



Important Doctors slides
Extra Information **Doctors notes**



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Biochemistry

*Investigating
infertile couple*

The difference between the novice and the master is that the master has failed more times than the novice has tried

OBJECTIVES

By the end of this lecture, the students should be able to know:

- Identify the causes of infertility in men and women
- Understand the diagnostic approaches to infertility in men and women
- Interpret the results of investigation of infertility in men and women

We need egg and sperm & the place to make the fertilization happen.

So investigation will detect:

- 1- Ovum (ovulation).
- 2- Sperm (Quantity & quality).
- 3- Place or site of fertilization.



Overview



Infertility / subfertility

- ❖ It's known as (Failure of a couple to conceive “becoming pregnant” after one year of regular, unprotected intercourse).
- ❖ Infertility may be caused by endocrine problems:
 1. Common in females (1/3rd patients).
 2. Rare in males.
- ❖ Hormone dysfunction is a rare cause of male infertility.
- ❖ In some couples no cause can be identified. (Idiopathic)

- If a normal healthy couple comes to you and the female age is below 35 and has no complication but there is no pregnancy you will ask them to try one more year, if no pregnancy happens, you will start the investigations.
- If the female is above 35 or the female or male have any problem that could affect the fertility then you have to do the investigations earlier (after 6 months).
- If the female age is above 40-45 years old you will start the investigations right away.

Physical examination

First of all we take history, we ask about: Age, menstruation, medications, frequency and timing of sexual intercourse and if it is protected or not, previous pregnancy (to decide whether it is primary or secondary infertility), Chronic diseases (here we will have hormonal changes and oxidative stress and altered metabolism), risk factors (Inflammation, Sexual Transmitted Diseases, Smoking which increases oxidative stress, previous investigations and appointments, use of contraceptives, uterine device and previous exposure to chemotherapy and radiotherapy (It destroys the oocytes).

Physical examination			
Information on physical examination should include			
Hypothalamo-pituitary, thyroid disorders. Symptoms : Goiter Exophthalmos	Cushing's syndrome Symptoms : Purple striae Central obesity	Galactorrhea 1. Lactation in the absence of pregnancy. 2. Most common due to hyperprolactinemia. Breast discharge	Hirsutism

- Primary infertility: Never get pregnant before
- Secondary infertility : got pregnant before

Endocrine investigations in subfertile woman

The first thing a should do is to ask about menstrual cycle if its regular or not.

Investigations are based on the phase of menstrual cycle

If the menstrual bleeding is accompanied by other usual symptoms of menstrual cycle as cramps and pain it means that it is an ovulatory cycle.

Serum progesterone should be measured in the middle of the luteal phase (**day 21**)

Progesterone normally is increased in luteal phase

High progesterone (>30 nmol/L) indicates ovulation

- If the level is below **10**, it means inovulatory cycle.
- If the level inbetween **10-30**, means ovulatory but there is a problem in the mid-luteal phase.

In oligomenorrhea or amenorrhea, hormone measurement is needed

- **Amenorrhea:** No mensuration for at least 6 months or more.
- **Oligomenorrhea:** 8 or less cycles in a year, with a gap at least 6 weeks.

Endocrine causes of female infertility

<p>1. Excessive secretion of ovarian androgens (androgens affects the gonads directly)</p>	<p>Obesity</p>
<p>2. Primary ovarian failure</p>	<p>Insulin resistance</p> <p>❖ High gonadotrophins, low oestradiol (postmenopausal hormonal pattern)</p> <p>Also Called :Hypergonadotropic hypogonadism</p> <p>Hormone replacement therapy can be given (will not treat infertility) given for libido</p>
<p>3. Hyperprolactinemia 4. PCOS*</p> <p>5. Cushing's syndrome (Cortisol causes increased level of androgens).</p>	<p>6. Hypogonadotropic hypogonadism :</p> <ul style="list-style-type: none"> ✓ Low gonadotrophin/oestradiol ✓ Rare ✓ Due to hypothalamic-pituitary lesion

* Polycystic Ovary Syndrome (PCOS)

Investigation of female infertility

Follow the chart and know the investigations

With symptoms: pain and bloating

Because of the ovarian failure there is no secretion of estrogen and therefore there is no feedback inhibition on the anterior pituitary.

