GONADAL FUNCTION: An Overview

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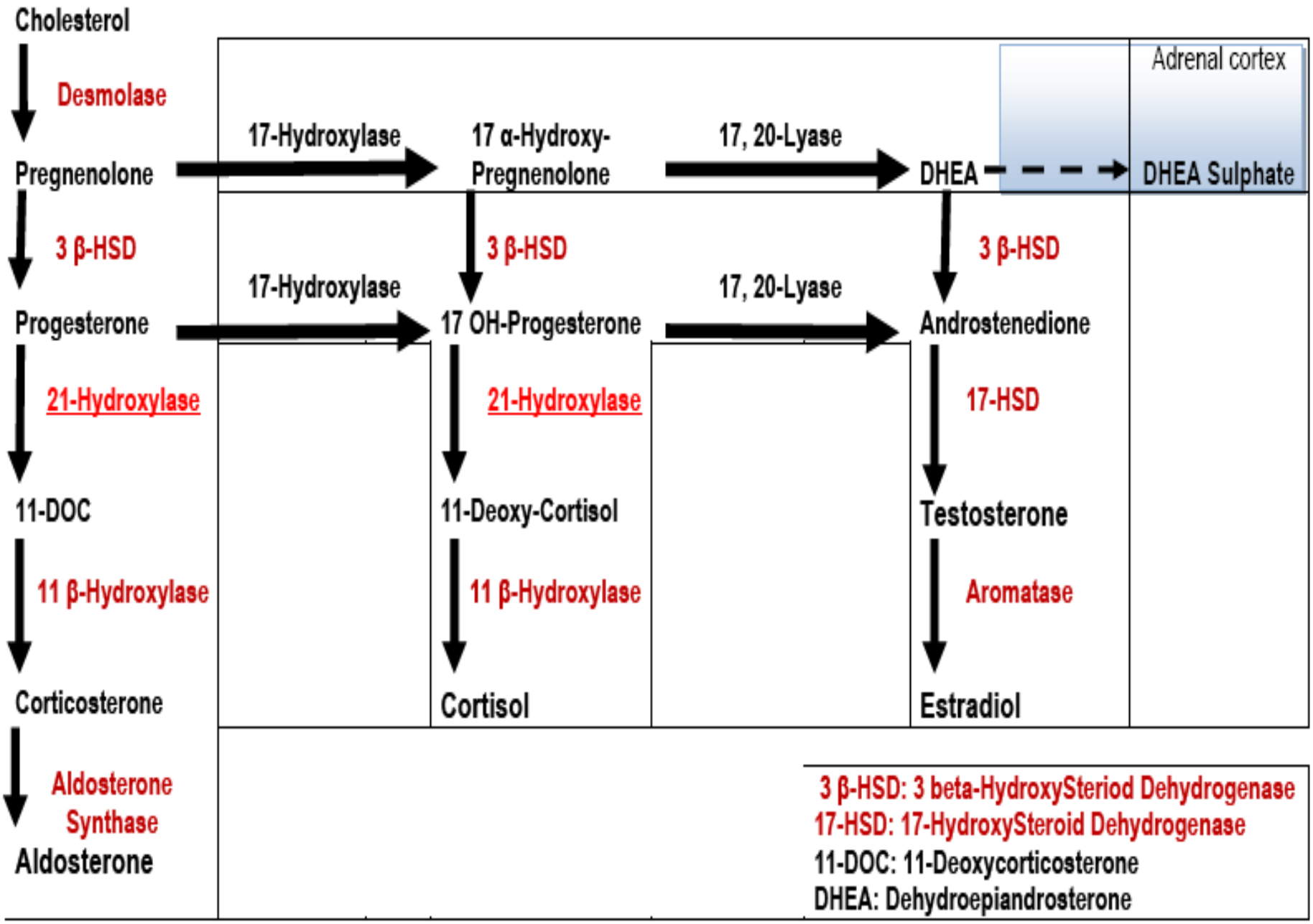
What are the Steroid hormones?

- **Hormones synthesized from Cholesterol**;
- Some important steroid hormones:
  - **Progesterone**: secreted in Corpus Luteum, involved in Luteral phase of menstrual cycle, differentiation of mammary glands;
  - **Estradiol (Oestradiol)**: Estrogen, produced in ovary, responsible for secondary female sex characteristics;
  - **Testosterone**: Androgen, produced in testes, responsible for secondary male sex characteristics;
  - **Aldosterone**: Principal Mineralocorticoid from Adrenal Cortex;
  - **Cortisol**: Principal Glucocorticoid from Adrenal Cortex;

Outline the pathways for biosynthesis of steroid hormones

- Pathways for biosynthesis of steroid hormones usually presented as a flow chart;
- Specific steroid hormone synthesized depends on:
  - Complement of Peptide Hormone Receptors in tissue,
  - Tissue response to Peptide Hormone Stimulation,
  - Genetically Expressed Complement of Enzymes in cells
- Flow chart does not go to completion in all tissues;
- **Fig. 1**: Schematic diagram of pathways for biosynthesis of different steroid hormones;

Fig. 1: Flow diagram of pathways for biosynthesis of steroid hormones



How do steroid hormones exist in blood plasma?

- Steroid hormones are **Hydrophobic**,
  - Exist in plasma mainly bound to Specific Hormone Binding Glycoproteins (Bound Fraction);
- Small amount of Steroid hormone exist Freely in plasma (Unbound or Free Fraction);
- **Unbound or "Free" fractions of steroid hormones in blood plasma are the biologically active fractions,**
- Measurements of "Free Fractions" of steroid hormones or Binding Protein levels are important for diagnosis of patients with certain steroid hormone disorders;

