Induction of ovulation

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Infertility is:

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

The most common cause of female infertility : ovulation disorders; ovulation disorders can be due to hypothalamic disorders, diseases of the ovary, diseases of the pituitary gland, increased levels of prolactin and could be due to unexplained causes.

How does increased prolactin cause infertility?

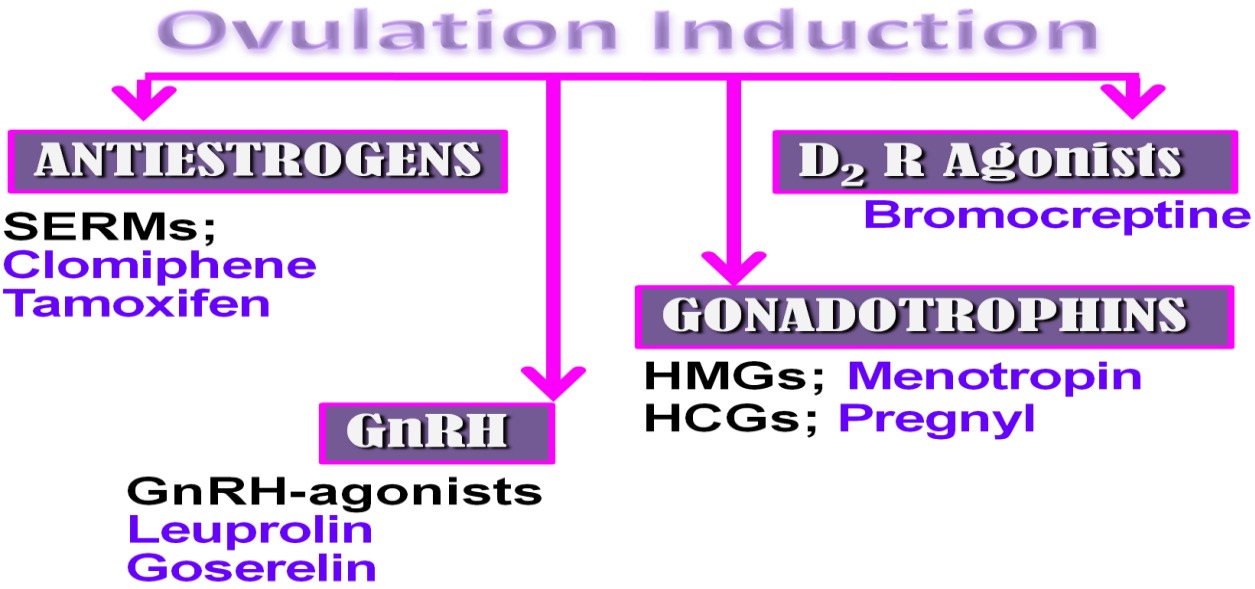
Answer: prolactin acts negatively on GnRH in the hypothalamus causing less release of gonadotropins which then will cause infertility.

Reminder of physiology:

- Normally the hypothalamus releases GnRH (gonadotrophin releasing hormone) in a pulsitile manner every one-three hours
- GnRH acts on the anterior pituitary to make it release gonadotropins which are LH/FSH
- LH/FSH affect the ovary and cause : follicular growth (FSH) ovulation and maintenance of the corpus luteum (LH)
- During the process the ovaries release estrogens and progesterone which have a negative feedback mechanism on the pituitary causing regulation of this release

introduction

** Drugs used in the treatment of Female infertility :



1. Anti-estrogens: (SERMs : Clomiphene ,Tamoxifen):

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

NOTE :

((in patients with high estrogen levels; the high levels of estrogen will negatively affect the release of GnRH and thus decreasing the levels of LH/FSH which will lead to no ovulation (↑estrogens >> ↓GnRH >> ↓LH , FSH =no ovulation)

we give this class of drugs so it compete with estrogen on its binding site in the hypothalamus and pituitary gland , so there will be no negative feedback on GnRH and that will cause GnRH to release more gonadotropins))

A. Clomiphene :

- **Specific MOA :**

- **On hypothalamus**: it decreases the negative feedback of endogenous estrogen on hypothalamus➔ leading to the increase pulses of GnRH which causes increase gonadotrophin production [FSH & LH] ➔ cause growth maturation & rupture of follicles➔ OVULATION
- **On pituitary**: it increases the response of gonadotrophins to GnRH

- **Indication :**

i. We give this class of drugs to " normogonadotrophic "patients , which are patients who don't have problems in the ovaries or pituitary (normal ovary & pituitary function).

NOTE:

Why?
If you give this drug to treat infertility in patients with ovarian failure no matter how much LH/FSH is produced there can be no ovulation because the ovary is damaged

If you give this to patients with pituitary disease then obviously there will be no LH/FSH release because the pituitary is damaged , and if there is no LH/FSH there will be no ovulation

ii. The success rate for ovulation ➔80% & pregnancy ➔40% . The difference between 2 rates is due to the antiestrogenic effects of clomiphene on uterus, cervix & vagina.

بمعنى ... ٤٠% ممكن يحملون من٨٠% اللواتي نجح عندهم الـ ovulation.... نتيجة تأثير **clomiphene** على أعضاء المرأة مما قد يؤدي إلى عدم تهيئتها تهيئة سليمة للحمل ...

- **Method of administration :**

i. Clomiphene given ➔ 50 mg/d for 5 days from 5th day of the cycle to the 10th day.
ii. If no response, the dose is doubled for 5 days again from 5th to10th day
iii. The drug can be repeated not more than 6 cycles .

Clomiphene is given from the 5th day of the cycle to the 10th. Why? because during that time is where estrogen levels are high

- **ADR's:**

Remember that SERM and estrogens compete on the same binding site; that definitely means they must be somehow similar in their compound >> this will cause some estrogenic side effects.