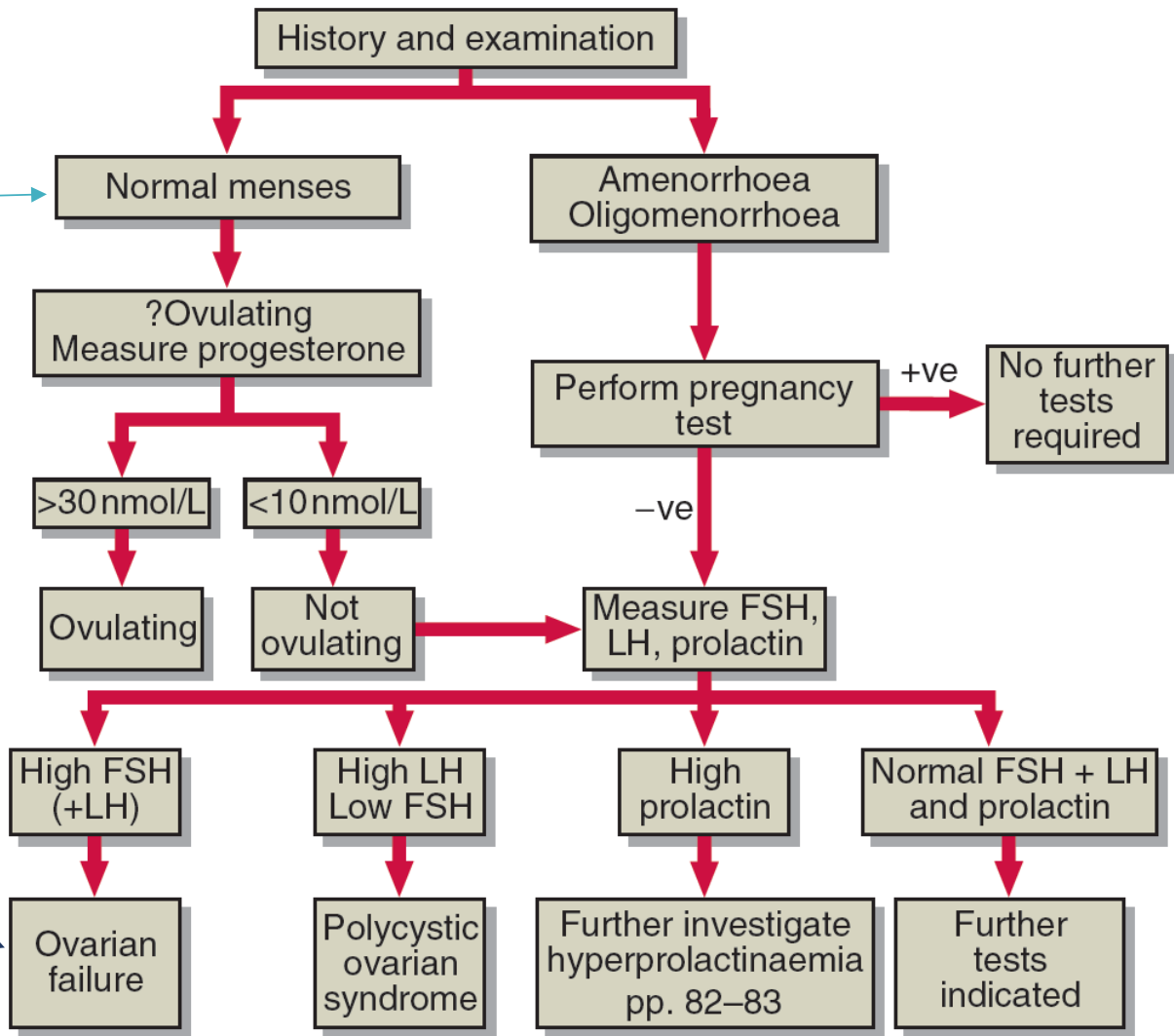


Fig 51.1 Diagnostic approach to subfertility in the woman.

Anti-Mullerian hormone (AMH)

In MALES it have another function which is to inhibit the female genitalia.

- ❖ A polypeptide hormone called Mullerian-inhibiting substance.
- ❖ Secreted by **growing ovarian follicles**.
- ❖ Secretion is proportional to follicular development.
- ❖ **Helps assess ovarian reserve and female fertility.**
- ❖ Ovarian reserve: number and quality of oocytes in the ovaries.