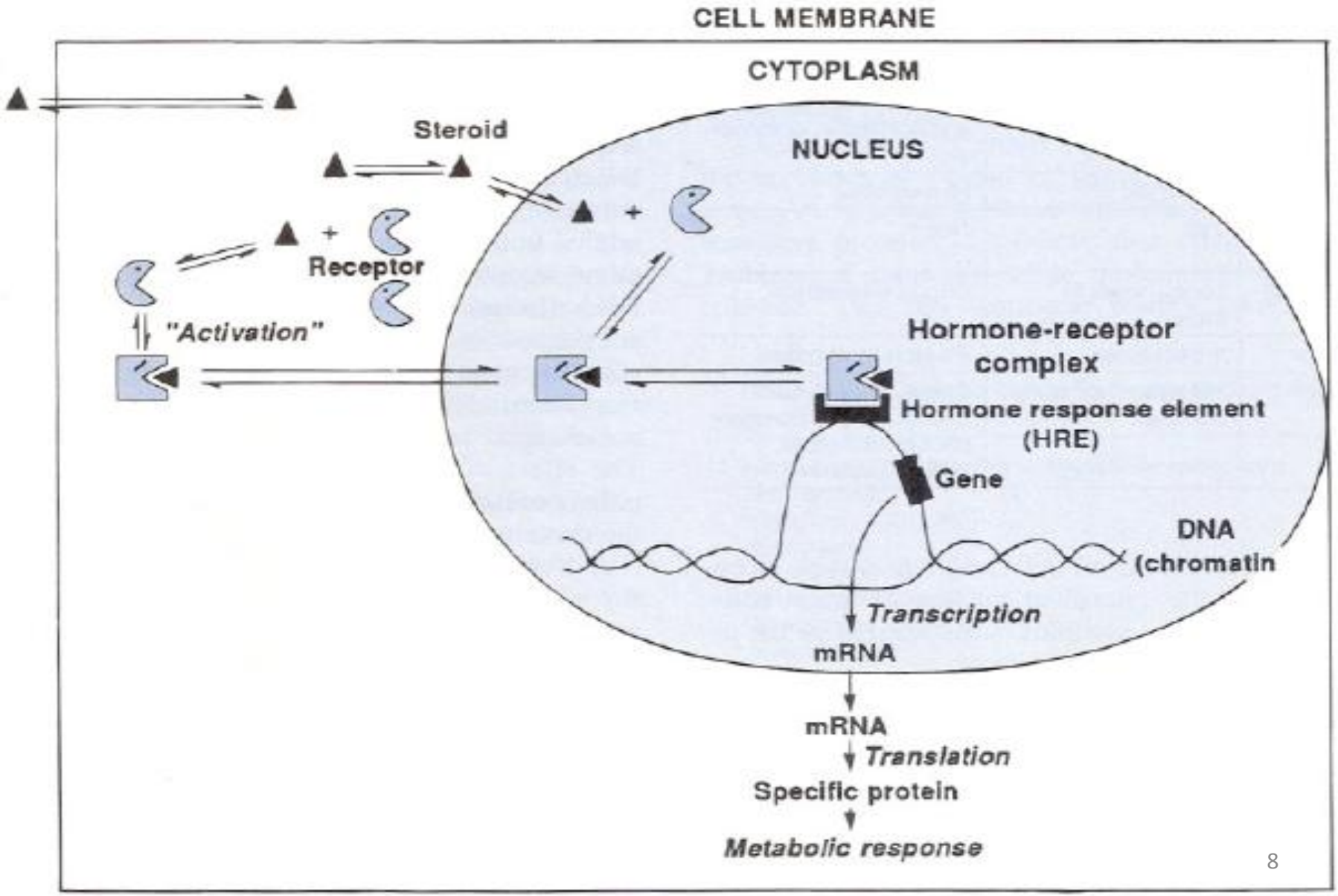
What is the general mode of action of steroid hormones?

- Free Fractions of Steroid hormones can pass through cell membrane in target tissues and bind to Intracellular receptors, forming **Steroid Hormone-Receptor Complex**,
- The Complex exerts its action on Nucleus of Target cells,
- Steroid Hormone-Receptor Complex binds to Specific Nucleotide Sequences on DNA of Responsive Genes,
  - Specific Nucleotide Sequences in DNA are called **Hormone Response Elements (HRE)**,
- Interaction of steroid hormone-receptor complexes with HRE in DNA leads to altered rates of Transcription of associated Genes in Target cells;

- Resulting in Transcription of the gene, to form Messenger RNA (m-RNA),
- Messenger RNA is released in Cytoplasm, interacts with Ribosome for Translation to occur,
- Translation leads to formation of Polypeptide chain,
- Polypeptide chain undergoes Post-translational modification in Golgi apparatus to form functional peptide or protein; **(Fig. 2)**

Fig 2: Schematic diagram, mode of action of steroid hormones

(Harper's Biochem, 24th Ed , 1996)



How does SHBG affect plasma levels of Sex Steroid Hormones?

- Testosterone and Estradiol circulate in blood plasma mostly bound to **Sex Hormone Binding Globulin (SHBG)**;
- SHBG has **higher affinity** for Testosterone than Estradiol,
- **Testosterone inhibits SHBG** synthesis in the liver,
- **Estradiol stimulates SHBG synthesis in** the liver,
- SHBG levels in females is about twice that in males,
- Factors that alter the concentrations of SHBG in blood plasma alter the Ratio of Free Testosterone to Free Estradiol,

- In both sexes the effect of:
  - An increase in SHBG level in blood plasma is to increase Estradiol-like effects, (**Why?**)
  - A decrease in SHBG level in blood plasma is to increase Androgen effects (**Why?)**

- As Estradiol itself increases SHBG level in blood plasma and Testosterone decreases it, the system functions as a Biological Servomechanism;

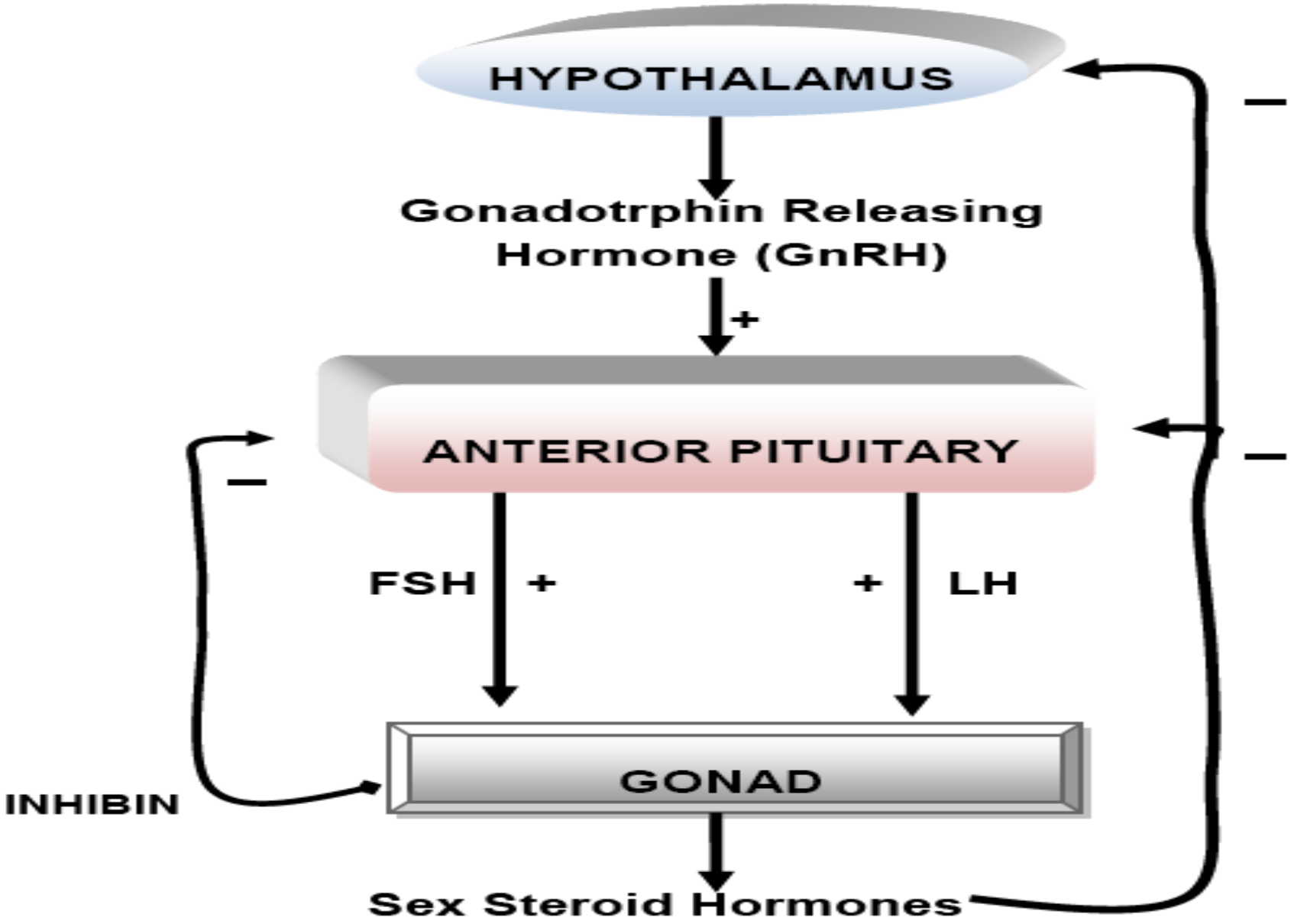
- Testosterone and SHBG concentrations in plasma are sometimes reported by laboratory as a Ratio **Free Androgen Index (FAI)**, which gives a clearer indication of Androgen status than does plasma Testosterone alone;

