College of Pharmacy

Fifth Stage

Clinical Chemistry

Dr. Maytham Ahmed

Lectutre 3

The Reproductive System

The Reproductive System

The reproductive system is the system that responsible for the production of hormones and maturation of the germ cells in the gonads.

Hypothalamic hormones

The hypothalamus secretes gonadotrophin-releasing hormone (GnRH), which regulates the secretion of the pituitary gonadotrophins [luteinizing hormone (LH) and follicle stimulating hormone (FSH)], and dopamine, a neurotransmitter, which also controls prolactin secretion.

Anterior pituitary hormones

The **gonadotrophins (LH and FSH)**, secreted by pituitary basophil cells, control the function and secretion of hormones by the testes and ovaries. The actions of the gonadotrophins are: **LH** primarily stimulates the production of hormones by the gonads, **FSH** stimulates the development of the germ cells. **Prolactin**, secreted by pituitary acidophil cells. It stimulates breast epithelial cell proliferation and induces milk production. Prolactin **differs** from all other pituitary hormones in its method of control. The secretion of prolactin is inhibited, not stimulated, by **dopamine** (prolactin inhibitory factor); therefore, impairment of hypothalamic control causes **hyperprolactinaemia**.

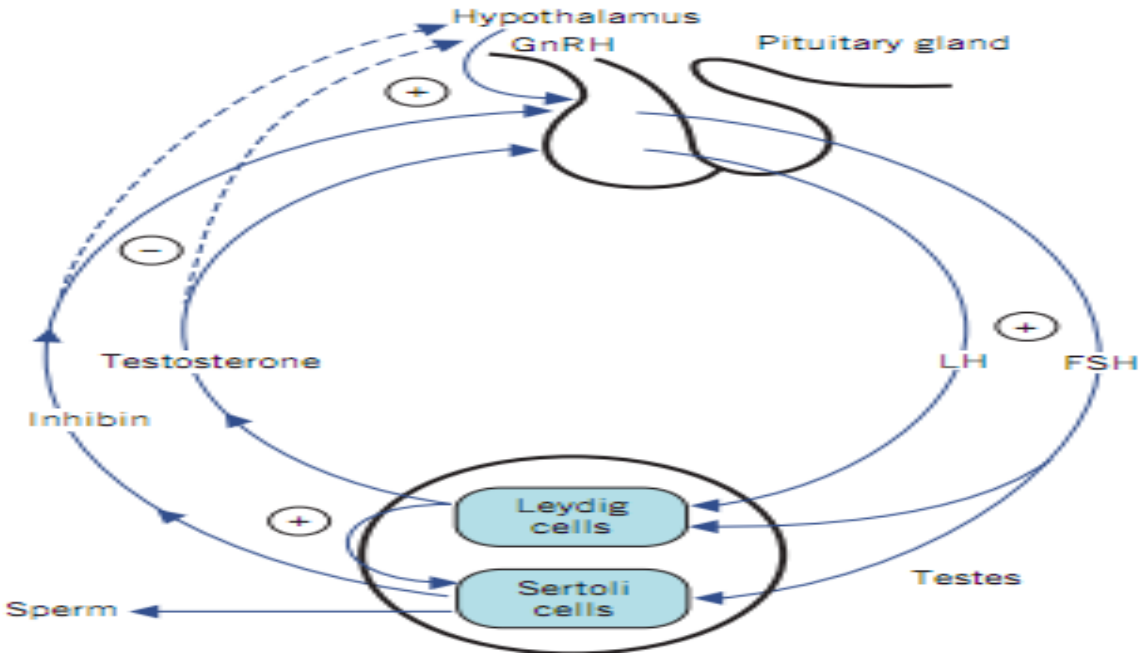
Ovarian hormones

Oestrogens, progesterone and androgens are secreted by the ovarian follicles of the ovaries, which consist of germ cells (ova) surrounded by granulosa and theca cells. Androgens (C19 steroids), synthesized by theca cells, are converted into oestrogens (C18 steroids) in the granulose cells. **Oestradiol** is the most important ovarian oestrogen. The liver and subcutaneous fat convert **ovarian and adrenal androgens** to oestrone. Oestrogens are essential for the development of female secondary sex characteristics and for normal menstruation. **Androstenedione** is the main androgen secreted by the ovaries. It is converted to oestrone and to the more active testosterone in extraovarian tissue. A small amount of **testosterone** is secreted directly by the ovaries. Plasma testosterone concentrations in women are about a tenth of those in men. Progesterone is secreted by the corpus luteum during the

