King Saud University

College of Medicine

2nd Year,

Reproduction Block

PHARMACOLOGY 433

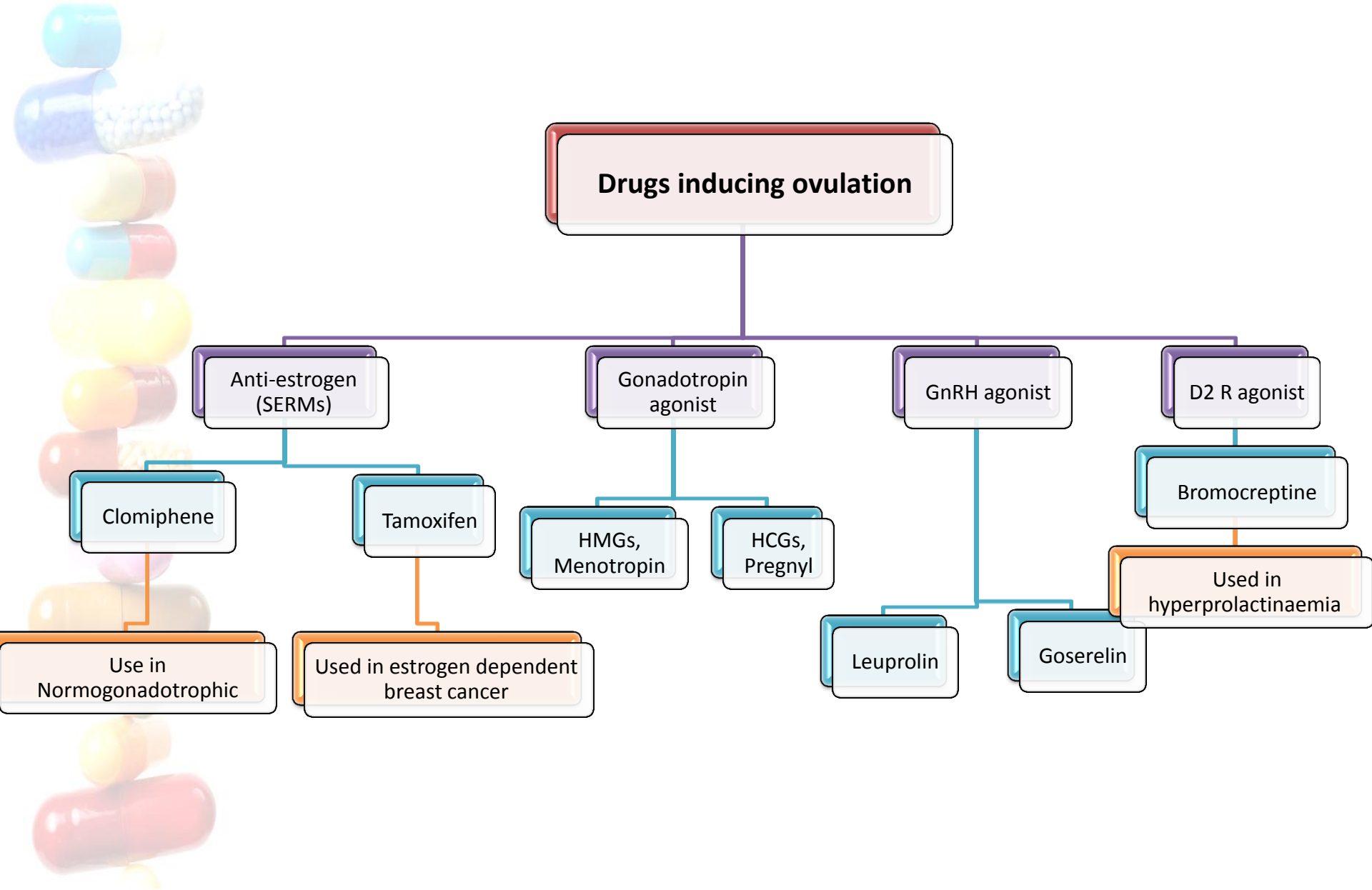
MED 433 Teams

L2- Drugs Inducing ovulation

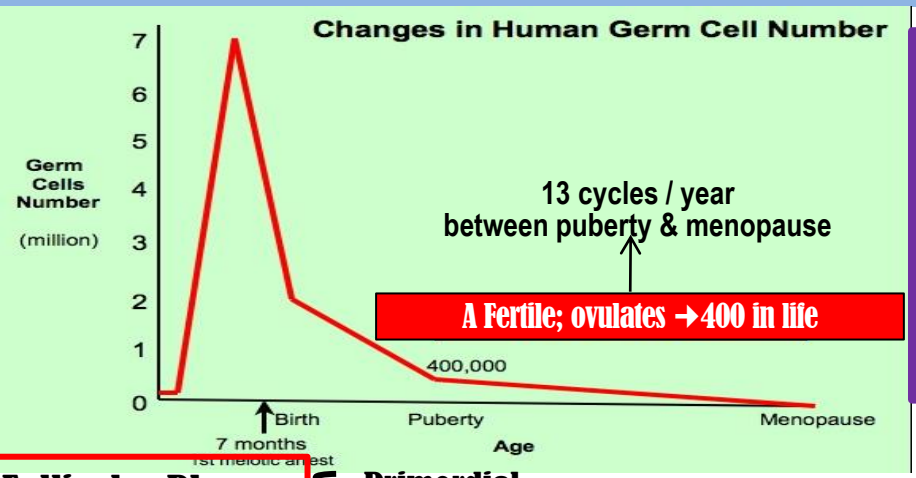
Objectives

- Recall how ovulation occurs and specify its hormonal regulation
- Recognize causes and types of female infertility
- Classify ovulation inducing drugs in relevance to the existing deficits
- Expand on the pharmacology of each group with respect to mechanism of action, protocol of administration, indication, efficacy rate and adverse effects.

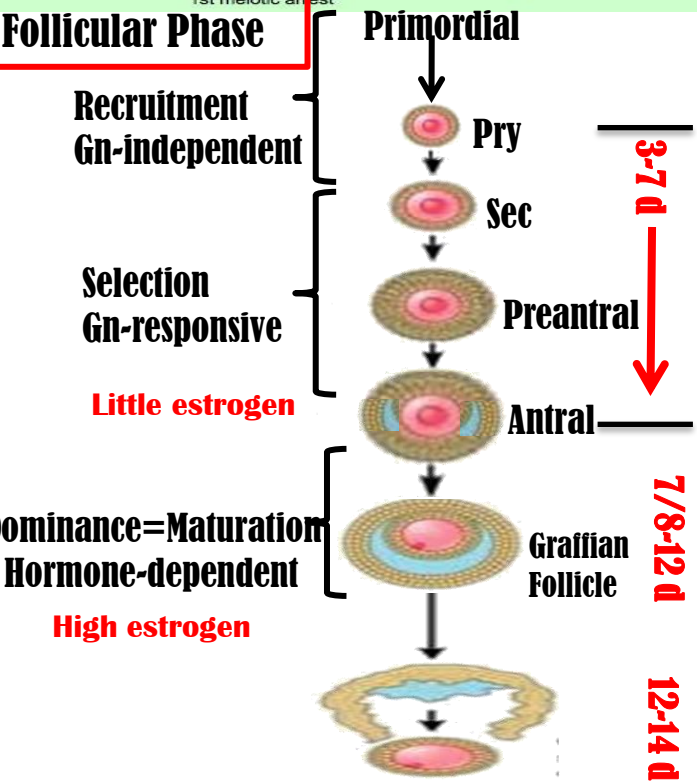
Mind Map


Drugs inducing ovulation
Anti-estrogen (SERMs)
Gonadotropin agonist
GnRH agonist
D2 R agonist
Clomiphene
Tamoxifen
HMGs, Menotropin
HCGs, Pregnyl
Bromocreptine
Used in hyperprolactinaemia
Use in Normogonadotrophic
Used in estrogen dependent breast cancer
Leuprolin
Goserelin

Introduction



1. At birth a baby have approximately 2 million primordial follicle
2. At puberty she starts ovulation and have 13 cycles each year
3. At menopause the female no longer have any ovoum



1. the Primordial enters the cycle by genetic program without the help of any hormones
2. After the 3rd day, it starts to be Gonadtrophins dependent (FSH\LH) until the 7th day when it starts secreting little estrogen
3. From the 7th day until the 12th the estrogen level increases and releases which lead to the release of more LH from AP
4. From 12th until 14th day the follicle will rapture and ovulation occurs