Oogonia then primordial then primary then secondary oocyte

In the ovary it inhibits the

1. Initial recruitment of primary follicles from primordial follicles.
2. Sensitivity of antral follicles to FSH during cyclical recruitment.

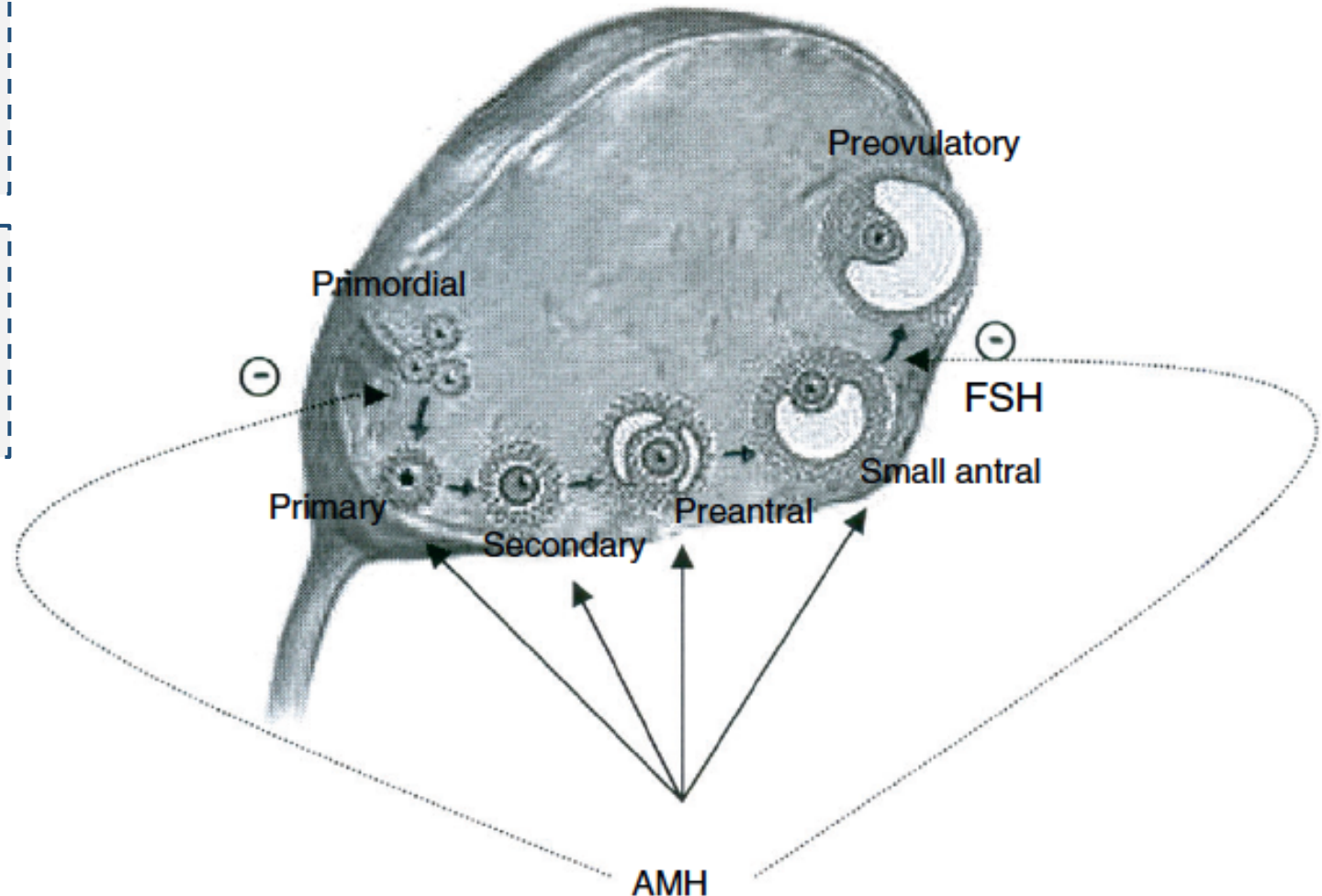
- ✓ AMH **prevents** premature depletion of follicles.
- ✓ The number of remaining primordial follicles correlate with the number of growing follicles. Since **only growing follicles produce AMH**, its plasma levels reflect the number of remaining primordial follicles. **We can measure the antral follicles count by transvaginal ultrasound, They are more helpful if female is going for IVF.**

Anti-Mullerian hormone (AMH)

AMH and folliculogenesis

Female are born with around 1 million of Follicle .And It keeps reducing over time , By the time that female reach fertile age she will have around 300-400 thousands follicle.