- ✓ Hot flushes and breast tenderness (estrogenic side effect)
- ✓ Gastric upset (nausea and vomiting)
- ✓ Visual disturbances (reversible)
- ✓ increase nervous tension & depression
- ✓ Skin rashes
- ✓ Fatigue
- ✓ Weight gain
- ✓ Hair loss (reversible)
- ✓ *N.B.* ↑ *incidence of multiple ovulation* ➔ twins in 10% *birth*

B. Tamoxifen :

- The difference between tamoxifen and Clomiphene is that tamoxifen is non steroidal
- Used in palliative treatment of hormone-dependent / estrogen receptor- positive advanced breast cancer (patients that show positive for having estrogen receptors on their cancer cells) *(but not clomiphene.why?)*

Note : We cannot use clomiphene in palliative treatment of hormone-dependent / estrogen receptor- positive because clomiphene is a steroid and it might cause the same effects of estrogen on the breast cancer, which is bad.

- Remember when we said at the beginning they act as antagonists or partial agonists depending on how they bind & the different target tissue of action

2. Gonadotropins : LH/FSH (MENOTROPIN,PREGNYL)

They are given with patients of pituitary disease when the body can't make Gonadotropins

a. They are naturally occurring hormones, they are extracted into pharmacological preparations:

- **Human Menopausal Gonadotrophins (hMG)** ➔ extracted from postmenopausal urine ➔ contains LH & FSH ➔ **MENOTROPIN**
- **Human Chorionic Gonadotrophins (hCG)** ➔ extracted from urine of pregnant women ➔ contains mainly LH) ➔ **PREGNYL**

b. MOA:

- FSH stimulates follicle growth (maturation)acting on the ovary
- LH act just to induce ovulation

c. Indication :

Stimulation & induction of ovulation in infertility 2ndry to gonadotropin deficiency (pituitary insufficiency)

d. Method of administration :

In these drugs we try to mimic the normal physiological cycle so:

1. During the first 14 days starting from day 2-3 until 14 we give preparations **containing FSH** (during follicular phase of the ovarian cycle)
2. And at the 14th day we give a preparation **containing LH** to induce ovulation (At the end of the follicular phase at time of the LH surge)
3. SO it is given like this : hMG(MENOTROPIN) is given IM at day 2-3 of the cycle for 7-14 days followed by hCG (PREGNYL) IM at 36 hrs. prior to: intrauterine insemination or intercourse

hMG is given IM every day for 10 days followed by hCG IM Given sequentially

e. ADR's :

- **FSH related :**

1. Fever
2. Ovarian enlargement (hyper stimulation)
3. Multiple Pregnancy (approx. 20%)

- **LH related:**

1. Headache & edema

3. GnRH agonists (Leuprolin, goserelin)

- GnRH is usually secreted in the body in a pulsatile matter (secreted every 1-3 hours)
- **There are two types of the GnRH agonists:**

a) Type is PULSATILE ➔ Mimic native GnRH :
stimulate gonadotropin release

NOTE: 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.

Uses : Induction of ovulation in patients with hypothalamic amenorrhea (GnRH deficient) ➔ S.C. pulsatile(drip) ➔ ↑ GnRH release

b) Type is CONTINOUS➔ Block GnRH Receptors

Uses: Given continuously, when gonadal suppression is desirable in case of :

- ✓ precocious puberty
- ✓ advanced breast cancer in women
- ✓ prostatic cancer in men

- **ADR's**

- GIT disturbances, abdominal pain, nausea
- Headache
- Hypoestrogenism on long term us. How? Because the continuous use of GnRH will cause the pituitary to be desensitized to GnRH ,, lead to :

1. Hot flashes
2. ↓Libido
3. Osteoporosis
4. Vaginal bleeding
5. Rarely ovarian hyperstimulation ➔ (ovaries swell & enlarge)

4. Dopamine receptor antagonists (receptor D2) : Bromocreptine

How can prolactin cause infertility ?

By antagonizing the effect of GnRH via negative feedback on the hypothalamus

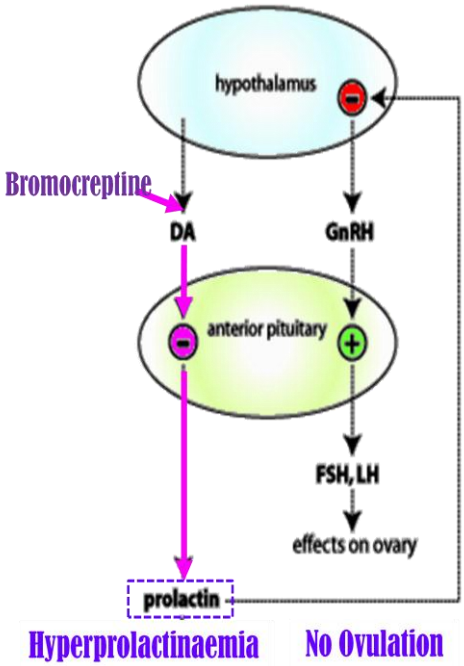
a. **MoA and indication :**

Female infertility secondary to hyperprolactinaemia (hypogonadotrophic)

b. **specific MoA** : D2 R Agonists ➔ -ve PRL (prolactin) secretion from anterior pituitary glands

c. ADR's :

- GIT disturbances; nausea, vomiting, constipation
- Headache dizziness & orthostatic hypotension
- Dry mouth & nasal congestion
- Insomnia



- Prolactin is released from the anterior pituitary.
- dopamine antagonizes the effect of prolactin by inhibiting its release from the anterior pituitary
- so dopamine stops the action of prolactin which is suppressing GnRH causing levels of GNRH to become normal