IN THE NAME OF GOD

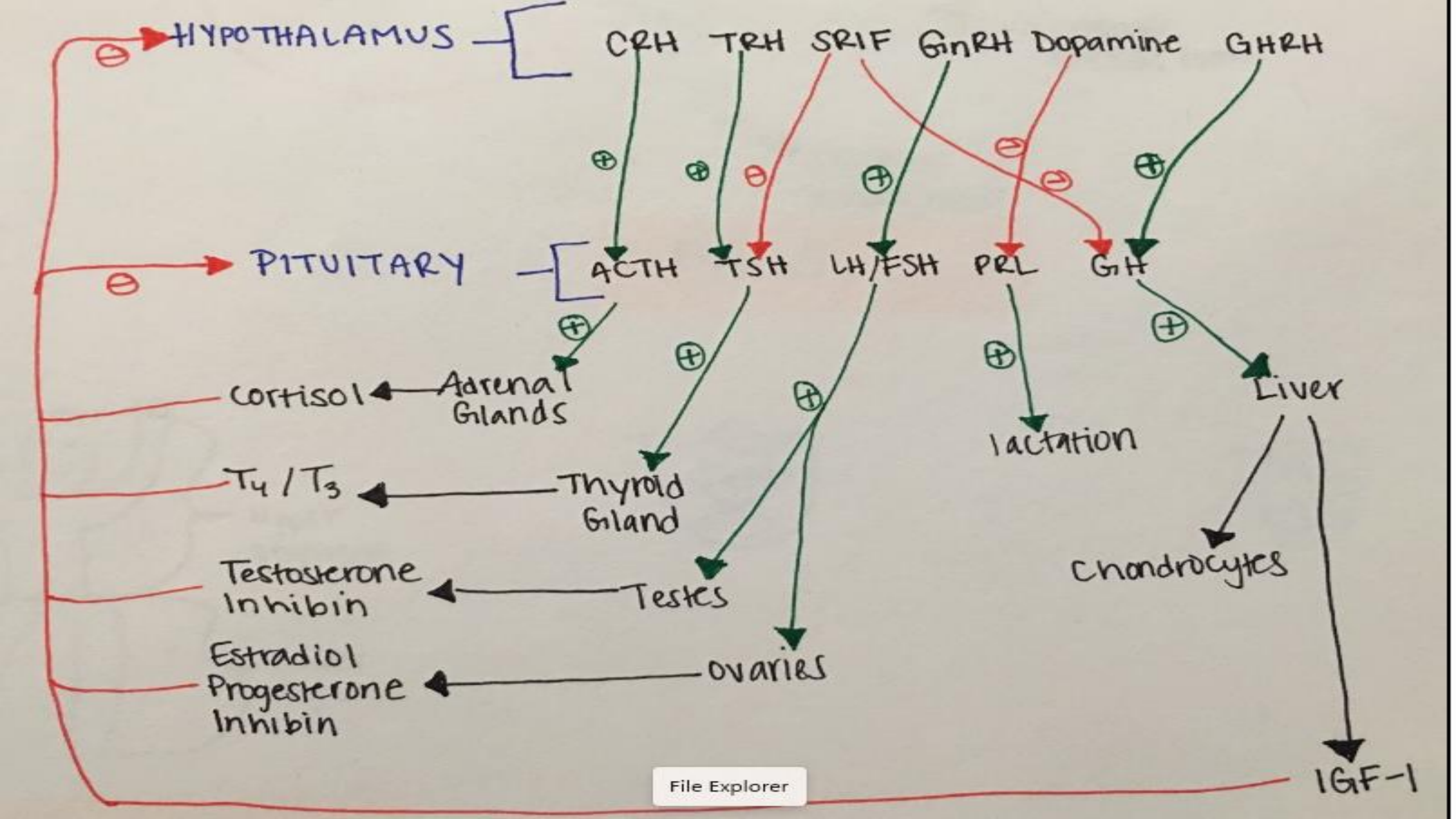
HYPERPROLACTINEMIA AND INFERTILITY

DR Zahra TAKHTI

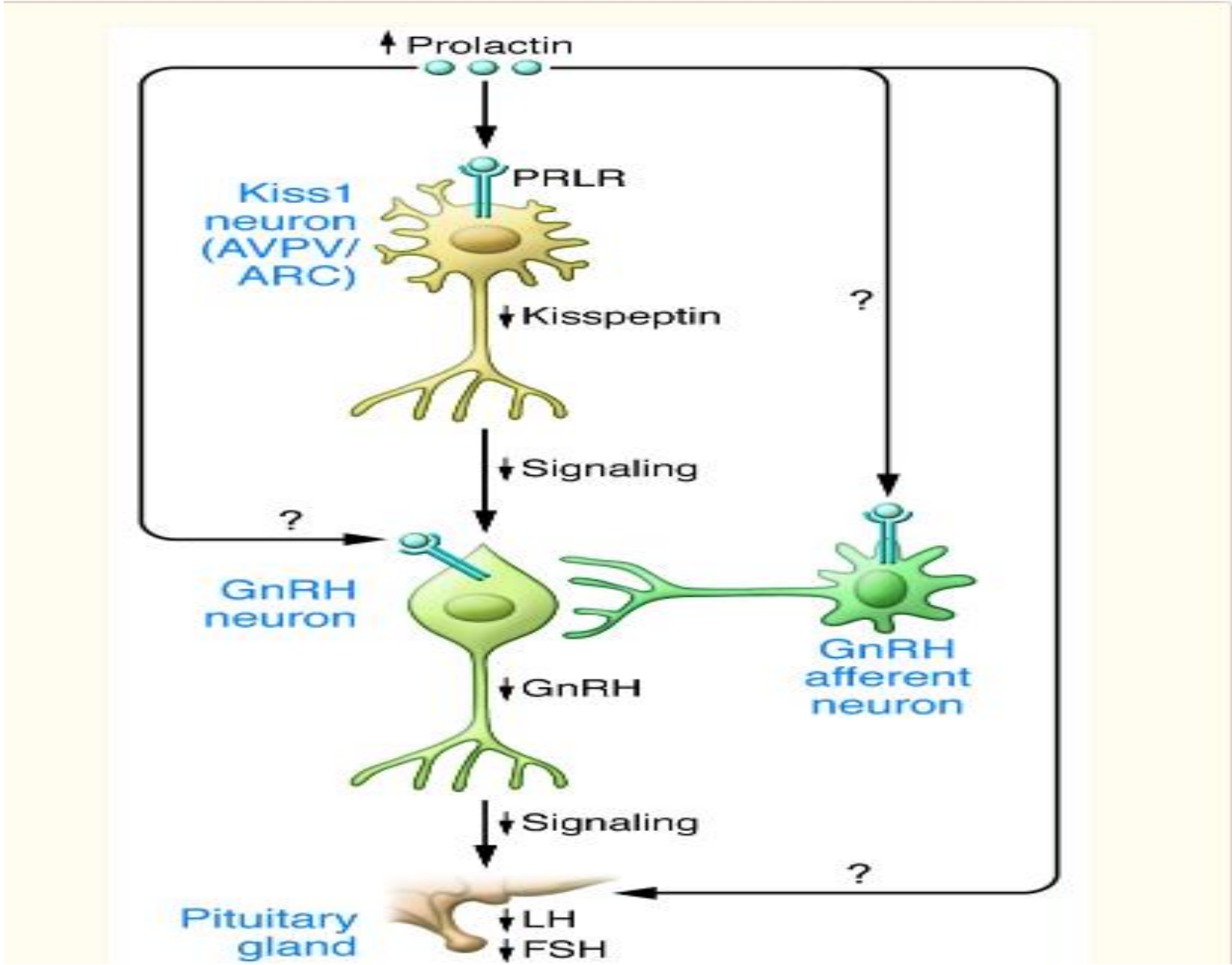
Hyperprolactinemia

Hyperprolactinemia is another specific example of anovulation resulting from a central defect. The mechanism involves disruption or inhibition of the normal GnRH pulse rhythm, resulting in ineffective or frankly low levels of pituitary gonadotropin secretion.

Elevated prolactin levels can result in a spectrum of ovulatory dysfunction, ranging from a short luteal phase to anovulatory cycles to amenorrhea and hypogonadotropic hypogonadism, depending on the extent to which the gonadotropin secretion is disturbed or suppressed



File Explorer


Prolactin
PRLR
Kiss1 neuron (AVPV/ ARC)
Kisspeptin
?
Signaling
?
GnRH neuron
GnRH afferent neuron
GnRH
Signaling
?
Pituitary gland
LH
FSH

Mild hyperprolactinemia
may cause only a short luteal phase, resulting from inadequate preovulatory follicular development.

Moderate hyperprolactinemia
frequently causes oligomenorrhea or amenorrhea

higher prolactin levels
typically result in frank hypogonadism with low estrogen level

A breast examination with gentle compression looking for evidence of galactorrhea and measurement of the serum prolactin concentration are important parts of the evaluation of all anovulatory women.