$$\text{FAI} = \frac{[\text{Total Testosterone}]}{[\text{SHBG}]}$$

What axis regulates secretion of sex steroid hormones?

- Regulation of secretion of sex steroids is by Negative Feedback mechanism on **HPG –Axis (Fig 3)**
  - **HPG-Axis:** Hypothalamic-Pituitary-Gonadal Axis;
- Hypothalamus releases **Gonadotrophin-Releasing Hormone (GnRH)**, which acts on Anterior Pituitary to produce **Gonadotrophins**:
  - **Luteinizing Hormone (LH),**
  - **Follicle-Stimulating Hormone (FSH)**
- Gonadotrophins act on Ovaries in females or Testes in males to stimulate Sex Hormone secretion,
- **Inhibin** from Gonads feedback inhibits FSH secretion;
- Sex steroid feedback inhibit LH secretion;

Fig. 3: Hypothalamus –Pituitary-Gonad Axis,
Negative Feedback regulation of secretion of Sex steroids



What axis regulates secretion of Testosterone in males?

- Regulation of secretion of Testosterone in males is by Negative Feedback mechanism of the **HPT-Axis**;
  - **HPT- Axis**: Hypothalamic-Pituitary-Testicular axis;
- Hypothalamus releases GnRH, which acts on Anterior Pituitary to produce Gonadotrophins:
  - **Follicle-Stimulating Hormone (FSH),**
  - **Luteinizing Hormone (LH),**
- FSH & LH act cooperatively on Testes to stimulate secretion of Testosterone;
- **Fig. 1: Schematic diagram of HPT-Axis**

Fig. 1a: Hypothalamus –Pituitary-Testicular Axis, for Feedback regulation of secretion of Testosterone