"The timing is so important dr.omnia said that"

slide | doctor's note | important | explanation

Introduction

INFERTILITY

A condition characterized by a reduction in ability to reproduce or to achieve conception

Causes

- **1/3 attributed to women**
- 1/3 attributed to male factors
- 1/3 both or unexplained

Most common cause of female infertility

- 40% ovulation disorders
- 30% tubal factors due to blockage or damage
- 14% Endometriosis
- 10% others
- 3% uterine and cervical factors ⇨ Miscarriage

Ovulation Induction

ANTIESTROGENS	GnRH	GONADOTROPHINS	D2 Agonists
1-SERMs; Clomiphene Tamoxifen In case of Normogonadotrophic	1-GnRH agonists Leuprolin Goserelin In case of Hypogonadotropic	1-HMGs; Menotropin 2-HCGs; Pregnyl In case of Hypogonadotropic	1-Bromocreptine In case of Hyperprolactinaemia

IN POLYCYSTIC OVARIAN SYNDROME

[Most common cause of infertility] → Insulin resistance and obesity so we Give METFORMIN to↓ body weight & ↑ response to ovulation induction drugs

We can add any of ovulation induction drugs to metformin

1. Normogonadotrophic = the hypothalamus and AP are normal but the problem is in the ovary
2. Hypogonadotropic = the problem either in hypothalamus or AP
3. Hyperprolactinaemia = high levels of prolactin hormone is found in lactating women and it interferes with ovulation because it decreases FSH/LH so we give dopamine to inhibit it releases

slide | doctor's note | important | explanation

Ovulation Induction

Hypothalamus

↓

GnRH

↓

Anterior Pituitary

↓

FSH / LH

↓

Ovary

↓

Estrogen

Progestins

Normally the high levels of estrogen or progestin directly inhibits the axis

1. If ovary is NOT secreting enough estrogen to induce ovulation or inhibit the axis, we give **ANTIESTROGENS** to stimulate the hypothalamus and AP hormonal secretion
2. If the problem was in the hypothalamus and it is not releasing enough GnRH, we give **GnRH agonists**
3. If the problem was in the anterior pituitary we give either **GONADOTROPHINS (FSH/LS) or GnRH and they are equally effective.**