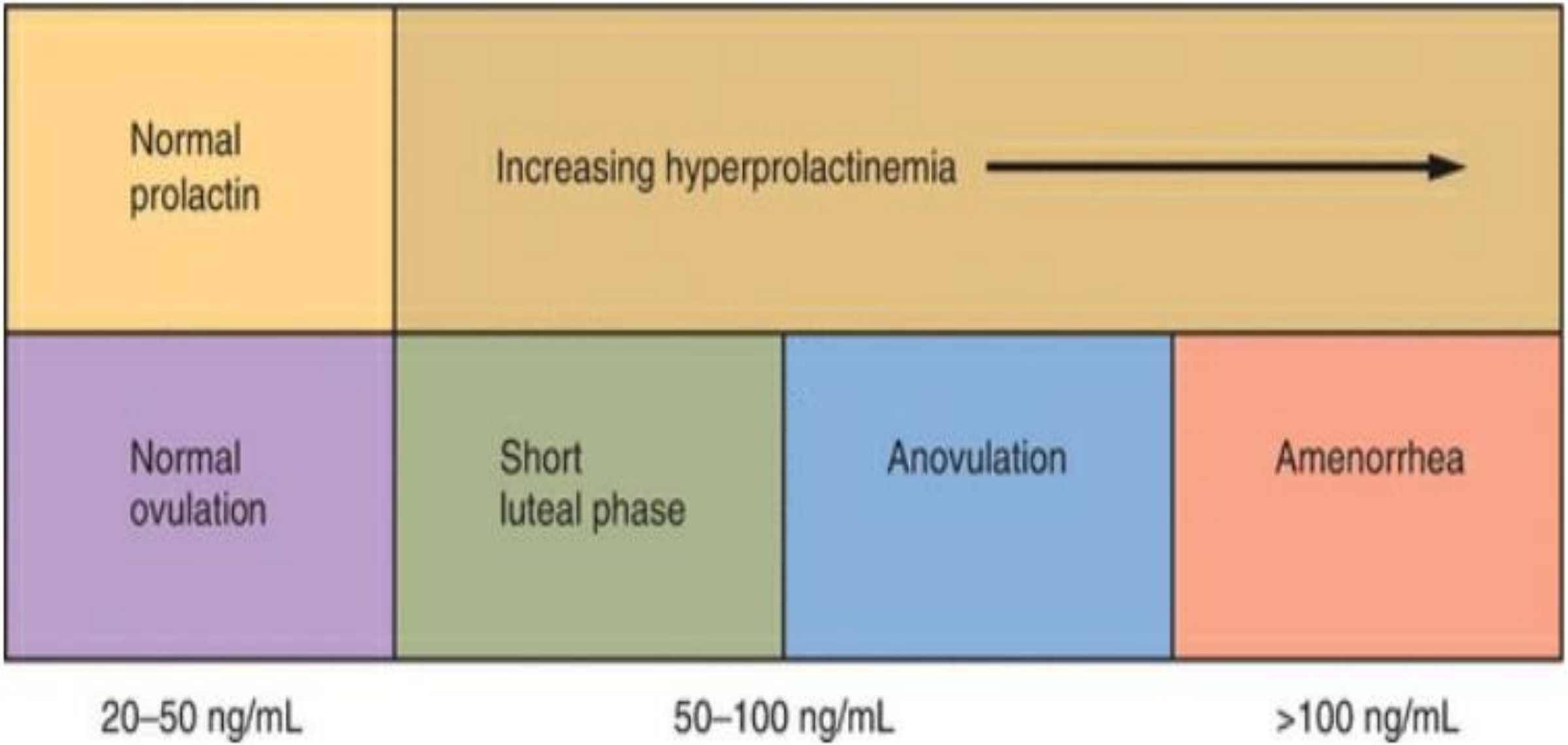

Normal prolactin
Increasing hyperprolactinemia
Normal ovulation
Short luteal phase
Anovulation
Amenorrhea
20–50 ng/mL
50–100 ng/mL
>100 ng/mL

FIGURE 11.2

History

- Obstetric history including gravidity, parity, pregnancy outcomes, and associated complications.
- Menstrual history including cycle length and characteristics and onset and severity of dysmenorrhea.
- Coital frequency and sexual dysfunction.
- Duration of infertility and results of any previous evaluation and treatment.
- Medical and surgical history, including episodes of pelvic inflammatory disease or exposure to sexually transmitted infections.
- Previous abnormal cervical cancer screening results and subsequent treatment.
- Current medications and allergies.
- Occupation and use of tobacco, alcohol, and other drugs.
- Family history of birth defects, mental retardation, early menopause, or reproductive failure.
- Symptoms of thyroid disease, pelvic or abdominal pain, galactorrhea, hirsutism, or dyspareunia.

Physical Examination

- Weight and BMI.
- Thyroid enlargement, nodule, or tenderness.
- Breast secretions and their characteristics.
- Signs of androgen excess.
- Pelvic or abdominal tenderness, organ enlargement, or mass.
- Uterine size, contour, position, and mobility.
- Vaginal or cervical abnormality, secretions, or discharge.
- Mass, tenderness, or nodularity in the adnexa or cul-de-sac.

CLASSIFICATION OF OVULATORY DISORDERS

WHO Group I: Hypogonadotropic Hypogonadal Anovulation

WHO Group II: Normal gonadotropic Normal estrogenic Anovulation

WHO Group III: Hypergonadotropic Anovulation

Hyperprolactinemic Anovulation

Approximately 5–10% of anovulatory women have hyperprolactinemia, which inhibits gonadotropin secretion.

Consequently, serum FSH concentrations generally are low or low-normal, and serum estradiol levels also tend to be relatively low. Most hyperprolactinemic women have oligomenorrhea or amenorrhea.

Hyperprolactinemia

Hyperprolactinemia is among the most common causes of secondary amenorrhea.

Hyperprolactinemia occurring in premenarchal years may even present as : delayed puberty and primary amenorrhea.

Checking serum prolactin level is therefore justified in all women with amenorrhea.

A normal random measurement (<15–20ng/mL in most clinical laboratories) excludes hyperprolactinemia.

Circulating prolactin levels are fairly stable throughout the day but can increase transiently during:
sleep, and with exercise, breast stimulation, and meals.

To avoid otherwise unnecessary and costly imaging, mildly elevated prolactin levels (20–40 ng/mL) are best repeated and confirmed before the diagnosis of hyperprolactinemia is made

Mild hyperprolactinemia (levels in the range of 20–50 ng/mL) may cause only a short luteal phase, resulting from poor preovulatory follicular development.

Moderate hyperprolactinemia (50–100 ng/mL) frequently causes oligomenorrhea or amenorrhea

higher prolactin levels (>100 ng/mL)typically result in frank hypogonadism with low estrogen levels and their clinical consequences genitourinary atrophy, and loss of bone mass).

Only about one-third of women with hyperprolactinemia exhibit galactorrhea, probably because breast milk production requires estrogen and hyperprolactinemia often results in anovulation or a more severe secondary hypogonadotropic hypogonadism and, consequently, low circulating estrogen levels.

Prolactin circulates in various forms that have varying bioactivity (manifested by galactorrhea) and immunoactivity (recognition by immunoassay)

predominant circulating form of prolactin (80–95%) is monomeric (molecular weight 23 kDa), which is more biologically active than the larger glycosylated variants that may combine to form dimers or trimers (“big prolactin,” 50–60 kDa) and other even larger varieties (macroprolactin, >100 kDa

If suspected, the diagnosis of macroprolactinemia can be confirmed by requesting the laboratory to pretreat the patient's serum with polyethylene glycol to precipitate the macroprolactin before performing the prolactin assay.