luteal phase of the menstrual cycle and by the placenta. It prepares the endometrium of the uterus to receive a fertilized ovum and is necessary for the maintenance of early pregnancy. It also is pyrogenic and increases the basal body temperature.

Testicular hormones

Testosterone is secreted by the **Leydig cells**, which lie in the interstitial tissue of the testes between the seminiferous tubules. The production of testosterone is stimulated by LH and it, in turn, inhibits LH secretion by negative feedback. **Inhibin** is a hormone produced by the **Sertoli cells**, part of the basement membrane of the seminiferous tubules, during germ cell differentiation and spermatogenesis. These processes require testosterone and are stimulated by FSH. Inhibin controls FSH secretion by negative feedback. **Testosterone** is involved in sexual differentiation, the development of secondary sexual characteristics, spermatogenesis and anabolism. In the male, the effects of **testosterone** depend on intracellular conversion to the more potent androgen **dihydrotestosterone** by the enzyme **5-α-reductase** in target cells.



The effect of the gonadotrophins hormones (LH and FSH) on testicular function

Hyperprolactinaemia

This is an important cause of **amenorrhoea**, **sexual dysfunction**, **infertility** and possibly **breast cancer**. High plasma prolactin concentrations inhibit the normal release of GnRH, the decrease GnRH lead to inhibition the release of gonadotrophins (LH and FSH) and inhibit gonadal steroid hormone synthesis, this lead to **infertility**. Plasma gonadotrophin and

oestrogen concentrations are therefore low, and the symptoms of oestrogen deficiency may occur.

Causes of hyperprolactinaemia

1. Physiological, e.g. stress or pregnancy.
2. Failure of hypothalamic inhibitory factors to reach the anterior pituitary gland due to:
   A. Damage to the pituitary stalk B. Surgical section of the pituitary stalk
3. Pituitary tumours:
   A. Microadenomas (< 10 mm) with plasma prolactin concentrations more than 2000 mU/L
   B. Macroadenomas (> 10 mm) with plasma prolactin concentrations more than 6000 mU/L
4. Drugs such as estrogens, dopaminergic antagonists, e.g. phenothiazines, haloperidol, metoclopramide and methyldopa.
5. Polycystic ovary syndrome.
6. Chronic kidney disease (due to reduced plasma prolactin clearance).
7. Severe primary hypothyroidism (due to anterior pituitary stimulation by high TRH concentrations from hypothalamus). The **TRH** stimulates the secretion of **prolactin**, as well as of **TSH** from the anterior pituitary, this action does not seem to be of physiological importance; it may, however, be important in pathological conditions.

Normal female gonadal function

At the onset of puberty, gonadotrophin secretion increases, as it does in the male. Ovarian oestrogen secretion rises and stimulates the development of female secondary sex characteristics and the onset of menstruation. At puberty the ovaries contain between 100000 and 200000 follicles. During each menstrual cycle a small number develop, but usually only one reaches maturation, which is extruded from the ovary as an ovum (ovulation), and is ready for fertilization. The menstrual cycle includes the following phases:

1. Follicular (pre-ovulatory) phase

At the beginning of the menstrual cycle, ovarian follicles are undeveloped and plasma oestradiol concentrations are low. The secretion of LH and FSH increases because of diminished negative feedback by oestrogens. Together, LH and FSH cause the growth of a

group of follicles. By about the seventh day of the cycle, one follicle becomes especially sensitive to **FSH** and matures, while the rest atrophy. Luteinizing hormone (**LH**) also stimulates oestradiol secretion, the plasma concentrations of which rise steadily. This stimulates the regeneration of the endometrium.

