

SEX STEROID HORMONES II: An Overview

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What axis regulates secretion of sex steroids in male & female?

- Regulation of secretion of sex steroids in male and female is by Negative Feedback mechanism;
- Males: **HPT-Axis**: Hypothalamic-Pituitary-Testicular axis;
- Females: **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 Testes in males and Ovaries in females to stimulate Sex Hormone secretion;
- **Fig. 1: Schematic diagram of HPT-Axis**
- **Fig. 2: Schematic diagram of HPO-Axis**

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

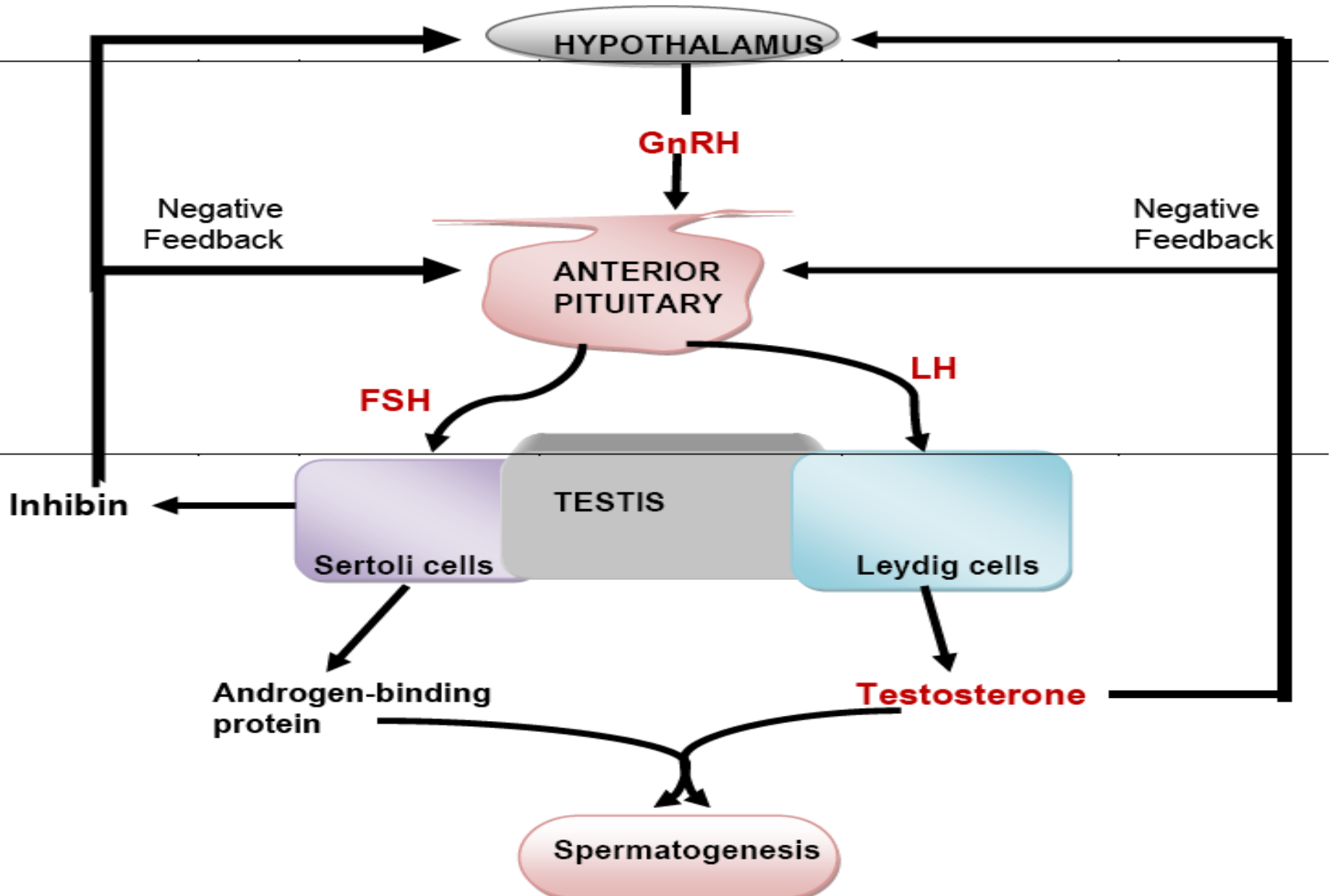


Fig 1b: Conversion of Free Testosterone to Dihydrotestosterone

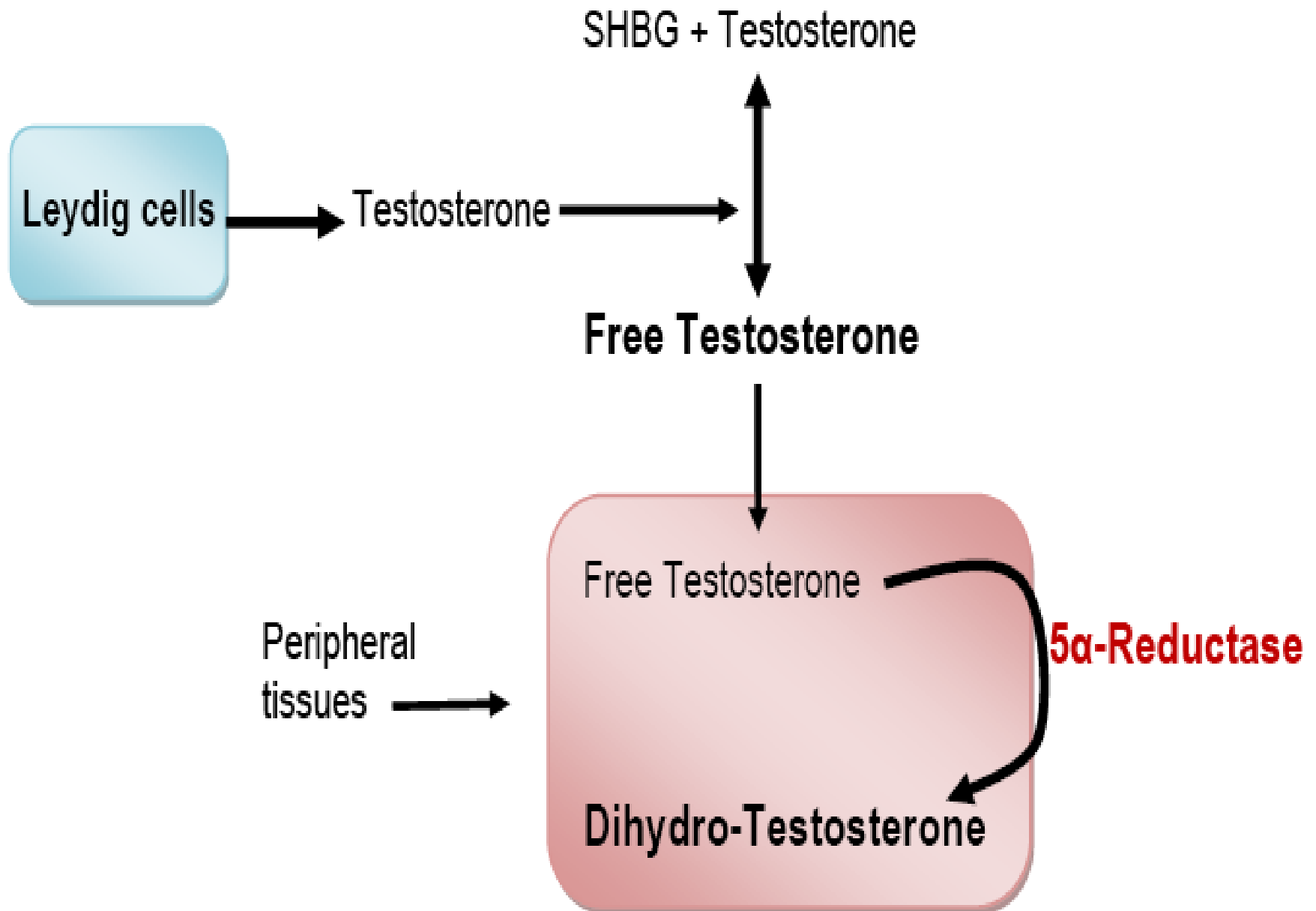
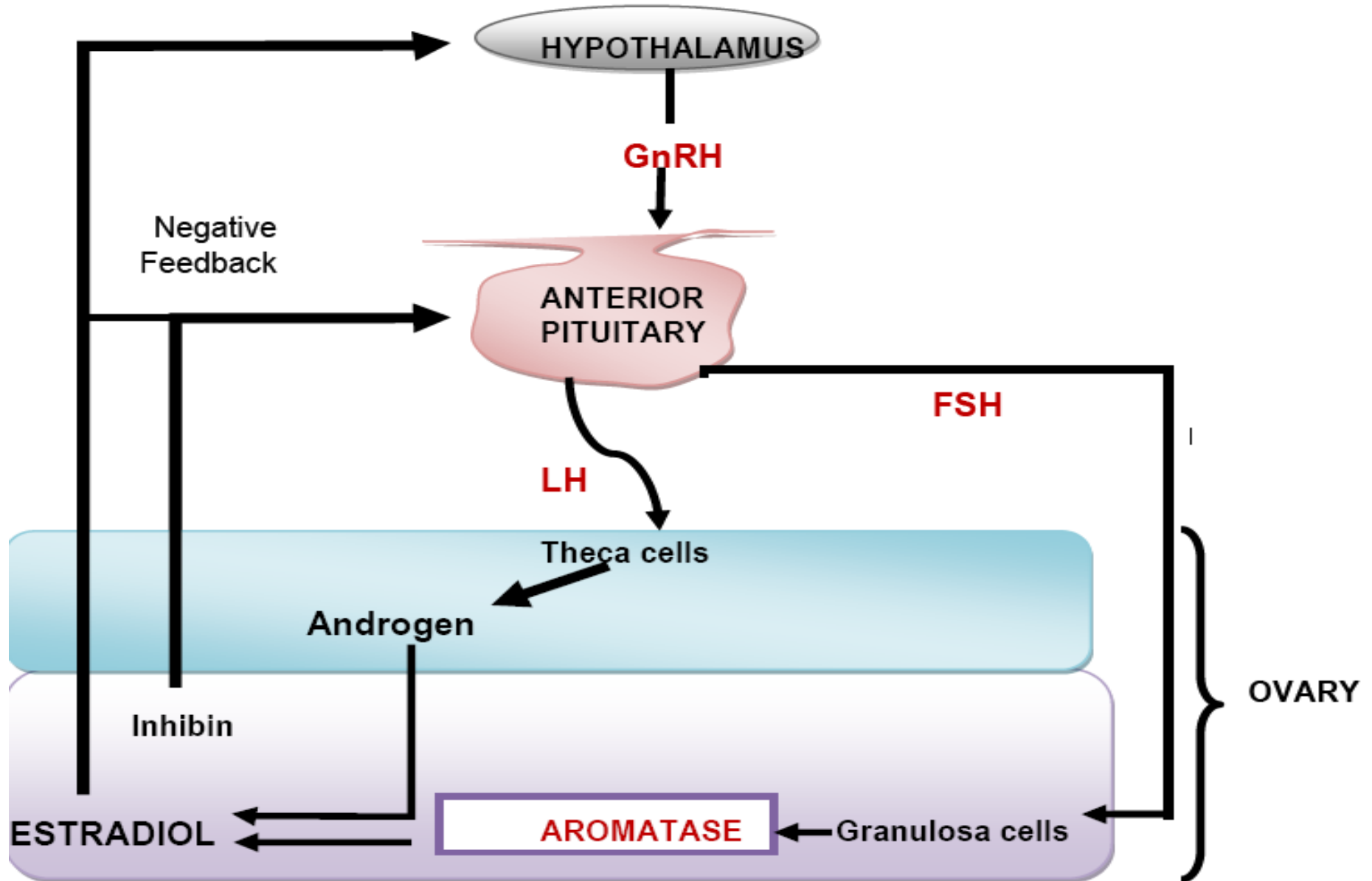