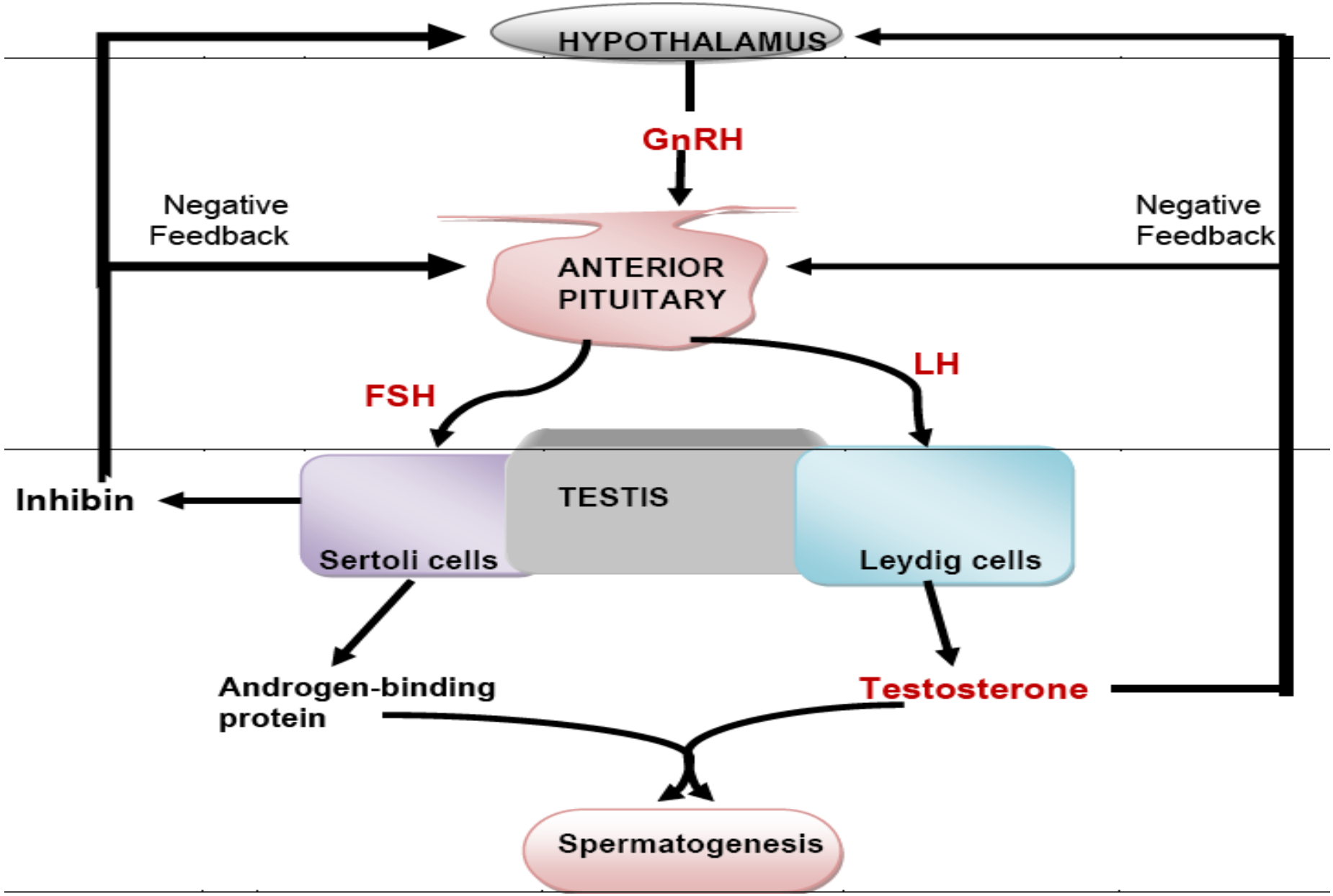
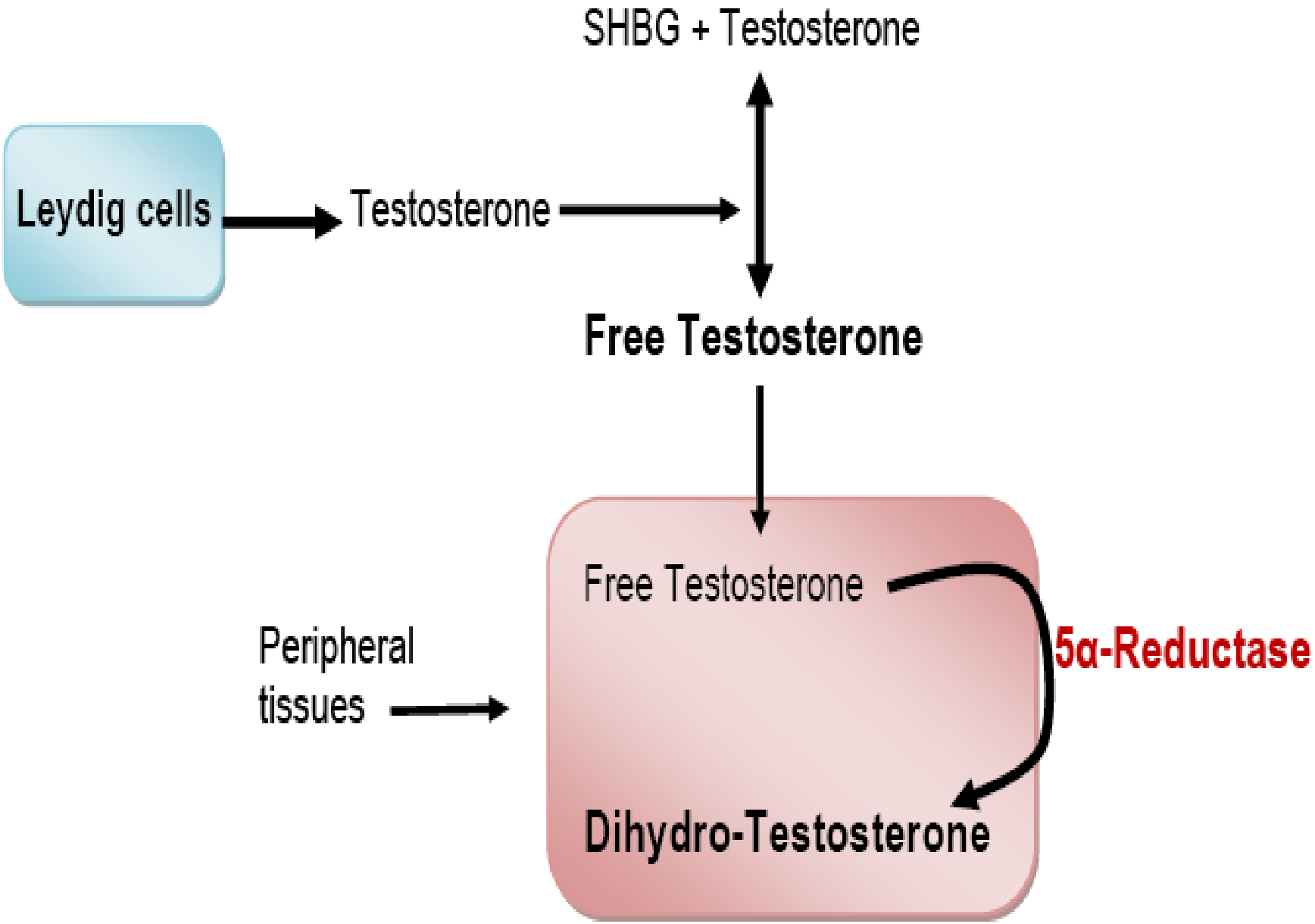


Fig 1b: Conversion of Free Testosterone to Dihydrotestosterone



What are the general functions of male gonads?

- Testes secrete Testosterone and produces Spermatozoa;
- LH acts of Leydig cells for secretion of Testosterone;
- FSH influences Sertoli cell function; (**Fig. 1a**);
- Testosterone is responsible for:
  - Growth and function of Prostate and Epididymis,
  - Development of male secondary sex characteristics (hair growth, deep voice and characteristic musculature)
- Biological activity of Testosterone is due to its conversion to **Dihydrotestosterone** by **5-alpha-Reductase** in some tissues (**Fig. 1b**);

What are some of the disorders of male sex hormones?

- Hypogonadism may result in deficient sperm production and decreased testosterone secretion;
- Hypogonadism may be caused by:
  - Testicular deficiency (Primary disorders, or **Hypergonadotrophic Hypogonadism**),
  - Defect in Hypothalamus or Pituitary (Secondary disorders or **Hypogonadotrophic Hypogonadism**)
- FSH & LH or LH may be absent in Hypogonadotrophic Hypogonadism,
- Generalized failure of Pituitary function may occur;

What are some of the causes of Primary Hypogonadism?

- Some caused of Primary Hypogonadism:
  - Congenital defects, such as, Klinefelter's syndrome or Testicular Agenesis;
  - Acquired defects due to Testicular Infections (e.g., Mumps),
  - Trauma,
  - Irradiation, or
  - Cytotoxic drugs

What are some of the causes of Secondary Hypogonadism?

- Secondary Hypogonadism may be due to:
  - Pituitary tumours
  - Hypothalamic disorders such as Kallmann's syndrome;

- **What is the test to establish Hypogonadism?**
  - Dynamic tests, such as:
    - Stimulation with GnRH may help to establish the cause of Hypogonadism in some patients

