"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Investigations of Infertile Couples

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

Reproductive block

Objectives:

- 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

Overview:

- Infertility /subfertility
- Clinica history and physical examination
- Endocrine investigations in subfertile women
- Endocrine causes of female infertility
- Endocrine investigations in subfertile men
- Diagnostic approaches to subfertility in women and men
- Hyperprolactinemia

Infertility / Subfertility[1]

- Failure of a couple to conceive after one year of regular, unprotected intercourse[2].
- Infertility may be caused by endocrine problems:
  Common in females (1/3rd patients) – Rare in males.
- Hormone dysfunction is a rare cause of male infertility.
- In some couples no cause can be identified "idiopathic".

Clinical History Taking

Information on clinical history of the patient should include:

Previous pregnancies[3]	Use of contraceptives[4]
Congenital abnormalities	Drug usage
Serious illness	Past Chemo/ radiotherapy[5]
Sexually transmitted disease	Frequency of intercourse

[1] Infertility is an absolute inability to conceive, but most of the cases are relative/ due to secondary causes, so we call it subfertility.

[2] we have to check the age,
- if the women is less than 35, you give them a year to try with some guidance.
- if the woman is more than 35 of age, you give them only 6 months.
- if the woman is 40 or above or has any other risk factors investigate immediately.

[3] to check if it primary infertility or secondary.
If there wasn't any previous pregnancy = primary pregnancy
If there were = secondary pregnancy

[4] Decrease fertility for a while after you stop taking them

[5] Damage oocytes

Physical Examination

Information on physical examination should include:

Hypothalamo-pituitary, thyroid disorders	**Cushing's syndrome**
Galactorrhea – Lactation in the absence of pregnancy – Most common due to hyperprolactinemia	**Hirsutism** Pointing to PCOS or androgen excess

First thing we look for is BMI, if the BMI is high we look for fat distribution, central obesity can lead to insulin resistance which affect androgen and there for gonads

Endocrine Investigations in Subfertile Women

- Investigations* are based on the phase of menstrual cycle
- Serum progesterone should be measured in the middle of the luteal phase (day 21)
- High progesterone (>30 nmol/L) indicates ovulation
- In oligomenorrhea or amenorrhea**, hormone measurement is needed

*Check progesterone to figure out if the cycle is ovulatory or anovulatory.
**Absence of menses for continuous 6 months or more.

Progesterone:
- Less than 10 = anovulatory
- 10 to 30 ovulatory but with a problem ex. PCOS

`If the cycle is irregular, check the progesterone 7 days before expected beginning of menstruation.

Endocrine Causes of Female Infertility

Excessive secretion of ovarian androgens	• Obesity • Insulin resistance
Primary ovarian failure* **Hyper**gonadotrophic hypogonadism	• High gonadotropins, low oestradiol (postmenopausal hormonal pattern) • **In this case,** Hormone replacement therapy can be given but it will not treat infertility.
Hyperprolactinemia	
PCOS	There will be increase androgen which will affect the gonads directly and also affect the folliculogenesis
Cushing's syndrome	Increase cortisol which will lead to increase the production of androgens
Hypogonadotrophic hypogonadism	• Low gonadotrophin/oestradiol • Rare • Due to hypothalamic-pituitary lesion

*** -** Primary ovarian failure "**Hyper**gonadotrophic hypogonadism" The problem is in the ovaries so it is not producing estrogen and progesterone "low" so they do not send negative feedback to the pituitary and hypothalamus to stop the release of gonadotrophin so there will be high FSH and LH

- Hypogonadotrophic hypogonadism FSH and LH will be low also estrogen and progesterone are low that could be due to a problem in the hypothalamus or the pituitary