Fig. 2: Hypothalamus –Pituitary-Ovarian- Axis, for Feedback regulation of secretion of Estradiol



What are the 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 are some functions of female sex hormone?

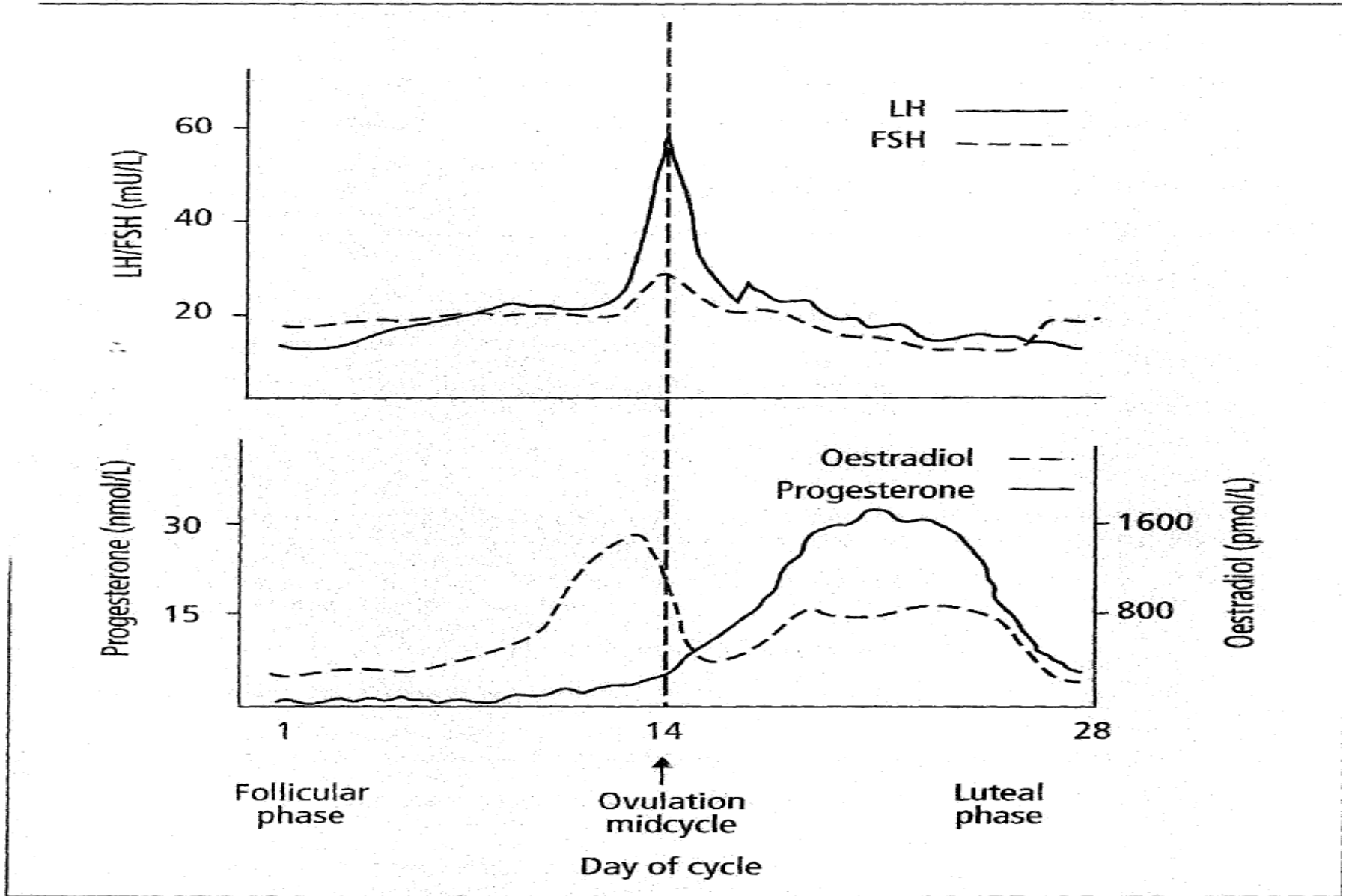
- Some functions of Estradiol:
 - Responsible for Female secondary characteristics;
 - Stimulation of follicular growth,
 - Development of the Endometrium;
- **TAKE NOTE:**
 - Estradiol secretion is low before puberty,
 - At puberty, Estradiol secretion rises rapidly and fluctuate cyclically throughout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

What hormones influence the menstrual cycle?

- Menstrual cycle is influenced 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-17 β and Estrone;
- Both are metabolized to a third Estrogen called Estriol;