2. Ovulation

The rapid development of the dominant follicle and the rise in plasma oestradiol concentration trigger a surge of LH release from the anterior pituitary gland by **positive feedback**. Ovulation occurs about 16 hours later.

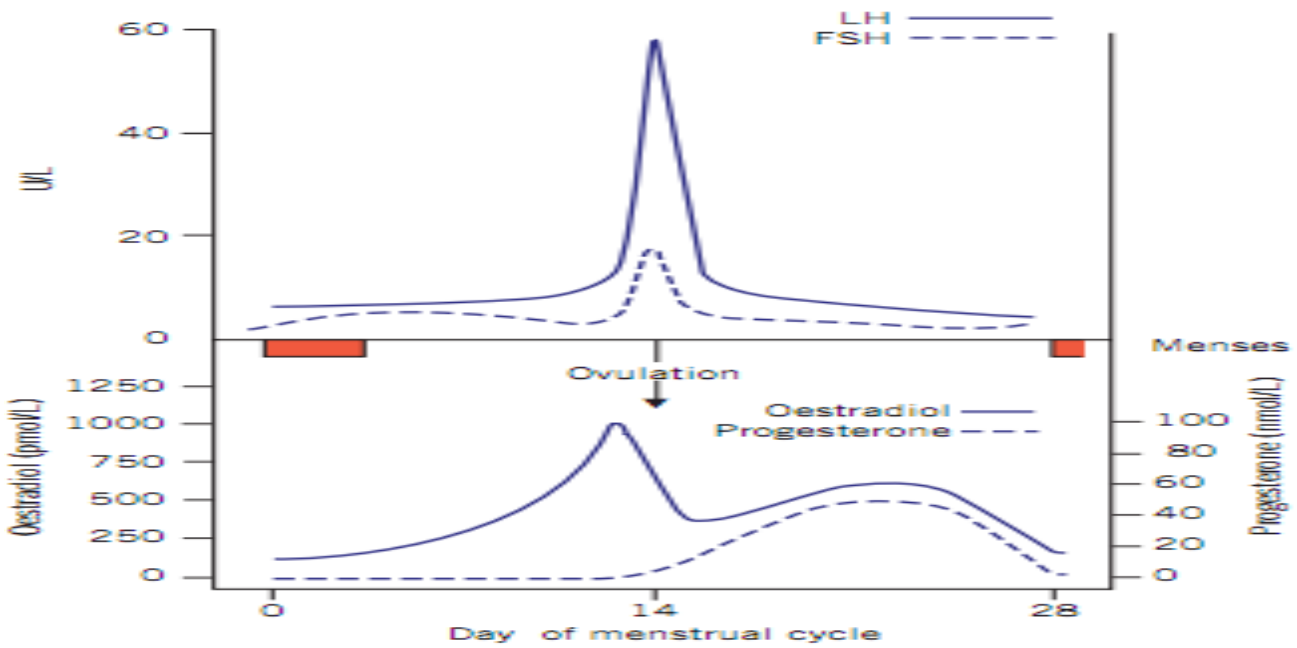
3. Luteal (post-ovulatory or secretory) phase

After ovulation, the **high LH** concentration stimulates the granulosa cells of the ruptured follicle to luteinize and form the corpus luteum, which synthesizes and secretes progesterone and oestradiol. **Progesterone** is the principal hormone of the luteal phase and prepares the endometrium for the implantation of the fertilized ovum. If the ovum is not fertilized, the corpus luteum regresses and plasma ovarian hormone concentrations fall; the menstrual cycle takes its course, with sloughing of the endometrium and menstrual bleeding.

It may be important to establish whether a patient who is complaining of infertility has ovulated, either spontaneously or as a result of treatment to induce ovulation. The plasma **progesterone** concentration should be **measured** in a blood sample taken during the second half of the menstrual cycle; usually **day 21**. A value within the reference range for the time of the cycle is good presumptive **evidence of ovulation**, whereas a value in the range expected in the follicular phase indicates the absence of a corpus luteum, and therefore absence of ovulation.