Hypergonadotrophic Conception remote, no place for medication therapy

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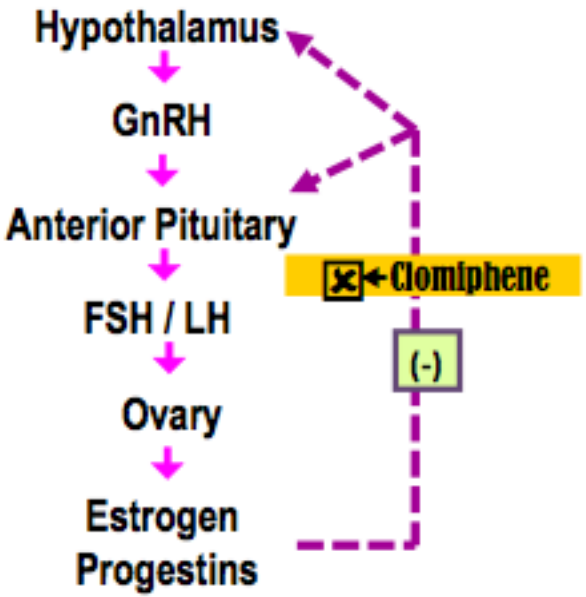
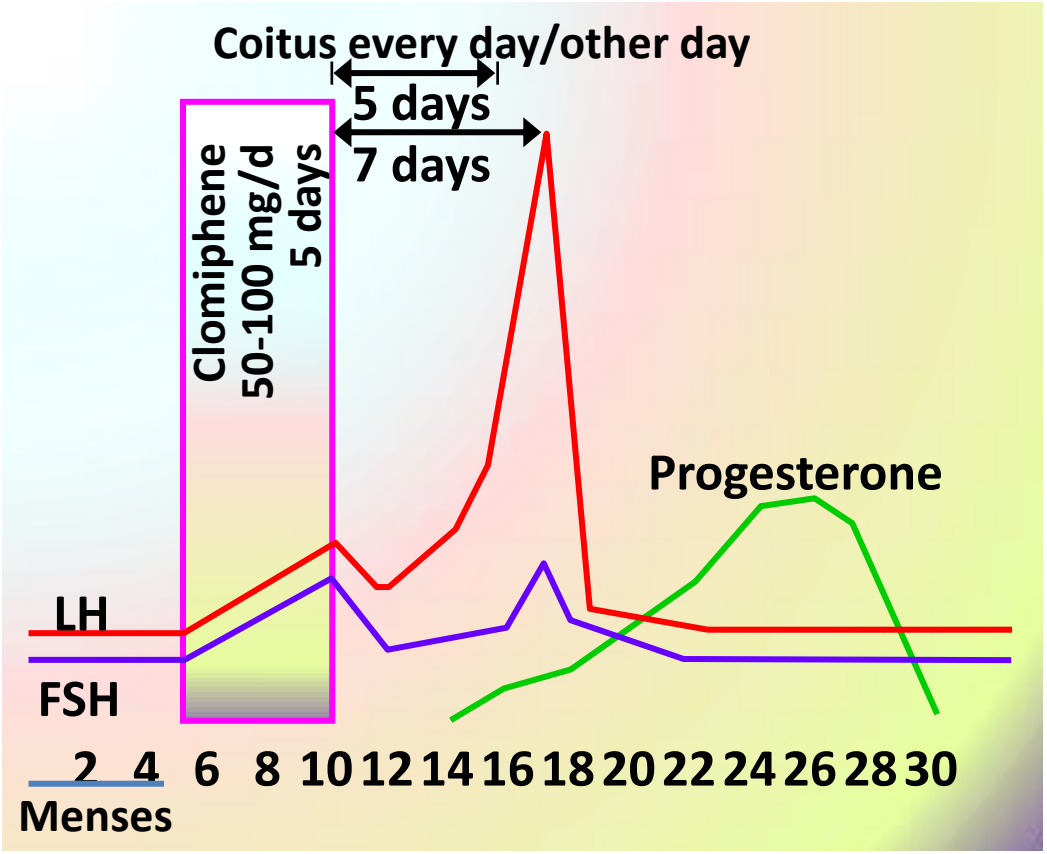
1. Anti-Estrogens:
Selective Estrogen Receptor Modulators (SERMs)

- Compete with estrogen on estrogen receptors in the nucleus.
- Doing so they act as **antagonists** or **partial agonists** depending on how they bind & the different target tissue of action.
- In the **hypothalamus** & **pituitary** they have **antagonistic action.**

Illustrations on Clomiphene:

(for better understanding, study the next slide first)





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1. Anti-Estrogens: Selective Estrogen Receptor Modulators (SERMs)

Clomiphene

Pharmacological Effects	On hypothalamus: ↓ -ve feed back of endogenous estrogen on hypothalamus → pulse ↑ GnRH → ↑ gonadotrophin production (FSH & LH) → cause growth maturation & rupture of follicles → OVULATION. On pituitary: ↑response of gonadotrophins to GnRH.	
Indication	Female infertility; not due to ovarian or pituitary failure → Normogonadotrophic The success rate for ovulation → 80% & pregnancy → 40%	
Method of Administration	Clomiphene given → 50 mg/d for 5 days from 5th day of the cycle to the 10th day. If no response give 100 mg for 5 days again from 5th to10th day The drug can be repeated not more than 6 cycles.	
ADRs	1. Hot Flushes & breast tenderness 2. Gastric upset (nausea and vomiting) 3. Visual disturbances (reversible) 4. ↑ nervous tension & depression	5. Skin rashes 6. Fatigue 7. Weight gain 8. Hair loss (reversible)
Note:	**↑ incidence of multiple ovulation → twins in 10% birth**	

Tamoxifen

- Similar & alternative to clomiphene but **differ in being Non Steroidal**.
- Used in palliative treatment of hormone-dependent / estrogen receptor- positive advanced **breast cancer.**

Why clomiphene not used in such cases of cancer breast?