In women with mildly elevated prolactin levels, diagnosis of macroprolactinemia avoids unnecessary and costly imaging aimed at excluding pituitary and hypothalamic mass lesions.

Galactorrhea refers to the mammary secretion of a milky fluid, which is non physiologic in that it is inappropriate (not immediately related to pregnancy or the needs of a child), persistent and sometimes excessive

Although usually white or clear, the color may be yellow or even green. In the latter circumstance, local breast disease should be considered

To elicit breast secretion, pressure should be applied to all sections of The breast beginning at the base of the breast and working up toward the nipple.
Galactorrhea can involve both breasts or just one breast. Hormonally induced secretions usually come from multiple duct openings in contrast to pathologic discharge that usually comes from a single duct.

A bloody discharge is more typical of cancer.

The quantity of secretion is not an important criterion.

Differential Diagnosis of Galactorrhea

1. pituitary tumors which function independently of the otherwise appropriate restraints exerted by PIFs from a normally functioning hypothalamus

2. A variety of drugs can inhibit hypothalamic dopamine

phenothiazine-like compounds, reserpine derivatives, amphetamines, and an unknown variety of other drugs (opiates, diazepams, butyrophenones, verapamil, α-methyldopa, plazil,and tricyclic antidepressants)

but essentially never as high as 100 ng/ml Approximately 30–50% exhibit galactorrhea that should not persist beyond 3–6 months after drug treatment is discontinued

3. Hypothyroidism (juvenile or adult) can be associated with galactorrhea. With diminished circulating levels of thyroid hormone, hypothalamic TRH is produced in excess and acts as a PRF to release prolactin from the pituitary

4. Excessive estrogen (oral contraceptives) can lead to milk secretion via hypothalamic suppression, causing reduction of dopamine and release of pituitary prolactin, and direct stimulation of the pituitary lactotrophs.

5. Prolonged intensive suckling can also release prolactin via hypothalamic reduction of dopamine Similarly, thoracotomy scars, cervical spinal lesions, eczema, and herpes .zoster can induce prolactin release by activating the afferent sensory neural arc, thereby simulating suckling. nipple piercing

6. Stresses can inhibit hypothalamic dopamine, thereby inducing prolactin secretion and galactorrhea. Trauma, surgical procedures, and anesthesia can be seen in temporal relation to the onset of galactorrhea.

7. Hypothalamic lesions, stalk lesions, or stalk compression (events that physical reduce production or delivery of dopamine to the pituitary) allow release of excess prolactin leading to galactorrhea.

8. Increased prolactin concentrations can result from nonpituitary sources such as lung, ovarian, and renal tumors and even a uterine leiomyoma. Severe renal disease requiring hemodialysis is associated with elevated prolactin levels due to
the decreased glomerular filtration rate

The Clinical Problem of Galactorrhea

Galactorrhea and hyperprolactinemia are not completely correlated. The reported incidence of women with hyperprolactinemia displaying galactorrhea is about 33%. The disparity may be due partially to the variable zeal with which the presence of nipple milk secretion is sought during physical examination, the usually accompanying hypoestrogenic state, or heterogeneity of tropic hormones

Mild hirsutism may accompany ovulatory dysfunction caused by hyperprolactinemia. Whether excess androgen is stimulated by a direct prolactin effect on adrenal cortex synthesis of dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) or is primarily related to the chronic anovulation of these patients (and hence ovarian androgen secretion) is not settled.

another possibility is hyperinsulinemia. Women with elevated prolactin levels have been reported to have an association with hyperinsulinemia because of an increase in peripheral insulin resistance

This association is independent of obesity; however , there is considerable variation and the mechanism is uncertain. We recommend that in patients with hyperprolactinemia who have a family history of early coronary heart disease or who have an abnormal lipid profile

In the pathophysiology of male hypogonadism, hyperprolactinemia is much less common, and the incidence of actual galactorrhea quite rare. Hyperprolactinemia in men usually presents with decreased libido and potency

All possible causes must be therefore be considered and excluded; a careful history can eliminate most of the possibilities.

When iatrogenic mechanism for prolactin excess is deemed as a plausible cause, a trial of drug discontinuation or use of an alternative medication can be considered, in consultation with the prescribing physician.

When discontinuation or drug substitution is not possible, further evaluation to exclude a pituitary or hypothalamic mass lesion is required before concluding that prolactin excess is entirely of iatrogenic origin

Women with amenorrhea and hyperprolactinemia that cannot be attributed confidently to medication or another specific cause require further evaluation with imaging to exclude pituitary tumors and hypothalamic mass lesions.

Treatment with a dopamine agonist restores ovulatory function and menses within several weeks in the large majority of women with hyperprolactinemia.

Although improvement in galactorrhea is anticipated with decline in circulating prolactin levels , the absolute resolution of milk leakage following normalization of prolactin levels often lags by weeks to even months.

Bromocriptine and cabergoline are two commonly utilized dopamine agonists in the management of hyperprolactinemia; both are highly effective.

Bromocriptine has a relatively short half-life, often necessitating a frequency of administration of 2 to 3 times daily; gastrointestinal side effects such as nausea are common, and bedtime dosing is better tolerated.

Cabergoline is a selective dopamine receptor type 2 agonist having fewer side effects than bromocriptine, greater potency, and a longer duration of action requiring less frequent administration (twice weekly) and can be effective in those who cannot tolerate or prove resistant to bromocriptine

its better tolerance and convenience of dosing, cabergoline is increasingly being utilized as the preferred of the two dopamine agonists.