The menopause

The menopause is defined as the time of permanent cessation of menstruation, the average age being about 50 years. The menopause occurs when all the follicles have atrophied. Plasma concentrations of oestrogens fall and those of FSH and, to a lesser extent, LH increase after removal of the negative feedback to the pituitary. These findings are therefore similar to those of primary gonadal failure (ovarian failure).



Plasma hormone concentrations during the menstrual cycle.

Disorders of gonadal function in females

Gonadal dysfunction in women usually presents with any or all of the following:

1. Amenorrhoea **2. Hirsutism** **3. Virilism** **4. Infertility**

Amenorrhoea

Amenorrhoea is defined as the absence of menstruation; it may be due to hormonal abnormalities. If there is ovarian failure, pituitary gonadotrophin concentrations in plasma are high (**hypergonadotrophic hypogonadism**); if the cause is in the hypothalamus or anterior pituitary gland, gonadotrophin secretion is reduced (**hypogonadotrophic hypogonadism**).

Amenorrhoea may be classified as either **primary** or **secondary**. **Primary amenorrhoea** occurs when the patient has never menstruated and is most commonly associated with delayed puberty. **Secondary amenorrhoea** occurs when previously established menstrual cycles have stopped and is most commonly due to **physiological factors** such as pregnancy or the menopause. **Other causes** include severe illness, excess or rapid weight loss for any reason, including anorexia nervosa, or stopping oral contraceptives. **A number of endocrine disorders**, such as hyperprolactinaemia, hyperthyroidism, Cushing's syndrome and acromegaly, may present with amenorrhoea.

Hirsutism and virilism

Increased plasma **free androgen** concentrations, or increased tissue **sensitivity to androgens**, produce effects ranging from increased hair growth (**hirsutism**) to marked masculinization, with **virilism**. Testosterone is the most important androgen. **Hirsutism** is defined as an excessive growth of hair in a male distribution and is common, possibly occurring in 10 per cent of women. **A common cause is familial hirsutism**. **Other causes** include polycystic ovary syndrome, adrenal or ovarian tumour, Cushing's syndrome and exogenous androgens drugs. **Virilism** is characterized by additional evidence of excessive androgen secretion increased hair growth of male distribution, deepening of the voice and breast atrophy. It is always associated with increased plasma androgen concentrations. Plasma DHEA concentration may also be increased. **The common causes of virilism** include adrenal or ovarian tumour, Cushing's syndrome and exogenous androgens drugs.

Polycystic ovary syndrome (PCOS)

This is a condition showing features of hyperandrogenism with anovulation and abnormal ovarian morphology and is the most common cause of anovulatory infertility. Presenting clinical symptoms may also include hirsutism, menstrual disturbances, enlarged polycystic ovaries and infertility. Plasma **testosterone** and **androstenedione** concentrations are often increased. The plasma **LH** may be elevated with normal **FSH**. Because plasma **SHBG** concentrations are reduced in obese individuals, the plasma concentration of free testosterone is often increased. The plasma **prolactin** concentrations may also be high. Multiple small subcapsular **ovarian cysts** may be demonstrated on **ultrasound** scanning of the ovaries. Polycystic ovary syndrome is also associated with insulin resistance, obesity and elevated plasma insulin concentrations. Individuals may also have hyperlipidaemia, glucose intolerance and hypertension.

Infertility

Infertility can be defined as **primary** when conception has never occurred despite at least 1 year of unprotected coitus, and **secondary** when there has been a previous pregnancy, either

successful or not. **Examination should include** looking for hirsutism, virilism, galactorrhoea and a history should also be taken for medications.

Investigations of female infertility

A woman may be infertile despite having a clinically normal menstrual cycle (about 95 per cent of such cycles are ovulatory). Thus, even if the cycle seems to be regular, it is important to determine whether ovulation is occurring and if luteal development is normal. **Anovulatory infertility** is probably **the most** common form of female infertility and is associated with oligomenorrhoea or amenorrhoea.