AMH level gives an idea about The number of remaining primordial follicles which correlates with the number of growing follicles ..



Endocrine investigations in subfertile man

Eugonadal men with normal sperm analysis do not require endocrine investigations

Endocrine cause of infertility in men are rare

In hypogonadal men:

1. Testosterone.
2. Gonadotrophins should be measured.

Semen analysis

1. Volume. Normal range at least 1.5 ml
2. Liquefaction time. Normally 20-30 mins
3. Sperm count. At least 15 million/ml
4. Motility. 38%
5. Presence of abnormal spermatozoa.
6. pH. 7.2 – 8 (Acidity destroys the sperms)
7. WBCs. Represents infection, shouldn't be present

Liquefaction time :
Time taken from sperm to convert form gel to liquid normally 20 to 30 minutes

Endocrine investigations in subfertile man

1. Primary testicular failure due to:	<ol style="list-style-type: none">1. Damage in the testes (interstitial, tubular) if only FSH is increased it is tubular, if both LH and FSH are decreased it will be interstitial.2. Low levels of testosterone.
2. Hypothalamic-pituitary disease:	<ol style="list-style-type: none">1. Decreased testosterone with low/normal gonadotrophins.2. Suggests hypogonadotropic hypogonadism.
3. Hyperprolactinemia (a rare cause in men).	