Investigation of Female Infertility

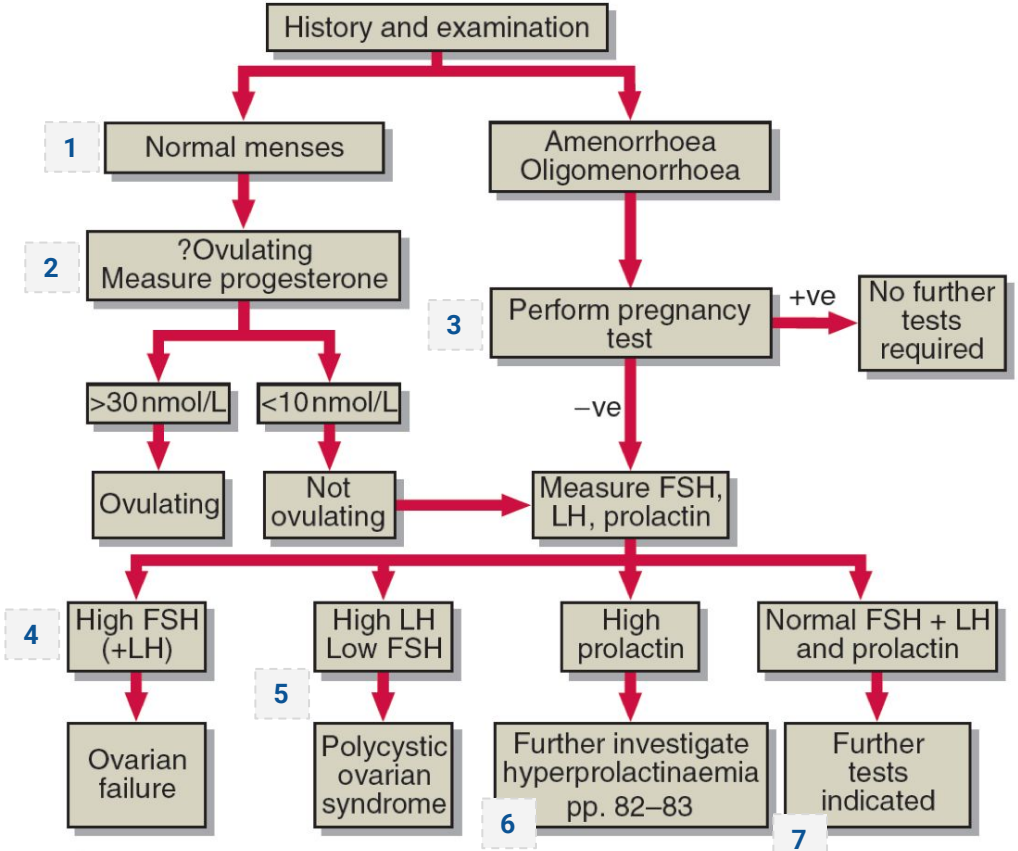


Fig 51.1 **Diagnostic approach to subfertility in the woman.**

1* Have normal menstruation and normal features of menstrual cycle

2* On day 21 of normal 28 cycle

3* pregnancy is the most common cause of amenorrhoea

4* But low estradiol

5* This is classical picture of PCOS. you look for the level of androgens and if it is high that's mean its PCOS

6* Like radiological examination and pituitary function

7* Look for other causes of infertility like structural anomalies it could be problem with anything else like the fallopian tube Orr the uterus it self

Anti-Mùllerian hormone (AMH)

In male it inhibit the mullerian duct to grow to female internal genital

What is it?	A polypeptide hormone called Mullerian-inhibiting substance
Secretion	- Secreted by growing ovarian follicles - Secretion is proportional to follicular development
Measurement	Helps assess **ovarian reserve** and female fertility

Ovarian capacity = ovarian reserve

Ovarian reserve: number and quality of oocytes in the ovaries

initially it is expressed by the granulosa cells then it is secreted from the growing follicle and circulated into the blood that's why its level can be measured.

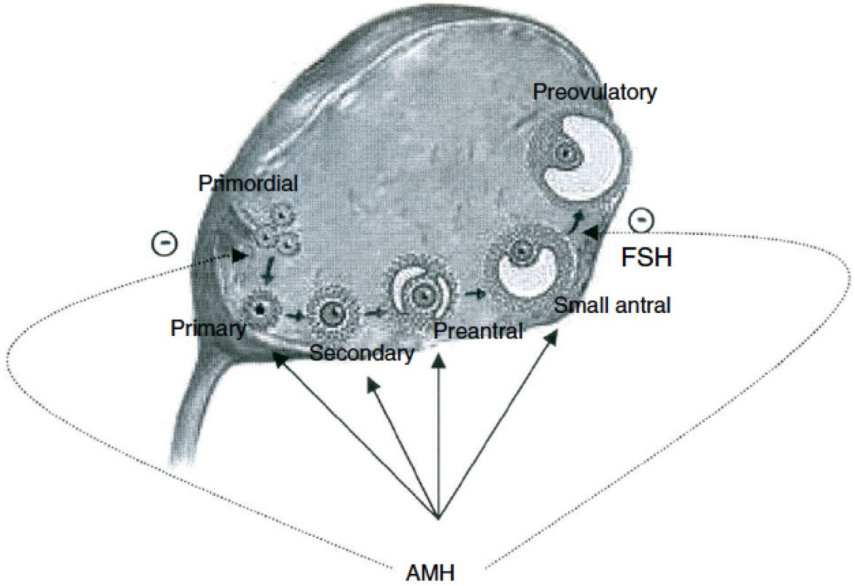
The amount of AMH in the blood is directly proportional to the amount of growing follicles and the growing follicle reflect the number of the remaining primordial follicles in the ovaries so we use AMH to asses the ovarian capacity.