Long-term use of dopamine agonists in relatively high doses, such as used in the management of Parkinson disease (>3 mg daily), has been associated with hypertrophic valvular heart disease; mitogenic stimulation of normally quiescent valve cells via activation of the serotonin receptors is a suspected mechanism for this uncommon but serious risk

Although the doses required for effective treatment hyperprolactinemia are much lower than used for treatment of Parkinson disease, concerns remain that long-term use of even relatively low doses of dopaminergic drugs may increase the risk of valvular heart disease.

Treatment should begin with a low-dose regimen, and dosing should be gradually adjusted in increments to achieve normalization of prolactin levels; the goal should be to utilize the lowest dose of cabergoline or bromocriptine required to normalize serum prolactin concentrations.

Given the concerns relating to long-term use of dopaminergic drugs, a trial discontinuation of treatment should be attempted if prolactin levels have been normal for 2 or more years.

In those who cannot tolerate oral treatment, vaginal administration is effective and associated with fewer side effects Either drug may be used in women planning to conceive since both appear to be safe in early pregnancy

Treatment with a dopamine agonist is the obvious choice when the objective is ovulation induction and pregnancy or the elimination of troublesome galactorrhea.

However, for those with neither specific indication, alternative treatments deserve careful consideration

The OCP(low dose estrogen) treatments are useful in the management of women with medication-induced hyperprolactinemia and hypogonadism
when the drug cannot be discontinued or an alternative substituted.
Dopamine agonists are best avoided in patients with medication-induced hyperprolactinemia, because they may interfere with or counteract the dopamine antagonist properties of their primary treatment.
Unfortunately, amenorrhea and galactorrhea often promptly recur within weeks after discontinuation of dopamine agonist treatment

Indications for Dopamine Agonist Treatment

Dopamine agonists are the treatment of choice for hyperprolactinemic infertile women with ovulatory dysfunction who wish to conceive

Although some hyperprolactinemic women will respond to clomiphene treatment, most do not, because the neuroendocrine consequences of hyperprolactinemia generally disrupt the mechanism by which clomiphene exerts its therapeutic action

Dopamine agonist treatment can be highly effective in women who have galactorrhea but normal serum prolactin levels. With few exceptions, the presence of galactorrhea can be regarded as a reliable indicator of excess prolactin secretion

Possible explanations for ***occult hyperprolactinemia*** include excess production of biologically active forms of prolactin not detected in all immunoassay systems and transient but exaggerated nocturnal prolactin secretion that goes unrecognized in randomly drawn blood samples.

Up to 30% of women with PCOS can exhibit mild hyperprolactinemia. Reduced levels of dopaminergic inhibition also have been implicated as a contributing cause of the elevated serum LH concentrations observed in women with the disorder

Consequently, dopamine agonists also have been advocated as adjuvant therapy for hyperprolactinemic anovulatory women with PCOS who require exogenous gonadotropin treatment

Limited evidence suggests that pretreatment with a dopamine agonist can temper the ovarian response to exogenous gonadotropins and may thereby help to decrease the risks of multiple pregnancy and ovarian hyperstimulation associated with such treatment.

Review > Pharmaceuticals (Basel). 2023 Jan 13;16(1):122. doi: 10.3390/ph16010122.

Prolactin Relationship with Fertility and In Vitro Fertilization Outcomes-A Review of the Literature

Thus, the question arises whether hyperprolactinemia should be treated before and during assisted reproduction techniques (ART) as these procedures may overcome the detrimental effects on ovulation induced by high prolactin levels

On the other hand, treatment for hyperprolactinemia might interfere with the possible beneficial effects of prolactin on other aspects of reproductive function.

We retrieved 258 results and we further perfected the search by analyzing the abstracts available for each of the studies and by searching for articles of interest included in the reference list of relevant articles

Finally, 88 studies were included in the current material.

pleiotropic role of prolactin in reproduction, growth, metabolism, electrolyte transport, behavior , immunity

a certain level of circulating prolactin might be necessary for optimal reproductive outcomes.