Investigation of male infertility

Investigation of male infertility

Follow the chart
and know the
investigations

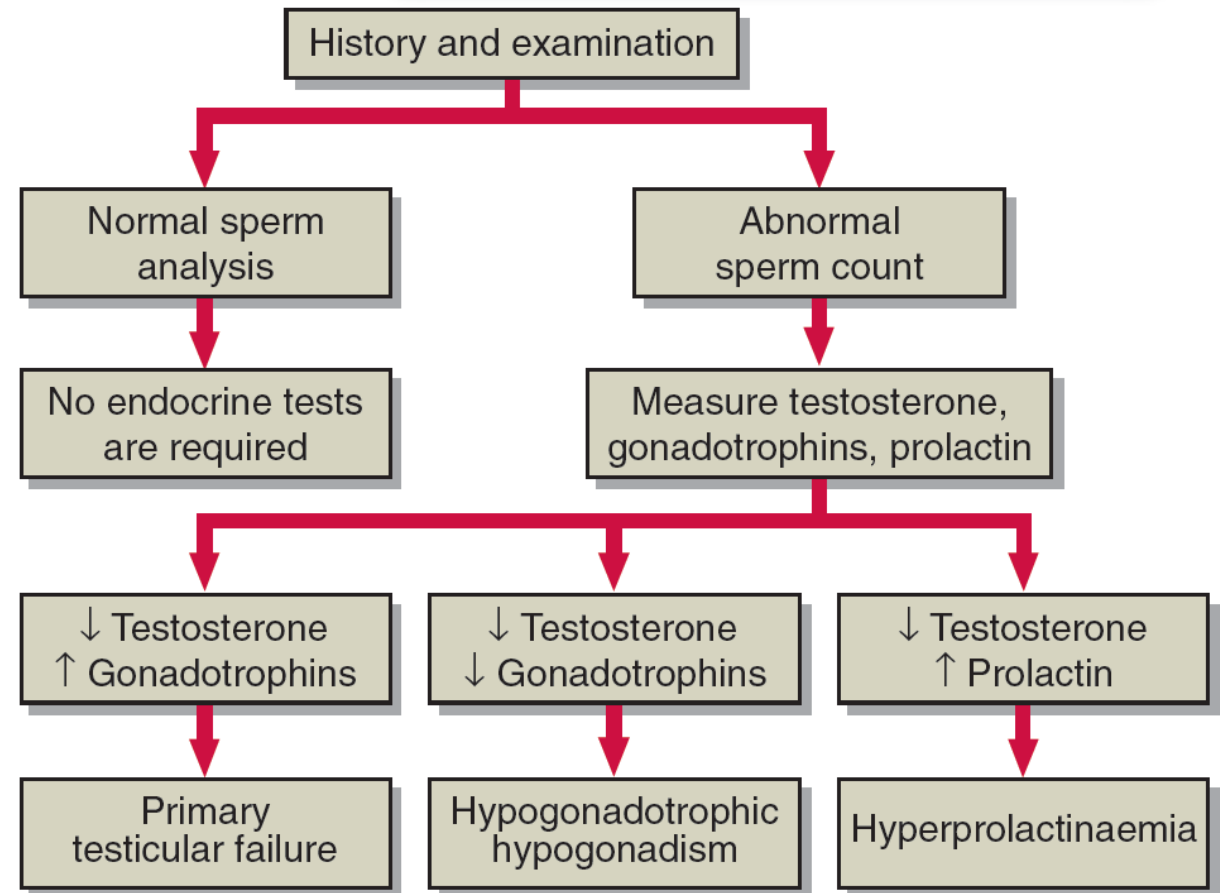


Fig 51.2 **Diagnostic approach to subfertility in the man.**

Hyperprolactinemia

- ❖ Prolactin is an anterior pituitary hormone
- Its secretion is tightly regulated:
 1. Stimulated by TRH from the hypothalamus
 2. Inhibited by dopamine from hypothalamus
- ❖ It **acts directly on the mammary glands** to control lactation

Follow the chart
and know the
investigations

❖ Elevated circulating prolactin :

- **Causes infertility in both sexes** due to gonadal function impairment

Early indication

In women : amenorrhea and galactorrhea

In men : none

Causes of hyperprolactinemia

Causes

Stress

Drugs (estrogens, phenothiazines, metoclopramide, α -methyl dopa)

Seizures

Primary hypothyroidism (prolactin is stimulated by raised TRH)

Other pituitary disease

Prolactinoma

Idiopathic hypersecretion (e.g. due to impaired secretion of dopamine that usually inhibits prolactin release)

Usually hyperprolactinemia shows symptoms in female (secretion of milk without pregnancy) but not in male unless it grows and compresses the adjacent area.

Diagnosis of hyperprolactinemia

Exclude
Stress
Drugs
Other diseases

Differential
diagnosis
Prolactinoma
Idiopathic
hypersecretion

And you have to exclude any other stimulant like touching the breast and pelvic area which temporary increases prolactin levels.

Take Home Message

- Endocrine causes of infertility are more common in women than men
- In women serum progesterone $>30\text{nmol/L}$ indicates ovulation
- Hyperprolactinemia is a rare cause of male infertility

Summary

Summary

Infertility / subfertility :

- Failure of a couple to conceive after one year of regular unprotected intercourse
- Causes :
 - 1- Endocrine problems
 - 2- Hormone dysfunction
 - 3- Idiopathic

Diagnostic approach

Clinical History

Previous pregnancies - Use of contraceptives - Serious illness - Past Chemo / radiotherapy - Congenital abnormalities - Drug usage - Sexually transmitted disease - Frequency of intercourse