In the ovary it inhibits the	- Initial recruitment of primary follicles from primordial follicles - Sensitivity of antral follicles to FSH during cyclical recruitment

- AMH prevents premature depletion of follicles
- The no. of remaining primordial follicles correlate with the no. of growing follicles
- Since only growing follicles produce AMH, its plasma levels reflect the number of remaining primordial follicles

AMH and Folliculogenesis

AMH level gives an idea about the number of remaining primordial follicles which correlates with the number of growing follicles ..
If AMH was high → high resserve → better fertility



Extra for more understanding:

- AMH is released by growing follicles as a response to a high number of recruitment of primordial follicles into the active maturation state. AMH goes up to prevent further recruitment by inhibiting FSH function on the prenatal follicle. High levels of AMH means there are a lot of follicles trying to mature. On the other hand, low follicle number means lesser AMH production

Endocrine Investigations in Subfertile Man

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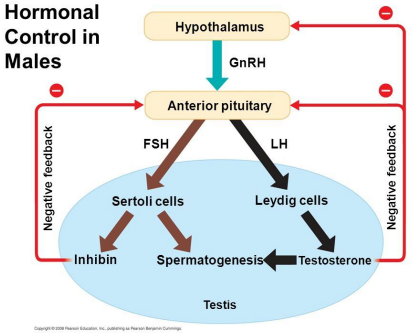
Eugonadal men with normal sperm analysis do not require endocrine investigations	Endocrine cause of infertility in men are rare	In hypogonadal men 1. Testosterone 2. Gonadotropins should be measured

Semen analysis:

- Volume. Normal range at least 1.5 ml
- Liquefaction time. Normally 20-30 mins
- Sperm count. At least 15 million/ml
- Motility. 38%
- Presence of abnormal spermatozoa.
- pH. 7.2 – 8 (Acidity destroys the sperms, and alkaline points to infection)
- WBCs. indicate infection, shouldn't be present



Extra to remember

Endocrine Investigations in Subfertile Man

- Primary testicular failure due to:
  - Damage in the testes (interstitial, tubular)
  - Low levels of testosterone
- Hypothalamic-pituitary disease:
  - Decreased testosterone with low/normal gonadotrophins
  - Suggests hypogonadotrophic hypogonadism
- Hyperprolactinemia (a rare cause in men)

Investigation of Male Infertility

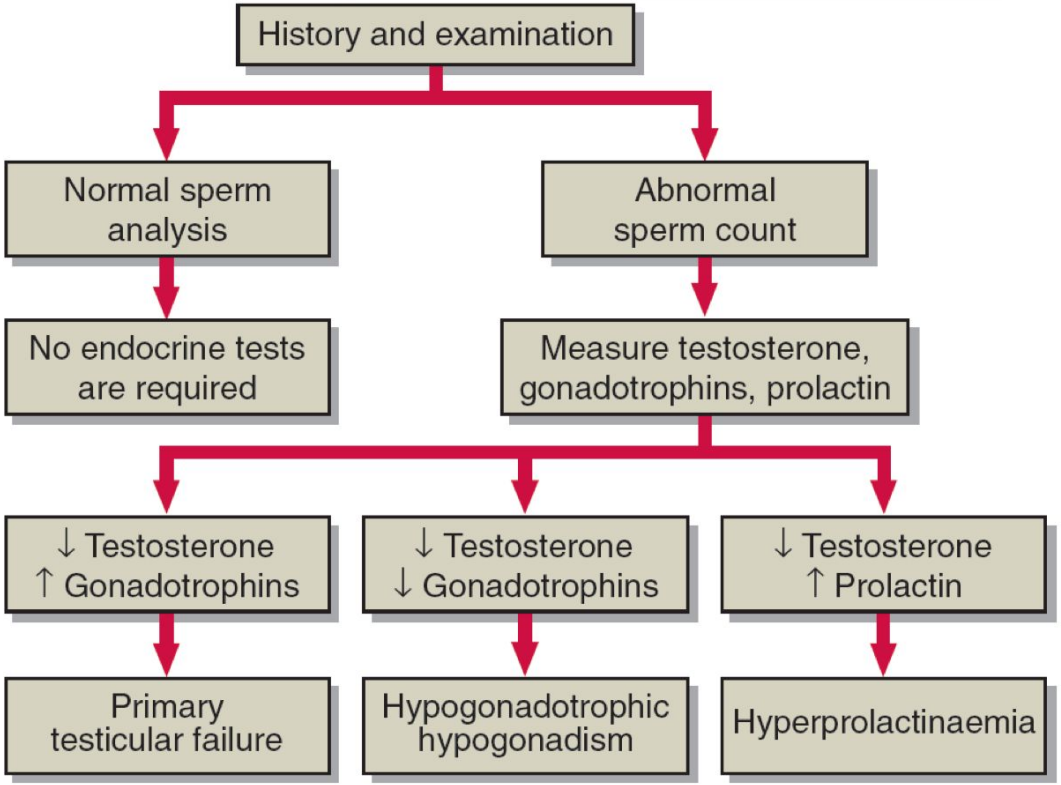


Fig 51.2 **Diagnostic approach to subfertility in the man.**

Hyperprolactinemia

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Prolactin Hormone

- It's an Anterior Pituitary Hormone.
- Tightly Regulated by:
  - ➕ Stimulated by TRH from Hypothalamus.
  - ➖ Inhibited by Dopamine from Hypothalamus.
- It acts Directly on the Mammary glands to control Lactation.