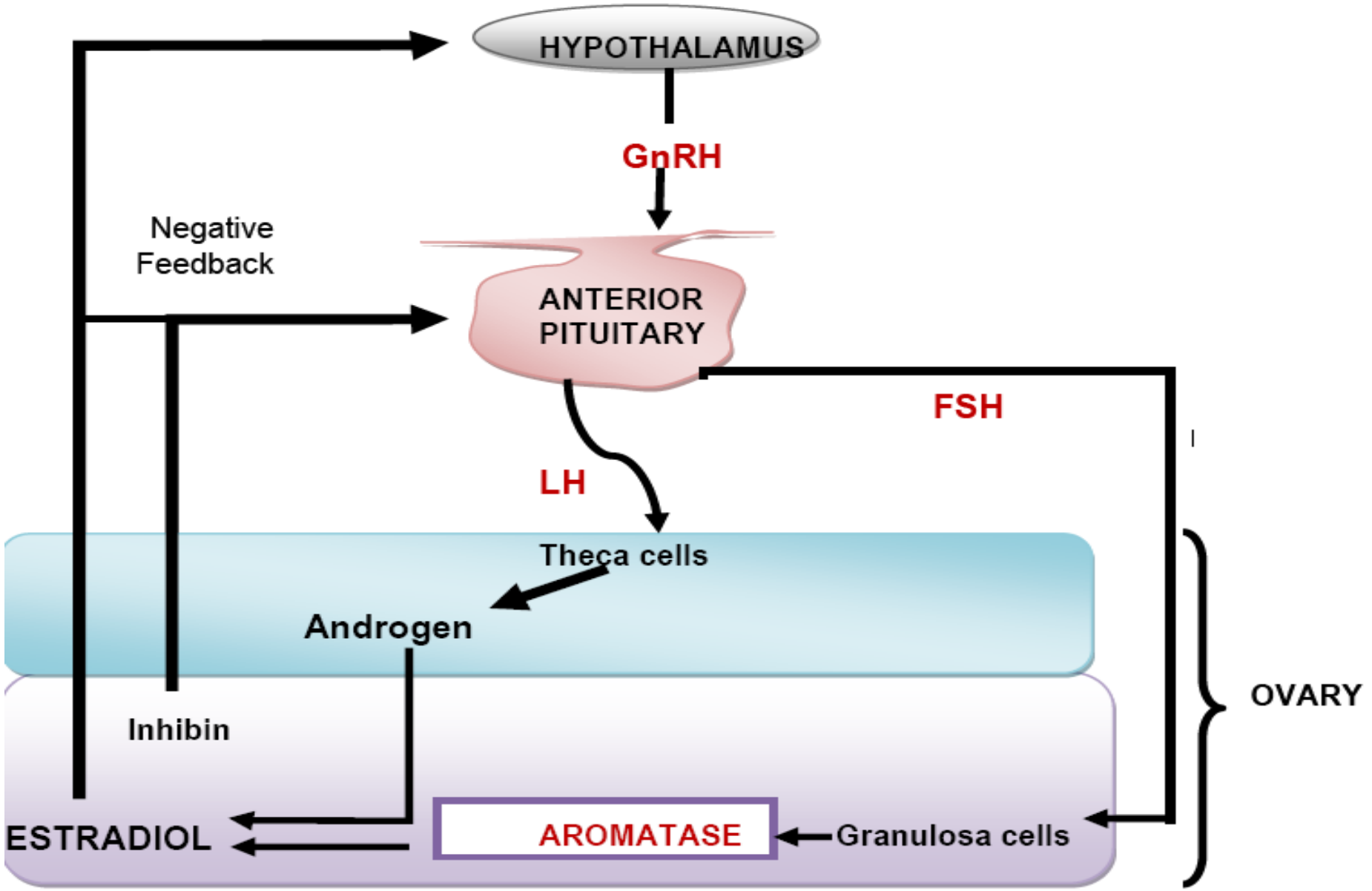
What are some of the disorders of male sexual differentiation?

- Disorders of male sexual differentiation are rare,
- Testosterone production may be impaired;
- In Testicular Feminization syndrome, Androgen receptors are inactive and target tissues cannot respond to stimulation by circulating Testosterone

What axis regulates secretion of Estradiol?

- Regulation of secretion of Estradiol in the female is by Negative Feedback mechanism of the **HPO-Axis**;
  - **HPO-Axis**: Hypothalamic-Pituitary- Ovarian Axis
- Hypothalamus releases GnRH, which acts on Anterior Pituitary to produce Gonadotrophins:
  - **Follicle-Stimulating Hormone (FSH),**
  - **Luteinizing Hormone (LH),**
- FSH & LH act cooperatively on Ovaries to stimulate secretion of Estradiol;
- **Fig. 2: Schematic diagram of HPO-Axis**

Fig. 2: Hypothalamus –Pituitary-Ovarian- Axis, for Feedback regulation of secretion of Estradiol



What are some functions of female sex hormone?

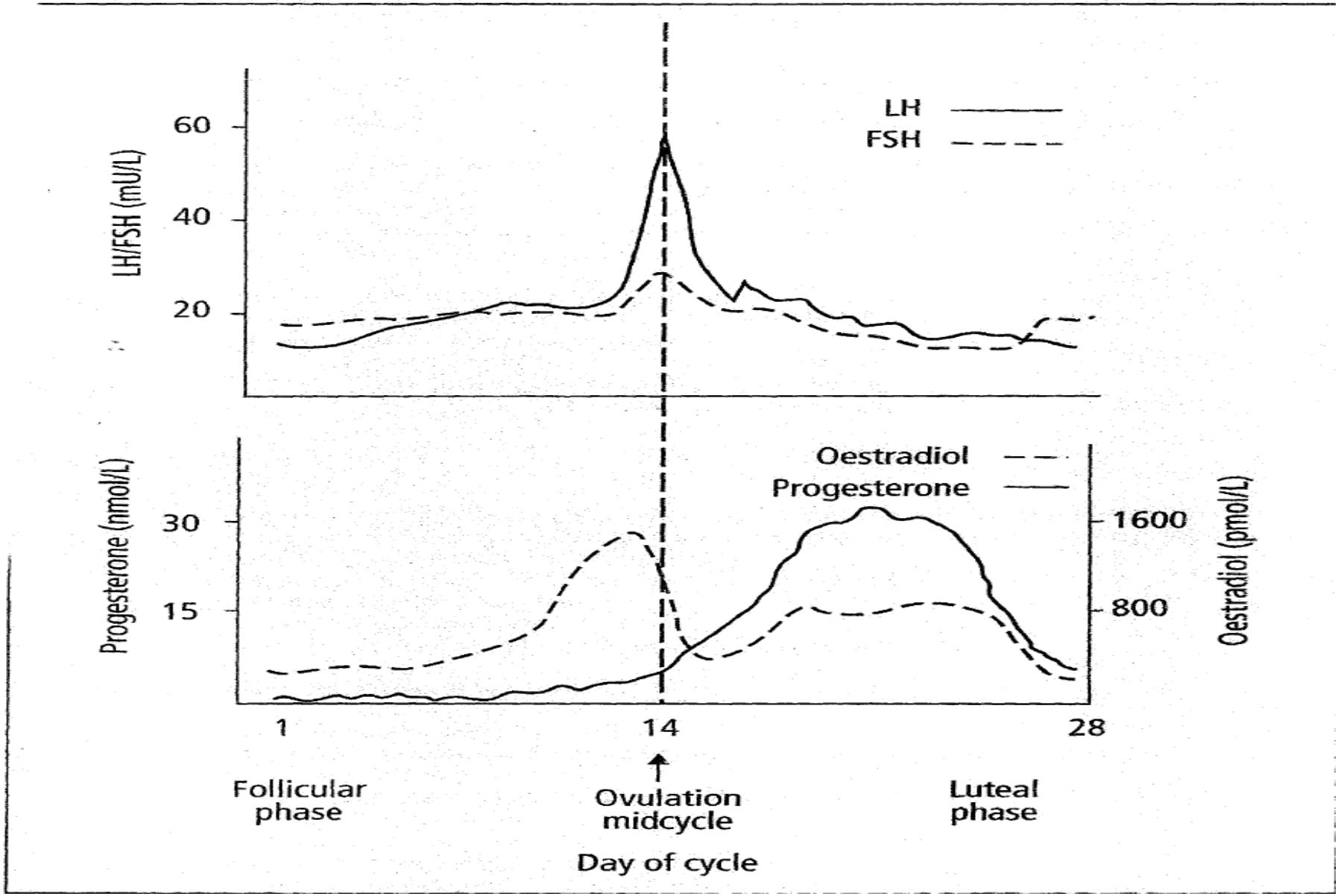
- Some functions of Estradiol:
  - Responsible for Female secondary characteristics;
  - Stimulation of follicular growth,
  - Development of the Endometrium;
- **TAKE NOTE**:
  - Estradiol secretion is low before puberty,
  - At puberty, Estradiol secretion rises rapidly and fluctuate cyclically throughout reproductive life,
  - After Menopause, plasma Estradiol level falls despite high circulating levels of Gonadotrophins;