Clomiphene is **steroidal** in nature, somehow acts like **estrogen** which has a high incidence inducing cancer.

slide **doctor's note** **important** **explanation**

2. Gonadotrophins: (FSH & LH)

- Naturally produced by the pituitary gland.
- For therapeutic use, extracted forms are available as; (CHEEP)
  1. **Human Menopausal Gonadotrophins (hMG)** ➔ extracted from postmenopausal urine ➔ contains LH & FSH ➔ MENOTROPIN
  2. **Human Chorionic Gonadotrophins (hCG)** ➔ extracted from urine of pregnant women ➔ contains mainly LH ➔ PREGNYL

N.B. Now new available preparations by recombinant technology

Mechanism of Action	• Preparations of FSH ➔ act on ovary directly, stimulating growth & maturation of Graafian Follicle(s). • Preparations of LH ➔ act just to induce ovulation **Therefore, Given sequentially.**
Indication	Stimulation & induction of ovulation in infertility 2^{ndry} to gonadotropin deficiency. (pituitary insufficiency)
Method of Administration	hMG is given i.m or subcut. every day starting at day 2-3 of cycle for 10 days followed by hCG on (10th - 12th day) for OVUM RETRIEVAL within 36 hrs. (intrauterine insemination MUST happen AFTER 36 hrs to make sure that the ovum is retrieved) When we indicate: • intrauterine insemination • or intercourse
ADRs	FSH containing preparations: • Fever • Ovarian enlargement (hyper stimulation) • Multiple Pregnancy (approx. 20%) LH containing preparations: Headache & edema

Timing
Administration of hCG=11th day
Intercourse time=13th and 14th day
Pregnancy test=28th day

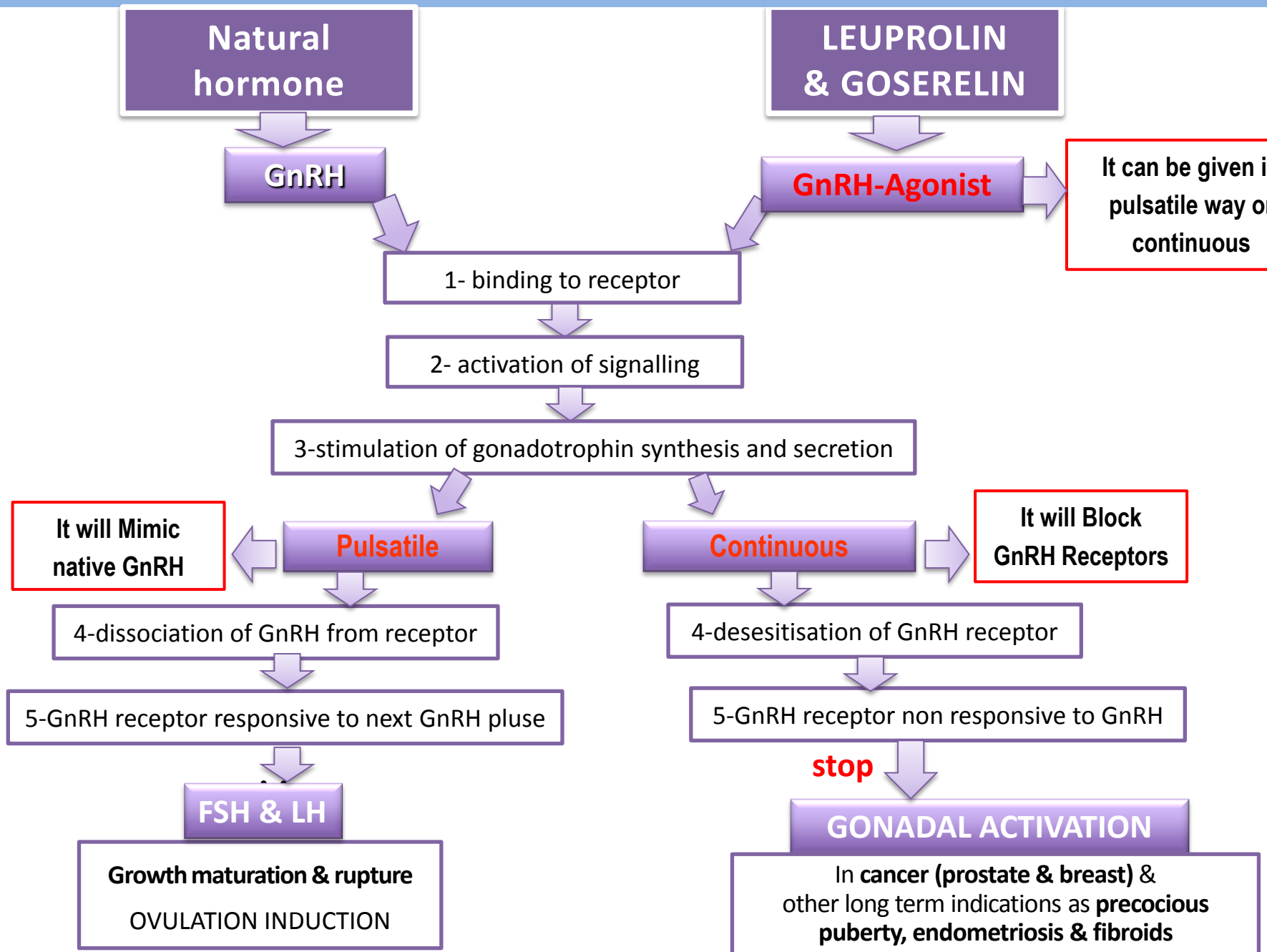
3. GnRH:

Leuprolin & Goserelin (GnRH agonists)

Mechanism of Action	**Native GnRH** is naturally produced by hypothalamus in a pulsatile manner. It is triggered when the negative feedback inhibition of ovarian hormones is lost by the end of the cycle. This activates FSH release from pituitary that stimulate growth and maturation of ova early during the follicular phase of the cycle. It also mediates estrogen induced LH surge that triggers ovulation. **GnRH-Agonists** ➔ bind to the receptors & mimic the native hormones provided it is given **PULSATILE**
Uses	• In OVULATION INDUCTION per se In hypothalmic amenorrhea (GnRH deficient) ➔ pulsatile S.C. or drip (1–10 µg / 60 – 120 min) ➔ ↑ GnHs release Start from day 2-3 of cycle up to day 10 • In ASSISTED REPRODUCTION, is part of a protocol for OVUM RETRIEVAL **(it's used in order to make sure that the ovum retrieval happen at the exact time which is 36 hrs after 12th day)**
Method of Administration	• Intranasal, injectable and implant formulations.
ADRs	• GIT disturbances, abdominal pain, nausea….etc • Headache • Hypoestrogenism on long term use: Hot flashes, Libido, Osteoporosis, Vaginal bleeding • Rarely ovarian hyperstimulation (ovaries swell & enlarge)

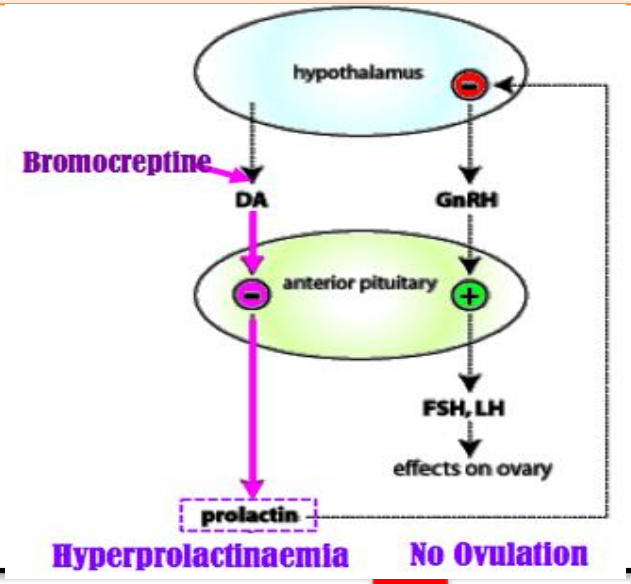
ASSISTED REPRODUCTION: it is reproductive technology used induce pregnancy (**fertility treatment),** & consist of several procedures beginning by 1st using fertility medication (gonadotropins and **GnRH**) & then followed by artificial insemination or in vitro fertilization.