Elevated circulating Prolactin, Causes:
Infertility in both sexes due to gonadal function impairment
Early Indications:
♀: Amenorrhea and Galactorrhea
♂: None*

The only early sign a man could have is headaches and visual disturbances due to tumor in the Pituitary gland.
*Gynecomastia will occur in the late stage (when there is very high level of prolactin).

Causes of Hyperprolactinemia:

- Stress
- Drugs (Estrogen, Phenothiazines, Metoclopramide, alpha-methyl dopa)
- Seizures
- Primary Hypothyroidism (prolactin is stimulated by raised TRH)
- Other Pituitary Diseases.
- Prolactinoma
- Idiopathic hypersecretion(e.g. Due to impaired secretion of dopamine that usually inhibit prolactin release)

Diagnosis of Hyperprolactinemia

Exclude

- Stress
- Drugs
- hypothyroidism
- Other Disease

Differential Diagnosis

- Prolactinoma (by radiology)
- Idiopathic hypersecretion (check dopamine)

Summary

Infertility / subfertility

Failure of a couple to conceive after one year of regular unprotected intercourse

Endocrine investigations

Investigations are based on the phase of menstrual cycle:

1. If menses is normal → Serum progesterone should be measured in the middle of the luteal phase (day 21):
   - _ High progesterone (>30 nmol/L) = ovulation.
   - _ low progesterone (< 10 nmol/L) = anovulation.
2. In oligomenorrhea or amenorrhea, perform pregnancy test:
   - _ Positive result = no further testing is required
   - _ Negative result = hormone measurement is needed

In these cases, (not ovulating in normal menses or –ve pregnancy test in oligomenorrhea/ amenorrhea), Measure FSH, LH and prolactin:

- o ↑FSH&↑LH=ovarian failure
- o ↑LH&↓FSH=PCOS
- o ↑ prolactin = further investigate hyperprolactinemia
- o normal hormone=further testing.

Based on Semen analysis: Based on Semen analysis:

_ Volume - Liquefaction time - Sperm count – Motility .

_Presence of abnormal spermatozoa – pH – WBCs.

1. Eugonadal men with normal sperm analysis do not require endocrine investigations, as endocrine cause of infertility in men are rare.

2. In hypogonadal men with abnormal sperm count, Measure Testosterone, Gonadotrophins, and prolactin:
   - o ↓ Testosterone & ↑ Gonadotrophins = primary testicular failure
   - o ↓ Testosterone & ↓ Gonadotrophins = hypogonadotropic hypogonadism
   - o ↓ Testosterone & ↑ prolactin = hyperprolactinemia.

Causes

Primary ovarian failure:
o High gonadotrophins, low oestradiol (postmenopausal hormonal pattern)

Hypogonadotrophic hypogonadism (Rare):
o Low gonadotrophin/oestradiol

Excessive secretion of ovarian androgens:
Obesity & Insulin resistance

Hyperprolactinemia, PCOS, and Cushing's syndrome

Primary testicular failure due to:
o Damage in the testes (interstitial, tubular)

Hypothalamic-pituitary disease:
o Suggests hypogonadotrophic hypogonadism

Hyperprolactinemia (a rare cause in men)

Take Home Messages

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

MCQs:

Q1: Which one of the following indicates infertility in physical examination:
A)Cushing's syndrome
B)Galactorrhea
C)hirsutism
D)All of them

Q2: In a subfertile women, we have to measure serum progesterone on:
A) day 21
B) day 13
C) day 7
D) day 26

Q3: What causes hypergonadotropic hypogonadism:
A) Primary ovarian failure
B)PCOS
C)Hypothalamic-pituitary lesion
D)Hyperprolactinemia

Q4: In polycystic ovarian syndrome:
A)Low FSH high LH
B)Low FSH low LH
C)High FSH high LH
D)High FSH Low LH

Q5: Which one of these hormones is secreted by growing ovarian follicles:
A)Mullerian hormone
B)Anti-Mullerian hormone
C)Estrogen
D)Progesterone

1- D
2- A
3- A
4- A
5- B

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Girls team

- ليلى الصّباغ
- منيرة المسعد
- رزان الزهراني
- لمياء القويز
- اروى الجهني
- مها القحطاني
- ريناد الغريبي

Boys team

Team leaders

- رهام الحلبي
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