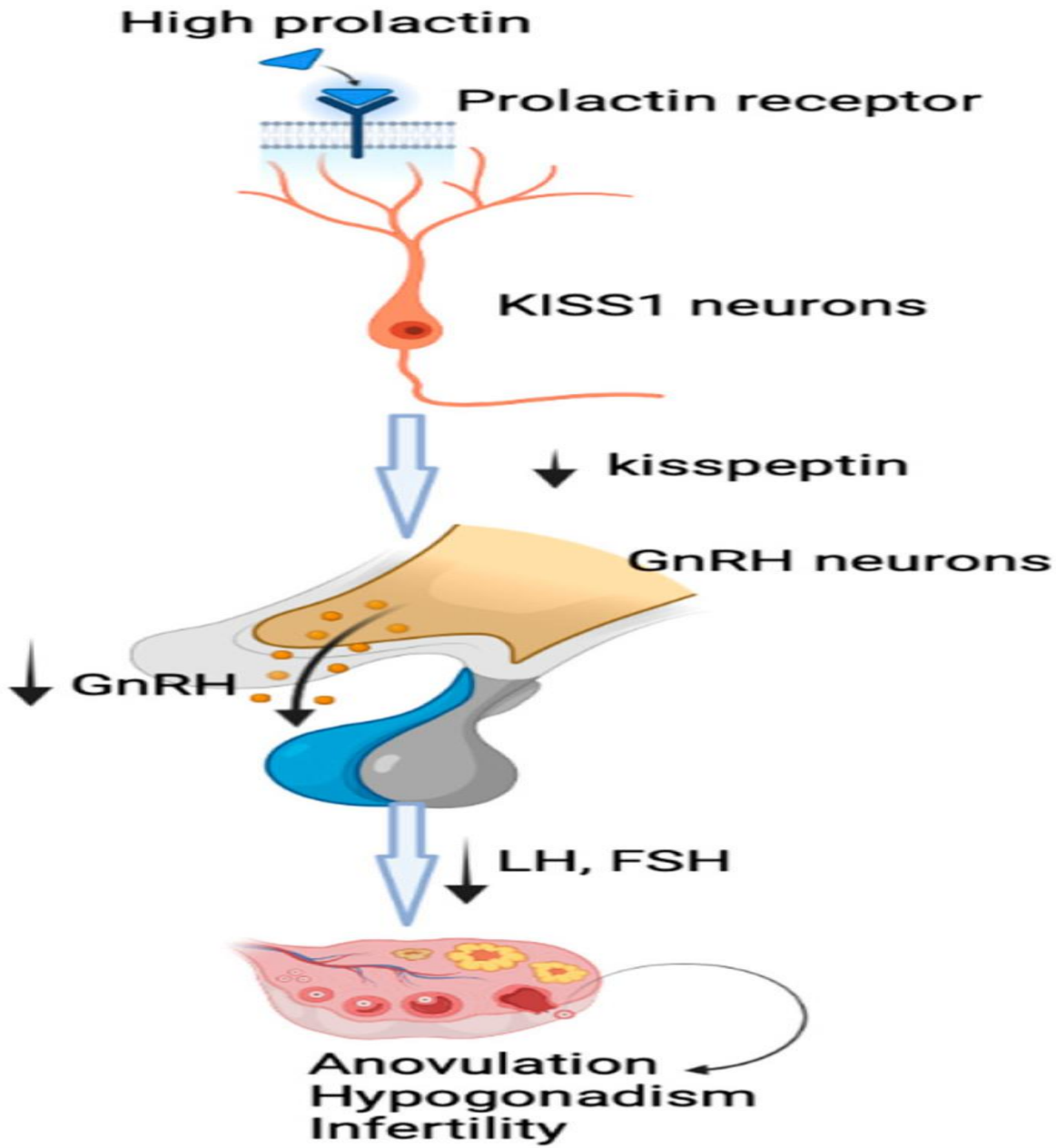
pathophysiological importance: the most studied implication is hyperprolactinemia-induced infertility

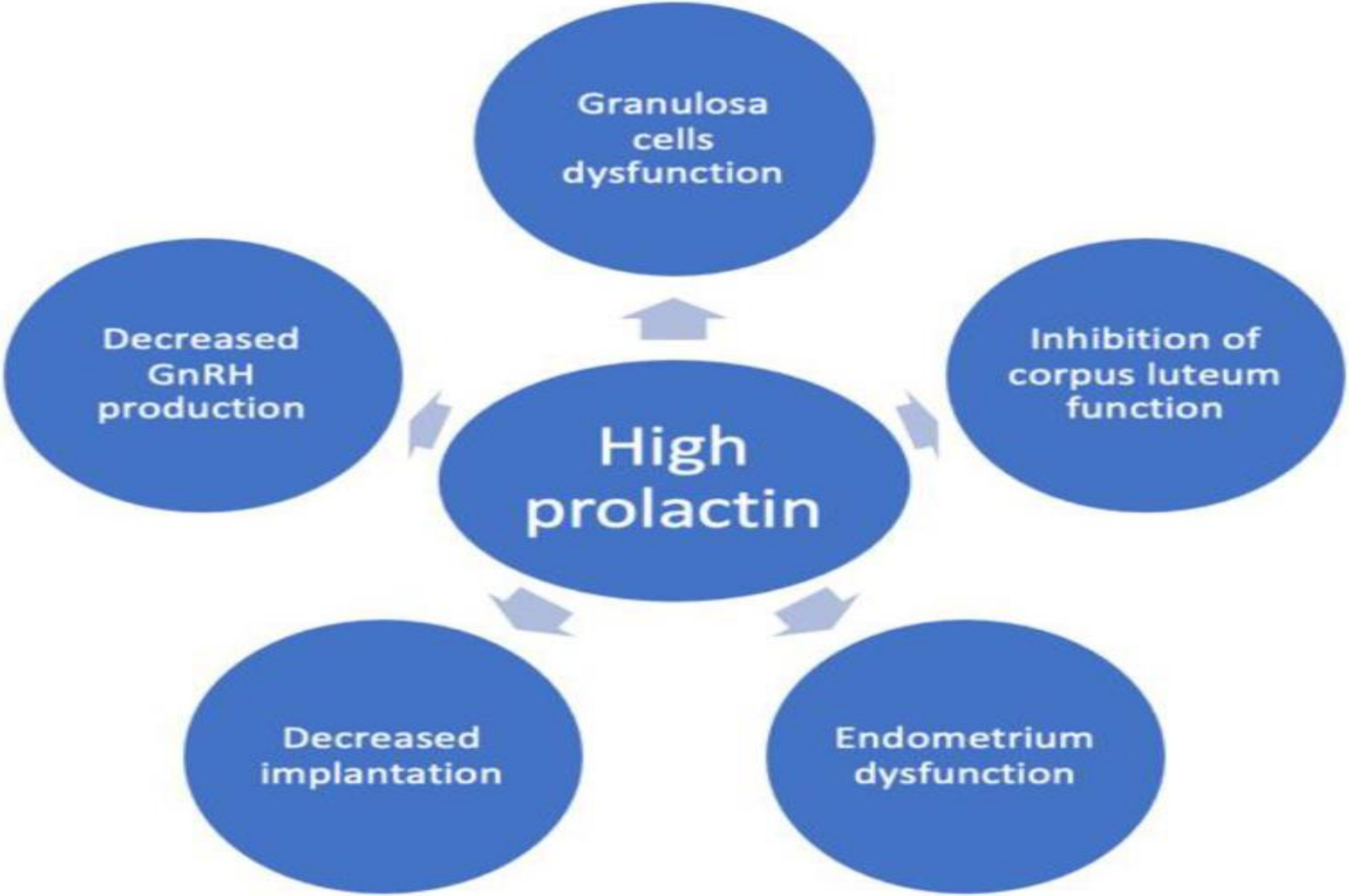
The main mechanism by which hyperprolactinemia leads to infertility is a decrease in gonadotrophin-releasing hormone (GnRH) secretion with subsequent hypogonadotropic hypogonadism and anovulatory infertility.