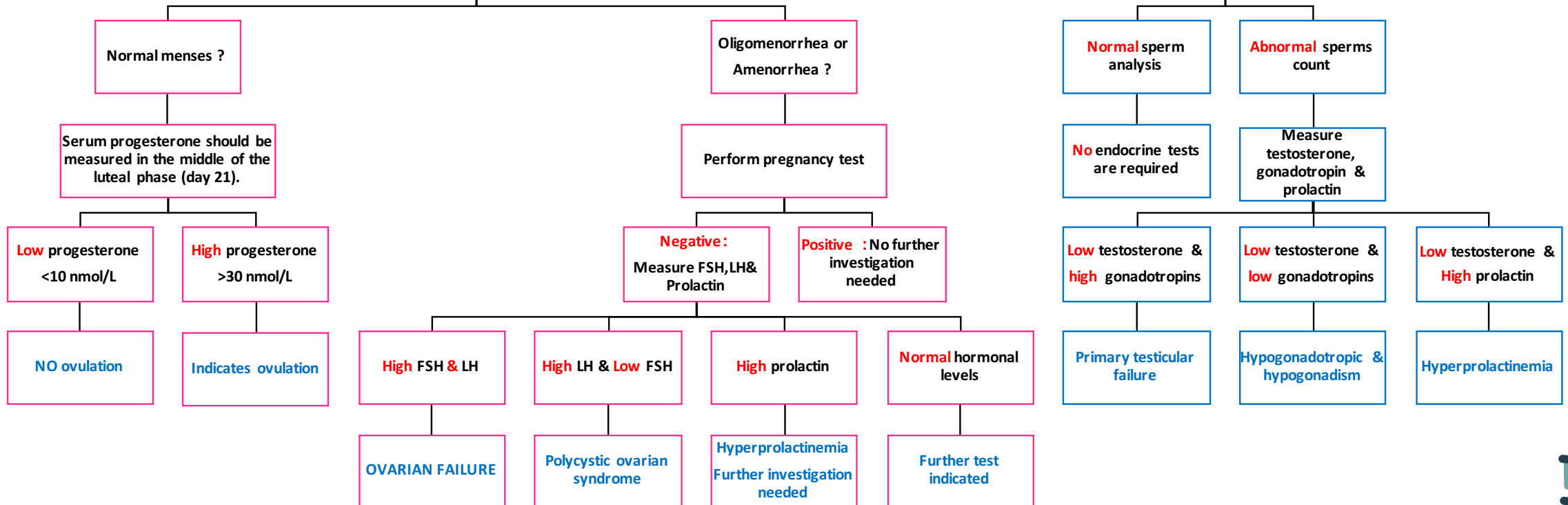
Clinical examination

Hypothalamopituitary disorders, thyroid disorders - Cushing's syndrome - Hirsutism - Galactorrhea (Lactation in the absence of pregnancy, Most commonly due to hyperprolactinemia)

Investigations of infertile couples

Endocrine investigations in subfertile female

Endocrine investigations in subfertile male



QUIZ

Q1 : Which one of the following prevents premature depletion of follicles?

- A. Estrogen
- B. Progesterone
- C. Anti-Mullerian hormone
- D. Mullerian hormone

Q2 : Which one of the following is correct in the investigations of female infertility?

- A. If progesterone is <10 nmol/L it means the patient is ovulating
- B. If patient has amenorrhea, there are no further tests required
- C. If patient is not ovulating we need to perform pregnancy test
- D. If patient has high FSH + LH diagnosis is Ovarian Failure

Q3 : Which one of the following is the least common cause in subfertility in men?

- A. Damage in the testes
- B. Hyperprolactinemia
- C. Low levels of testosterone
- D. Hypothalamic-Pituitary disease

Q4 : Which one of the following indicates Primary testicular failure?

- A. Increased Testosterone, Decreased Gonadotrophins
- B. Decreased Testosterone, Increased Prolactin
- C. Decreased Testosterone, Increased Gonadotrophins
- D. Decreased Testosterone, Decreased Gonadotrophins

Q5 : All of the following are correct about prolactin except?

- A. Secretion is stimulated by TRH
- B. Secretion is inhibited by dopamine
- C. Acts directly on the mammary glands
- D. Acts directly on the uterine glands

Q6 : Which one of the following would indicate subfertility on physical examination?

- A. Cushing disease
- B. Hirsutism
- C. Both
- D. Non of the above

QUIZ

Q7 : 27 year lady came to your clinic with complains of inability to become pregnant for the past 3 years, she also complained of disturbances in her period for the past 6 months. Physical examination revealed that she has some hirsutism around the lips.

The investigations are indicated below:

Negative Pregnancy test

High LH levels, Low FSH levels, Normal Prolactin levels.

A) What is the probable diagnosis according to these findings?

Polycystic ovarian syndrome

B) Mention 3 other causes of infertility in women.

1. Hyperprolactinemia
2. Ovarian Failure
3. Cushing's Syndrome

C) Mention 3 Hormones that are related to fertility.

1. Anti-Mullerian Hormone
2. Prolactin
3. Testosterone
4. FSH
5. LH

D) Mention 4 drugs that cause hyperprolactinemia

1. Estrogens
2. Phenothiazines
3. Metoclopramide
4. Alpha-Methyl Dopa

*Suggestions and
recommendations*

1) C 2) D 3) B 4) C 5) C 6) B



TEAM MEMBERS



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THANK YOU

FOR CHECKING OUR WORK



PLEASE CONTACT US IF YOU HAVE ANY ISSUE

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