What hormones influence the menstrual cycle?

- Menstrual cycle is influences by cyclic variations of hormones produced by:
  - Hypothalamus (**Gn-RH**),
  - Anterior Pituitary (**FSH & LH**),
  - Ovary (**Estradiol** and **Progesterone**);
- **Figs 3a** shows changes in plasma levels of FSH, LH, Estradiol and Progesterone in normal menstrual cycle;
- Developing Graafian follicles in Ovaries respond to cyclical stimulus of Gonadotrophins by secreting Estradiol-17β and Estrone;
- Both are metabolized to a third Estrogen called Estriol;

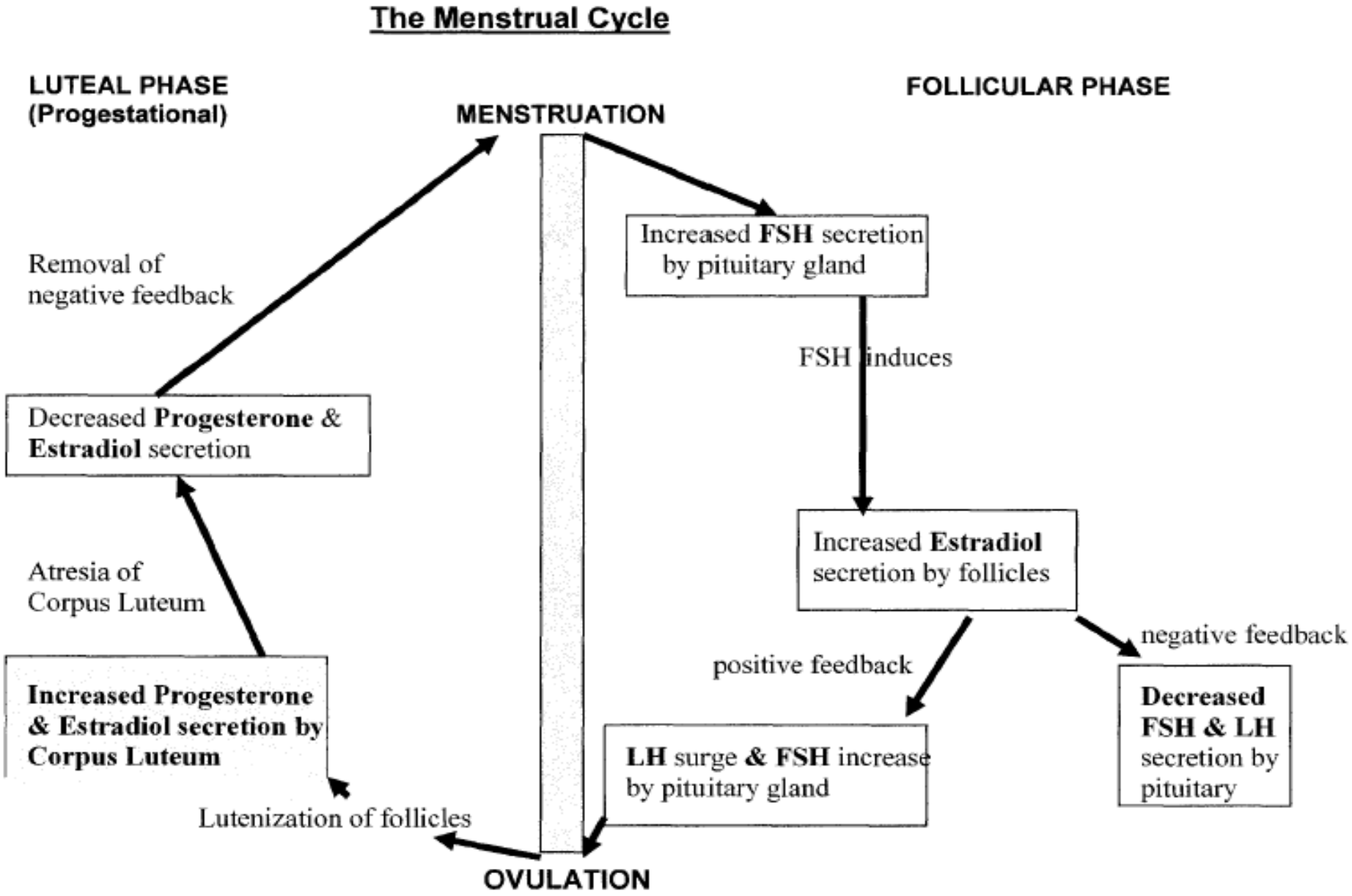
Fig. 3a: Hormonal changes in the menstrual cycle

(Clinical Biochem 7th Ed, 2008)



- After Ovulation, Corpus Luteum secretes Progesterone and Estrogens;
- Changes in Uterus are due to levels of Ovarian Steroids,
  - Changes are modified if pregnancy occurs,
- Progesterone acts on Uterus, which is essential for maintenance of early pregnancy,
- Estradiol-17β may stimulate or inhibit secretion of Gonadotrophins, depending on its level in plasma;
  - Stimulating effect of Estradiol-17β can be prevented by high plasma levels of Progesterone; (**Fig. 3b**)

Fig. 3b: Hormonal changes in Menstrual cycle showing positive and negative feedback effects of Estradiol



What are some disorders of Female Sex Hormones?