1. If the patient is menstruating regularly, measure plasma **progesterone** concentration during the luteal phase on day **21** of the cycle. A normal plasma concentration is strong evidence that the patient has ovulated. A low plasma concentration of < 30 nmol/L suggests ovulatory failure. However, a plasma progesterone concentration of more than 100 nmol/L suggests pregnancy.

2. Plasma **FSH**, **LH** and **oestrogen** concentrations should be measured:

A. If the plasma FSH and LH are increased while oestrogen decreased, the results suggest hypergonadotrophic hypogonadism (ovarian failure).

B. If the plasma FSH, LH and oestrogen are decreased, the results suggest hypogonadotrophic hypogonadism (pituitary or hypothalamic disease).

3. Low concentrations of plasma gonadotrophins (FSH and LH) may necessitate a gonadotrophin-releasing hormone (**GnRH**) test. Intravenous injection of GnRH is given. Plasma LH and FSH concentrations are measured in blood drawn before and after the injection.

A. If the plasma LH and FSH levels are doubled from their basal levels, this mean normal subjects.

B. If the plasma LH and FSH levels are failed to rise from their basal levels, this mean pituitary hypofunction.

C. If the plasma LH and FSH levels are exaggerated response may be seen in patients with hypothalamic disease.

4. **Hyperprolactinaemia** should be excluded by checking the plasma **prolactin** concentration (high plasma prolactin concentrations inhibit the normal release of GnRH, the decrease GnRH lead to inhibition the release of gonadotrophin (LH and FSH) and inhibit gonadal steroid hormone synthesis, this lead to infertility).

5. **Thyroid function test** should be done to exclude thyroid disease (in primary hypothyroidism, high TRH concentrations increase prolactin secretion).

6. Follicular development and ovulation may be monitored by **ovarian ultrasound** examination. Polycystic ovary syndrome should be excluded.

7. Anti-Müllerian hormone (**AMH**) is released by granulosa cells of the ovarian follicle and low serum concentrations suggest poor ovarian 'reserve' (the size of the ovarian ovum supply). Serum AMH may, thus, have a place in the investigation of infertility.

Disorders of gonadal function in males

Investigations of male infertility

1- **Semen analysis:** the volume should be at least 2 mL. There should be more than 20×10^9/L spermatozoa, more than 50 per cent being motile at 4 hours post ejaculation and more than 30 per cent normal morphology.

2- Plasma **testosterone**, **LH** and **FSH** concentrations should be measured.

A. Raised plasma FSH and LH concentrations with a low testosterone concentration (hypergonadotrophic hypogonadism) indicate a testicular problem such as Leydig cell failure.

B. Low plasma FSH and LH and testosterone concentrations suggest pituitary or hypothalamic disease (hypogonadotrophic hypogonadism). In the case of the latter, a GnRH test may be required.

C. A raised plasma FSH concentration in comparison with LH may indicate seminiferous tubular failure (Sertoli cell failure), irrespective of the plasma testosterone concentration. There is usually azoospermia or oligospermia. Oligospermia with a low plasma FSH concentration suggests pituitary or hypothalamic disease.

3- Low concentrations of plasma gonadotrophins (FSH and LH) may necessitate a **GnRH** test. Intravenous injection of GnRH is given. Plasma LH and FSH concentrations are measured in blood drawn before after the injection.

A. If the plasma LH and FSH levels are doubled from their basal levels, this mean normal subjects.

B. If the plasma LH and FSH levels are failed to rise from their basal levels, this mean pituitary hypofunction.

C. If the plasma LH and FSH levels are exaggerated response may be seen in patients with hypothalamic disease.

4- Plasma **prolactin** should be measured to exclude hyperprolactinaemia.

5- **Thyroid function test** should be done to exclude thyroid disease.

6- A human chorionic gonadotrophin (**hCG**) stimulation test may be indicated if absence of testes is suspected or to assess Leydig cell reserve. The hCG shares a common subunit with LH and stimulates testicular Leydig cells to release androgens. It has a long half-life and elicits a rise in plasma testosterone after 72–120 h.