : Cause storage of FSH and no action on LH.
- High E2 level : Inhibit FSH and stimulate LH release and storage.
- Low progesterone : Stimulate LH and FSH release.
- High Progesterone : Inhibit LH, Stimulates FSH storage.

Pituitary down regulation :

- Endogenous GnRH → Short half life → Short action → Receptors recycled.
- GnRH agonist → Long action → Agonist continuously present → Receptors desensitized.
- Leads to loss of receptors (Tachyphylaxis).
- Receptor-effector uncoupling seen.
- Suppression seen earlist by D7, latest by D21.

Note :

- GnRH antagonist causes immediate stoppage in FSH, LH secretion.
- Administering GnRH agonist → Displaces GnRH antagonist → Secretion of FSH, LH.

-- Active space -----

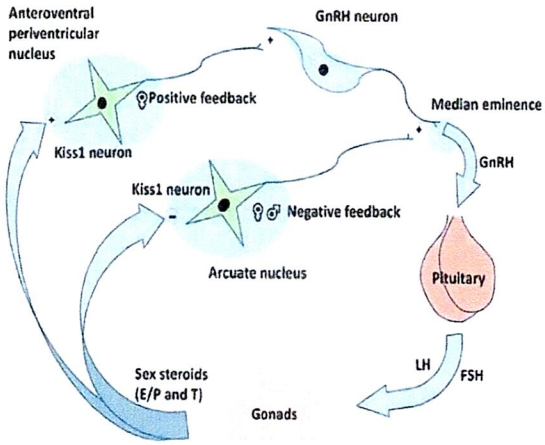
KNDy neurons :

Consists of :

1. Kisspeptin : Stimulates GnRH release.
2. Neurokinin B (NK B) : Stimulates Kisspeptin release.
3. Opioids (Dynorphin) : Inhibits Kisspeptin release.

Involved in :

- Puberty.
- Sex steroid feed back.
- Stress effects.
- Nutritional effects.
- Action on arcuate nucleus : Causes negative feedback.
- Action on antero-ventral periventricular nucleus (AVPV) : Causes positive feedback.



Action of Kisspeptin

Theories on folliculogenesis :

1. Cyclical recruitment :
   Follicles are recruited in each cycle.
   Old concept but widely accepted.

2. Continuous recruitment :
   Recruitment occurs throughout continously.
   Not very well accepted.

3. Follicular wave theory :
   Newer concept.
   Recruitment occurs in major and minor waves.
   Stimulation at the time of the wave causes follicular formation.