- Some disorders include:
  - **Sub-fertility,**
  - **Amenorrhea,**
  - **Oligomenorrhoea**;
  - **Hirsutism**:
    - Increase body hair, with male pattern distribution,
    - In most cases it is genetic in origin and benign,
    - May be due to Polycystic Ovarian Syndrome (PCOS),

- **Virilism**:
  - Although uncommon it is a sign of serious disease;
  - Testosterone levels are usually elevated, thus evidence of excessive Androgen action may occur:
    - Clitoral enlargement,
    - Hair growth in a male pattern,
    - Deepening of the voice,
    - Breast atrophy;
- Tumors of ovary or of Adrenal are the likely cause;

- **Oligomenorrhoea and Amenorrhoea**:
- Women with Oligomenorrhoea or Amenorrhoea may present because of their concerns:
  - Bleeding pattern,
  - Infertility,
  - Hirsutism,
  - Virilism, or a combination of these;
- Need to exclude the following as possible cause:
  - Physiological causes of Amenorrhoea:
    - Pregnancy, Lactation,
  - Anatomical abnormalities;

- Amenorrhoea may be:
  - Primary (i.e., patient has never menstruated), abnormal development may be likely cause,
  - Secondary to various causes as in **Table below**
- **TABLE**:
  - Summary of some endocrine causes of infertility that may have to be considered, especially if there are menstrual abnormalities;

Site of Lesion	Examples:
Hypothalamus	▫ Anorexia Nervosa, ▫ Severe weight loss, ▫ Stress (Psychological and/or Physical), ▫ Gn-RH deficiency (Kallmann's syndrome), ▫ Tumours (e.g., acromegaly)
Anterior Pituitary	▫ Hyper-prolactinaemia, ▫ Hypopitutarism, ▫ Functional tumours (e.g., Cushing's disease), ▫ Isolated deficiency of FSH or of LH
Ovaries	▫ Polycystic ovary syndrome, ▫ Ovarian failure (auto-immune, chromosomal, iatrogenic i.e., after cancer therapy, or idiopathic), ▫ Ovarian tumours
Receptor defect	▫ Testicular feminization syndrome
Other endocrine diseases	▫ Diabetes Mellitus, ▫ Thyrotoxicosis, ▫ Adrenal dysfunction (e.g., late-onset CAH)

What suggested laboratory tests can assist in diagnosis?

- Suggested Lab tests for diagnosis:
  - Measure plasma levels of hormones that can affect the HPO-axis:
    - **FSH, LH,**
    - **Estradiol-17β,**
    - **Prolactin,**
    - **TSH and FT4;**
  - If Hirsutism or Virilisation is present, measure plasma (This is referred to as the **Androgen screen**):
    - **Testosterone,**
    - **Androstenedione,**
    - **Dehydroepiandrosterone Sulphate (DHAS);**

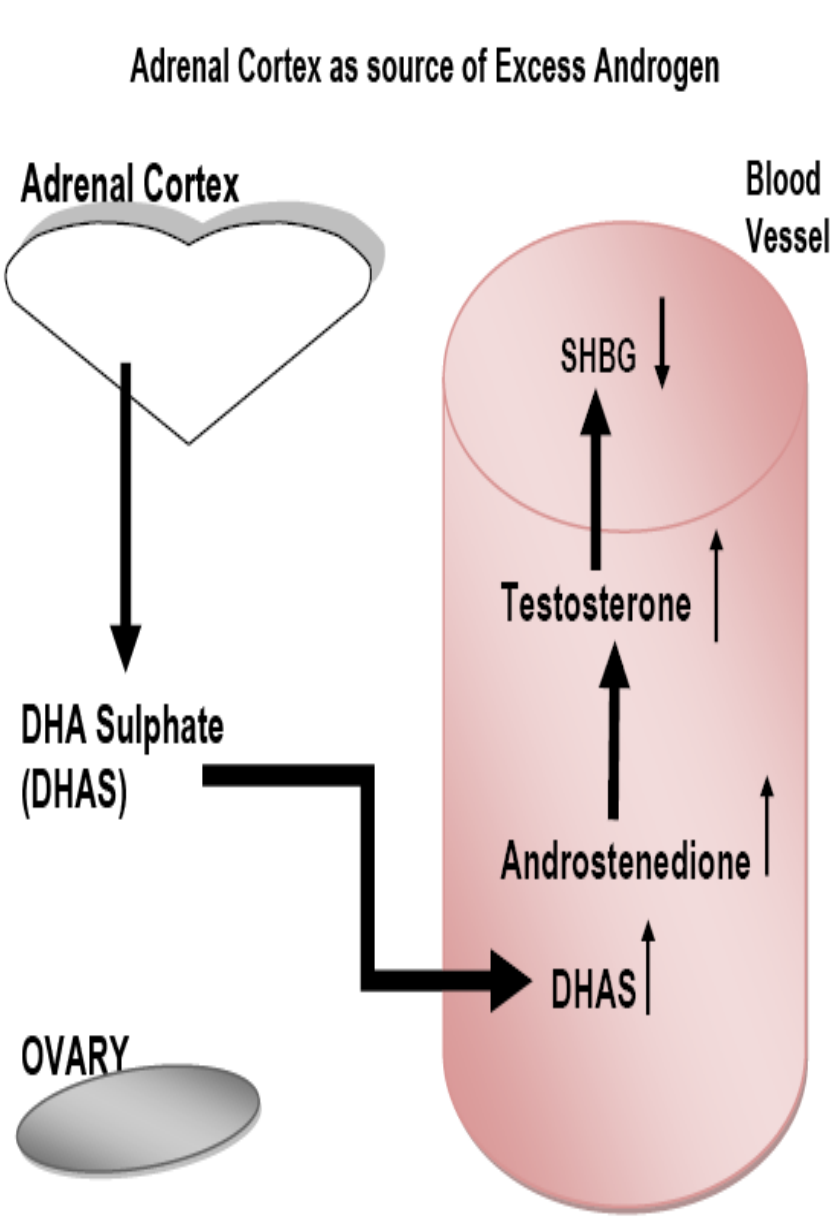
Why carry out the Androgen Screen in female?