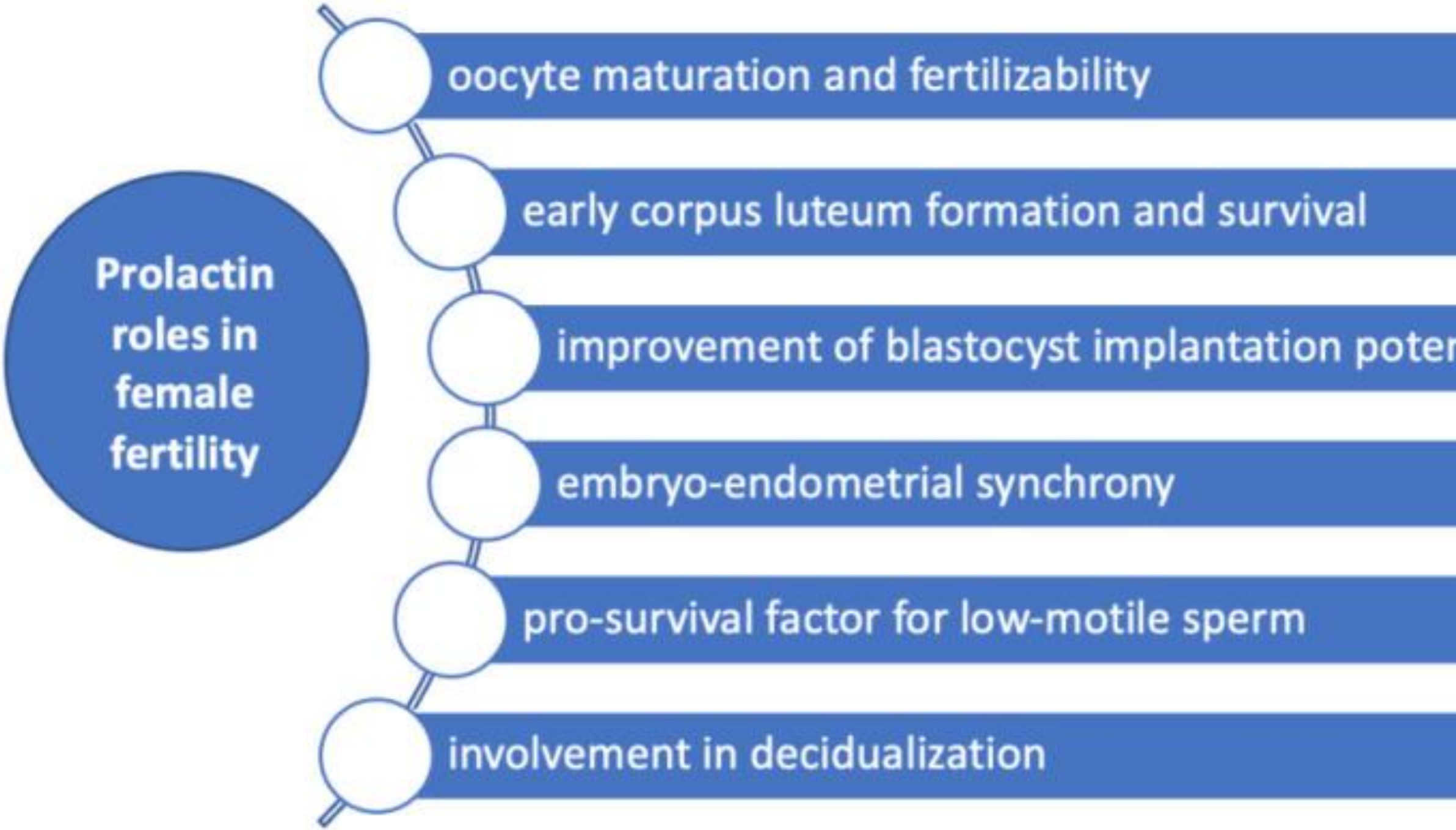
Prolactin alteration in endometrial function and implantation through both structural and immunological factors

Some authors found prolactin receptors only in the human luteinized granulosa cells, but not in early follicles, and concluded that prolactin may ***play a role in the mature follicle during the time of ovulation***

hyperprolactinemia in infertile women is at least ten times higher than in the general population


High prolactin
Prolactin receptor
KISS1 neurons
kisspeptin
GnRH neurons
GnRH
LH, FSH
Anovulation
Hypogonadism
Infertility


Granulosa cells dysfunction
Decreased GnRH production
Inhibition of corpus luteum function
High prolactin
Decreased implantation
Endometrium dysfunction