3. GnRH:Method of Administration



4. D_2 Receptor Agonists:

Bromocreptine	
Mechanism of Action	**D_2 R Agonists bind to dopamine receptors in anterior pituitary ➔ -ve PRL secretion.**
Indications	Female infertility 2ndry to hyperprolactinaemia (hypogonadotrophic)
ADRs	• GIT disturbances; nausea, vomiting, constipation • Headache dizziness & orthostatic hypotension • Dry mouth & nasal congestion • Insomnia



SUMMARY

	DRUGS	Mechanism	USES	SIDE EFFECTS
ANTIESTROGENS (SERMs)	1-CLOMIPHENE	**compete with estrogen on estrogen receptors in the nucleus , Doing so they act as antagonists or partial agonists depending on how they bind & the different target tissue of action.**	Female infertility not due to ovarian or pituitary failure ➔ Normogonadotrophic	1.Hot Flushes & breast tenderness 2. Gastric upset (nausea and vomiting) 3. Visual disturbances (reversible) 4. ↑ nervous tension & depression 5. Skin rashes 6. Fatigue 7. Weight gain 8. Hair loss (reversible)
	2-TAMOXIFEN		palliative treatment of hormone-dependent / estrogen receptor- positive advanced breast cancer	--------
GONADOTROPHINS	**HMGs** 1-Menotropin **HCGs** 2-Pregnyl	**Given sequentially -FSH : act on ovary directly, stimulating growth & maturation of Graafian Follicle(s) -LH : act just to induce ovulation**	Stimulation & induction of ovulation in infertility 2ndry to gonadotropin deficiency (pituitary insufficiency)	-FSH containing preparations : Fever Ovarian enlargement (hyper stimulation) Multiple Pregnancy (approx. 20%) -LH containing preparations : Edema Headache

slide | doctor's note | important | explanation

SUMMARY

	DRUGS	Mechanism	USES	SIDE EFFECTS
GnRH-Agonist	1-LEUPROLIN 2-GOSERELIN	**bind to the receptors & mimic the native hormones provided it is given PULSATILE**	-In OVULATION INDUCTION -In ASSISTED REPRODUCTION is part of a protocol for OVUM RETRIEVAL	-GIT disturbances, abdominal pain, nausea….etc -Headache -Hypoestrogenism on long term use : • Hot flashes •↓Libido •Osteoporosis • Vaginal bleeding - Rarely ovarian hyperstimulation → (ovaries swell & enlarge)
D2 R Agonists	1-BROMOCREPTINE	**D2 R Agonists bind to dopamine receptors in anterior pituitary → -ve PRL secretion**	Female infertility 2ndry to hyperprolactinaemia (hypogonadotrophic)	-GIT disturbances; nausea, vomiting, constipation -Headache dizziness & orthostatic hypotension -Dry mouth & nasal congestion -Insomnia

slide doctor's note important explanation

Quiz yourself

Q1: obese women who get married two years ago, came to you because she not get pregnant . After investigation you find that she has polycystic ovarian syndrome and insulin resistance. Which of the following is the best treatment in this case?
A) Metformin
B) Clomiphene
C) Bromocreptine

Q2: Which of the following drugs given in case of female infertility secondary to hyperprolactinaemia?

A) Metformin
B) Clomiphene
C) Bromocreptine

Q3: which one of the following given in case of hypergonadotropic female ?

A) Clomiphene
B) Conception to ovulation, no place for therpy.
C) Bromocreptine

Q4: In which of the following cases we use clomiphene?

A) HyperprolacKnaemia
B) Hypogonadotropic
C) Normogonadotrophic

Q5: Which one of the following drugs is used in treatment of Hormone dependent breast cancer?

A) Leuprolin
B) Goserelin.
C) Tamoxiffen.

Q6: The most prominent action of bromocriptine is:

A) Dopamine D2 agonist
B) Dopamine D2 antagonist
C) GnRH agonist

Q7: The Drug pregnyl contains:

A) FSH
B) LH
C) FSH&LH

Q8: When should you retrieve the ovum after giving hCG:

A) Immediately
B) 36h
C) 60h

Q9: In which of the following formulas should you give GnRH-agonistsas In case of infertility treatment :

A) Continuous
B) Sequentially
C) Pulsatile

Q10: which of the following true about method of administration of clomiphene ?

A) 50 mg/d for 5th day of the cycle to the 10th day
B) the drug can be repeated not more than 6 cycles
C) given on 10th to 12th day of the cycle
D) A & B

Answers: 1-A 2-C 3-B 4-C 5-C 6-A 7-B 8-B 9-C 10-D

Done by

PHARMACOLOGY 433

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