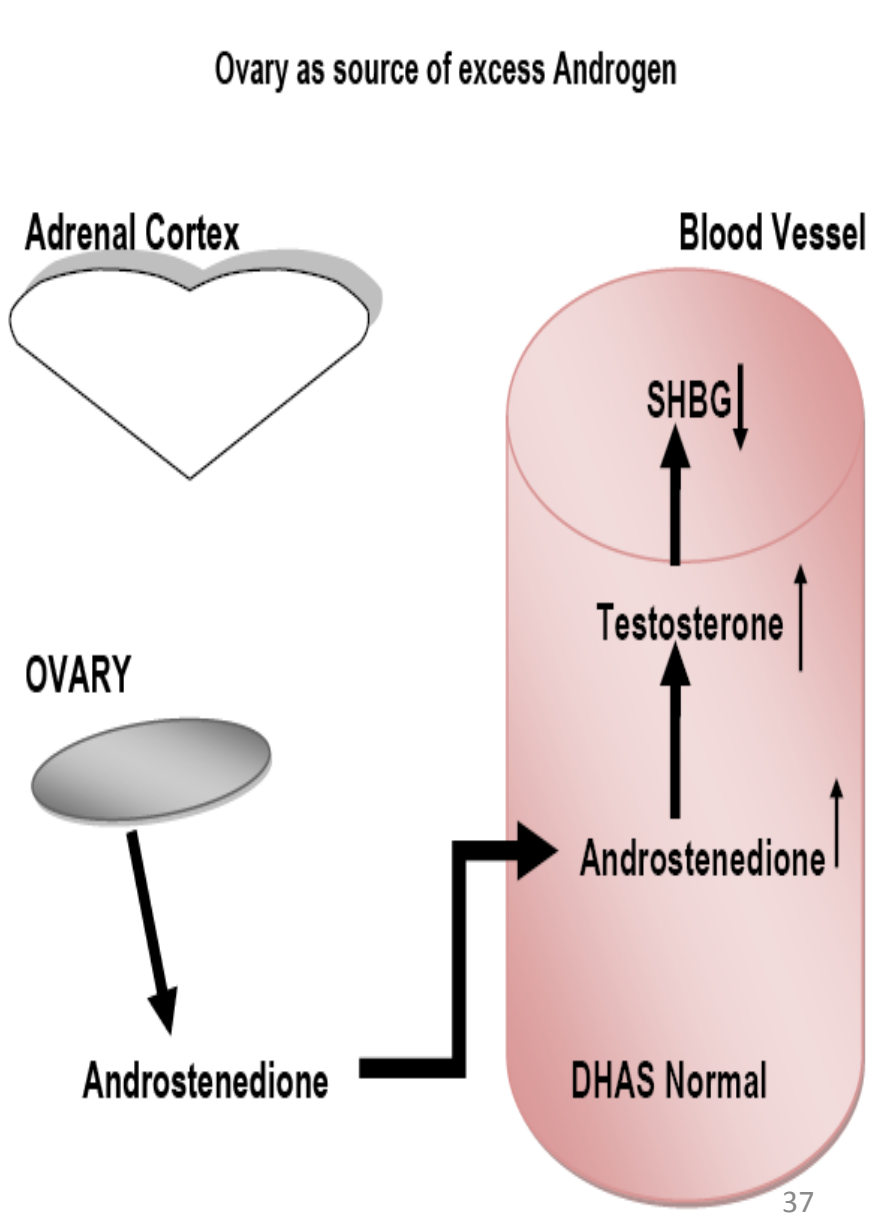
- Observation of elevated Testosterone in a female should always be investigated further;
- Decrease in plasma level of SHBG is evidence of elevated Androgen, because Testosterone inhibits SHBG synthesis in the liver;
- It may not be immediately apparent whether the source of Testosterone is the Ovary or the Adrenal Cortex;
- "**Androgen Screen**" is used to establish the source of the Testosterone;

- Androgen Screen is carried out by measuring the levels of other Androgens in plasma, such as:
  - **Dehydroepiandrosterone Sulfate (DHAS), and**
  - **Androstenedione;**
- Schematic representation of Androgen Screen is presented in **Figs. 4a & 4b**;

Androgen Screen: Fig 4a

Fig. 4b





How is Androgen Screen test interpreted?

- If **DHA Sulfate** and **Androstenedione** are elevated, it suggests that:
  - **Adrenal gland** is overproducing Androgens;

- If **DHS Sulfate** is normal but **Androstenedione** is elevated, it suggests that:
  - **Ovary** is overproducing Androgen;

Endocrine Investigation in the Sub-fertile Female

- Investigation of Infertile Female depends on Phase of Menstrual Cycle;

If there is a **Regular Menstrual Cycle**:

  - Progesterone should be measured in the middle of the Luteal Phase (day 21);
- If Progesterone is high (> 30 nmol/L):
  - Patient has ovulated and there is no need for further Endocrine Investigation;
- Other causes of subfertility should be sought;
- If Progesterone is low (< 10 nmol/L), ovulation has not occurred;

- For females with **Irregular or Absent Menstruation** (**Oligomenorrhoea or Amenorrhea**) or who are not ovulating, hormone measurements may be diagnostic;
- Established lab protocols for Investigation can be used;
- Measurement of Estradiol and Gonadotrophin levels in plasma may detect:
  - Primary Ovarian Failure, or
  - Polycystic Ovarian Syndrome;
- Measurement of Prolactin, and Androgens may assist;

What are some of the Endocrine causes of Subfertility in females?

- **Primary Ovarian Failure**:
  - **Hypergonadotrophic – Hypogonadism**: Indicated by elevated plasma levels of FSH & LH and Low level of Estradiol (Post-Menopausal Pattern);
  - Hormone replacement therapy assists libido and prevents Osteoporosis, but may not restore fertility,
- **Hypogonadotrophic – Hypogonadism**:
  - Subnormal plasma levels of FSH, LH and Estradiol, suggests presence of Hypothalamic-Pituitary lesion;
  - Mechanisms for Amenorrhea or Oligomenorrhoea in female with normal plasma levels of FSH, LH and Estradiol are not fully understood;

- **Polycystic Ovarian Syndrome**:
  - Indicated by elevated LH and normal FSH in plasma
  - Estradiol measurements are often unhelpful,
  - Hirsutism, a feature of this condition, is associated with raised Testosterone and subnormal plasma level of SHBG;

- **Hyperprolactinaemia**:
  - Prolactin acts on mammary glands to control lactation,
  - Gonadal function is impaired by elevated plasma levels of Prolactin;
  - Hyperprolactinaemia causes Infertility in both sexes;
  - An early indication in women is Amenorrhea and Galactorrhoea;
- **Some causes of Hyperprolactinaemia**:
  - Stress;
  - Drugs (e.g. Estrogens, Phenothiazines, α-Methyl Dopa)
  - Primary Hypothyroidism (TRH can stimulate Prolactin);
  - Pituitary diseases;

STUDY QUESTIONS

- What are steroid hormones?
- How do steroid hormones exist in plasma?
- What is the general mode of action of steroid hormones?
- What are the Sex Steroid Hormones?
- What is the function of SHBG?
- How does SHBG affect plasma levels of Sex Steroid hormones?
- Why does increase in SHBG causes increase in Estradiol-like effects?
- Why does decrease in SHBG causes increase in Androgen effects?
- What Axis Regulates Secretion of the Sex Steroid Hormones?
- What are the functions of the Female Sex Hormone?
- What are some of the disorders of the Female Sex Hormone?
- Briefly describe the Androgen Screen and interpretation of the results.
- Briefly describe endocrine Investigation in a sub fertile female.
- What are some of the endocrine causes of sub-fertility in the female?

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