Prolactin roles in female fertility
oocyte maturation and fertilizability
early corpus luteum formation and survival
improvement of blastocyst implantation poter
embryo-endometrial synchrony
pro-survival factor for low-motile sperm
involvement in decidualization

Hyperprolactinemia :
1-influences directly the granulosa cells' function

2-exerting a direct inhibitory effect on gonadotropin action in the ovary

3-In granulosa cells, prolactin inhibits estradiol production and stimulates progesterone production by activating distinct signaling pathways

4-The mechanism by which excess prolactin inhibits follicle-stimulating hormone (FSH)-induced estradiol secretion in preovulatory follicles has been reported to be due to the reduction of aromatase activity

5-clinical data support an inhibitory effect of high prolactin levels on the function of the corpus luteum

Experimental animal studies offer some insights into the additional mechanism by which high levels of prolactin might contribute to decreased fertility by alteration in endometrial function and implantation

Thus, metoclopramide-induced hyperprolactinemic mice were found to have fewer pinopodes in the endometrium and a lower pregnancy rate Moreover, the same mouse model has a different glycosaminoglycan content in the endometrium which might affect the decidualization process

macroprolactinemia cannot be considered a completely harmless condition as it may be associated with infertility and autoimmune conditions

Duan et al performed a retrospective study and found that the cumulative live birth rates, number of pregnancies and perinatal outcomes were similar between patients with treated hyperprolactinemia and those with normal prolactin levels undergoing IVF

Doldi et al. divided patients with mild hyperprolactinemia before COS (mean values of serum prolactin in the study group of 24.7 ng/mL), undergoing ICSI, into two groups: one group received dopamine agonists, either cabergoline or bromocriptine, and the other group did not receive treatment. They found that in the group with untreated hyperprolactinemia a decreased FSH requirement, a higher number of good-quality oocytes (metaphase 2, mature oocytes), increased fertilization rate and higher numbers of embryos transferred were noticed

administration of bromocriptine in patients with transient hyperprolactinemia in previous stimulated cycles was associated with higher fertilization rate in comparison with patients with untreated transient prolactin increase, but similar fertilization rates in patients without prolactin increase during ovarian stimulation

Jinno et al. proposed a new method of ovarian stimulation for IVF in patients with previous IVF failure, the bromocriptine rebound (BR) method
They administrated bromocriptine from day 4 of the preceding cycle until 7 days before stimulation in patients treated with long agonist protocol and HMG. They reported that patients treated with the BR method had higher numbers of follicles, fertilized oocytes, embryos with superior morphology, clinical pregnancy and live birth rates in comparison with patients who did not receive bromocriptine

authors concluded that IVF failure is the consequence of a granulosa cell resistance to prolactin action and that the bromocriptine-induced hypoprolactinemia contributes to the restoration of prolactin responsiveness and, subsequently, improved oocytes maturation

Conclusions and Future Directions

Hyperprolactinemia is a ***well-known cause of infertility*** through an inhibitory effect on gonadotropin production.

Treatment of transient hyperprolactinemia during IVF or spontaneous cycles was suggested to be beneficial in terms of fertilization rates and conception rates, although a limited amount of evidence is available

Administration of bromocriptine followed by withdrawal of treatment might be successful for obtaining a pregnancy in previous IVF failure patients by restoring granulosa cells' responsiveness to prolactin.

Int J Reprod Biomed. 2021 Dec; 19(12): 1085–1090.
Published online 2022 Jan 12. doi: 10.18502/ijrm.v19i12.10059

PMCID: PMC8792383
PMID: 35098010

Evaluation of hyperprolactinemia risk factors in infertile women referred to Yazd Infertility Center: A cross-sectional study

Conclusion

Idiopathic hyperprolactinemia and polycystic ovary syndrome are the most common reasons for hyperprolactinemia.

POSTER PRESENTATION | VOLUME 109, ISSUE 3, SUPPLEMENT , E31, MARCH 2018

The predictive value of hyperprolactinemia in detecting prolactin-secreting tumors

Nola Herlihy, MD • Lucky Sekhon, MD • Taraneh Nazem, MD • ... Noah Copperman • Tanmoy Mukherjee, MD • Alan B. Copperman • Show all authors

DOI: https://doi.org/10.1016/j.fertnstert.2018.02.059 •

Prolactin level (mIU/mL)	Number of patients	Normal MRI	Microadenoma	Macroadenoma
25-29	23	18 (78%)	5 (22%)	0 (0%)
30-34	48	23 (48%)	25 (52%)	0 (0%)
35-39	27	18 (66%)	8 (30%)	1 (4%)
40-44	26	17 (65%)	9 (35%)	0 (0%)
45-49	25	18 (72%)	7 (28%)	0 (0%)
50-54	15	12 (80%)	3 (20%)	0 (0%)
55-59	8	7 (88%)	1 (12%)	0 (0%)
60-64	13	8 (62%)	5 (38%)	0 (0%)
65-69	7	5 (71%)	2 (29%)	0 (0%)

JBRA Assist Reprod. 2019 Jul-Sep; 23(3): 225–229.
doi: 10.5935/1518-0557.20190020

PMCID: PMC6724390
PMID: 30969738

Prolactin concentration in various stages of endometriosis in infertile women

Conclusion:

Higher prolactin levels were observed in infertile women with more severe endometriosis when compared to infertile women without endometriosis. Prolactin levels act as a probable prognostic biomarker to detect endometriosis stages III/IV vs. I/II and segregate infertile women with endometriosis from subjects without endometriosis.


Thank you for your
attention