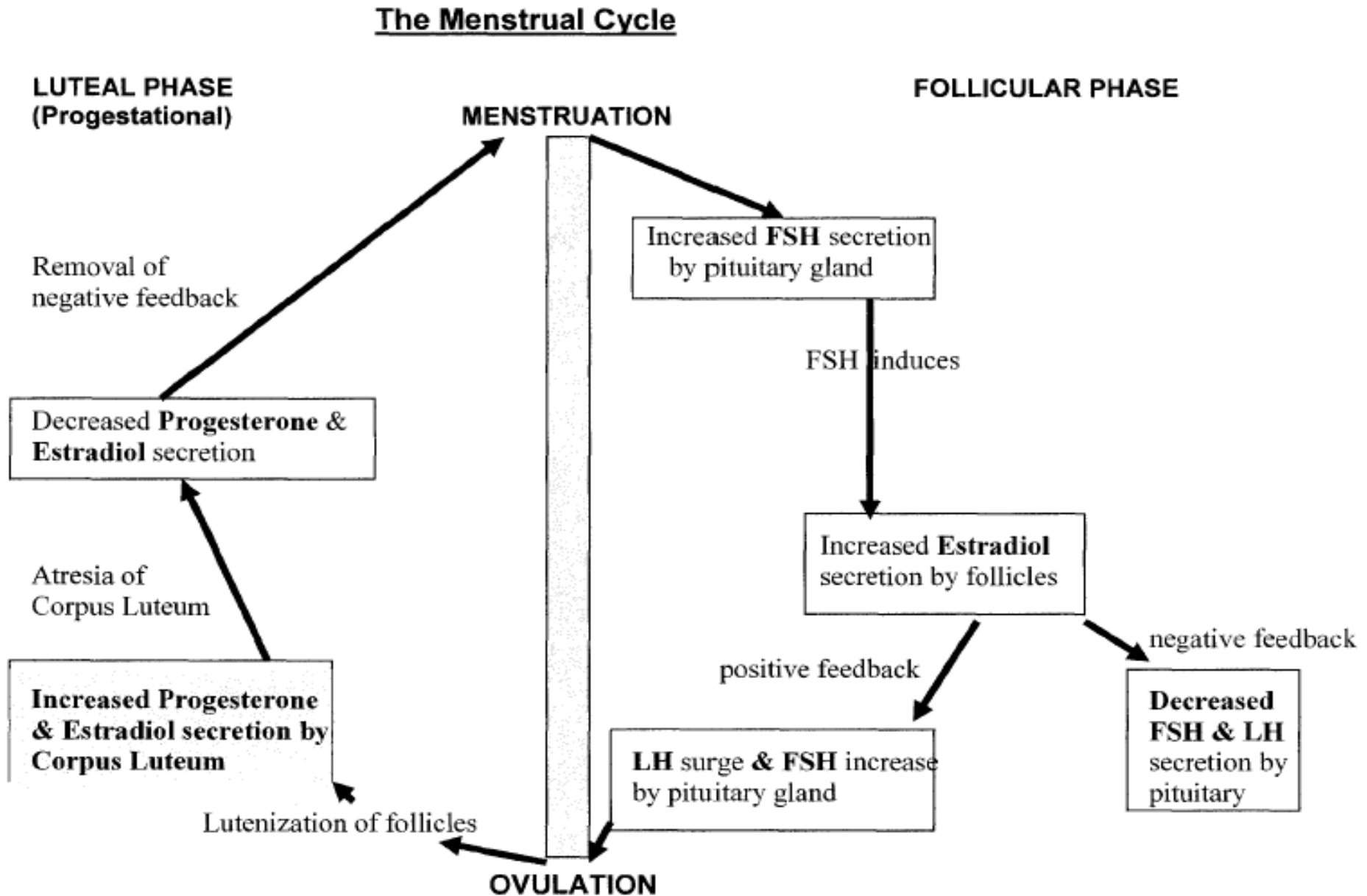
Fig. 3a: Hormonal changes in the menstrual cycle

(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-17 β may stimulate or inhibit secretion of Gonadotrophins, depending on its level in plasma;
 - Stimulating effect of Estradiol-17 β 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	<ul style="list-style-type: none"> □ Anorexia Nervosa, □ Severe weight loss, □ Stress (Psychological and/or Physical), □ Gn-RH deficiency (Kallmann's syndrome), □ Tumours (e.g., acromegaly)
Anterior Pituitary	<ul style="list-style-type: none"> □ Hyper-prolactinaemia, □ Hypopituitarism, □ Functional tumours (e.g., Cushing's disease), □ Isolated deficiency of FSH or of LH
Ovaries	<ul style="list-style-type: none"> □ Polycystic ovary syndrome, □ Ovarian failure (auto-immune, chromosomal, iatrogenic i.e., after cancer therapy, or idiopathic), □ Ovarian tumours
Receptor defect	<ul style="list-style-type: none"> □ Testicular feminization syndrome
Other endocrine diseases	<ul style="list-style-type: none"> □ Diabetes Mellitus, □ Thyrotoxicosis, □ Adrenal dysfunction (e.g., late-onset CAH)₂₀

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-17 β ,**
 - **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

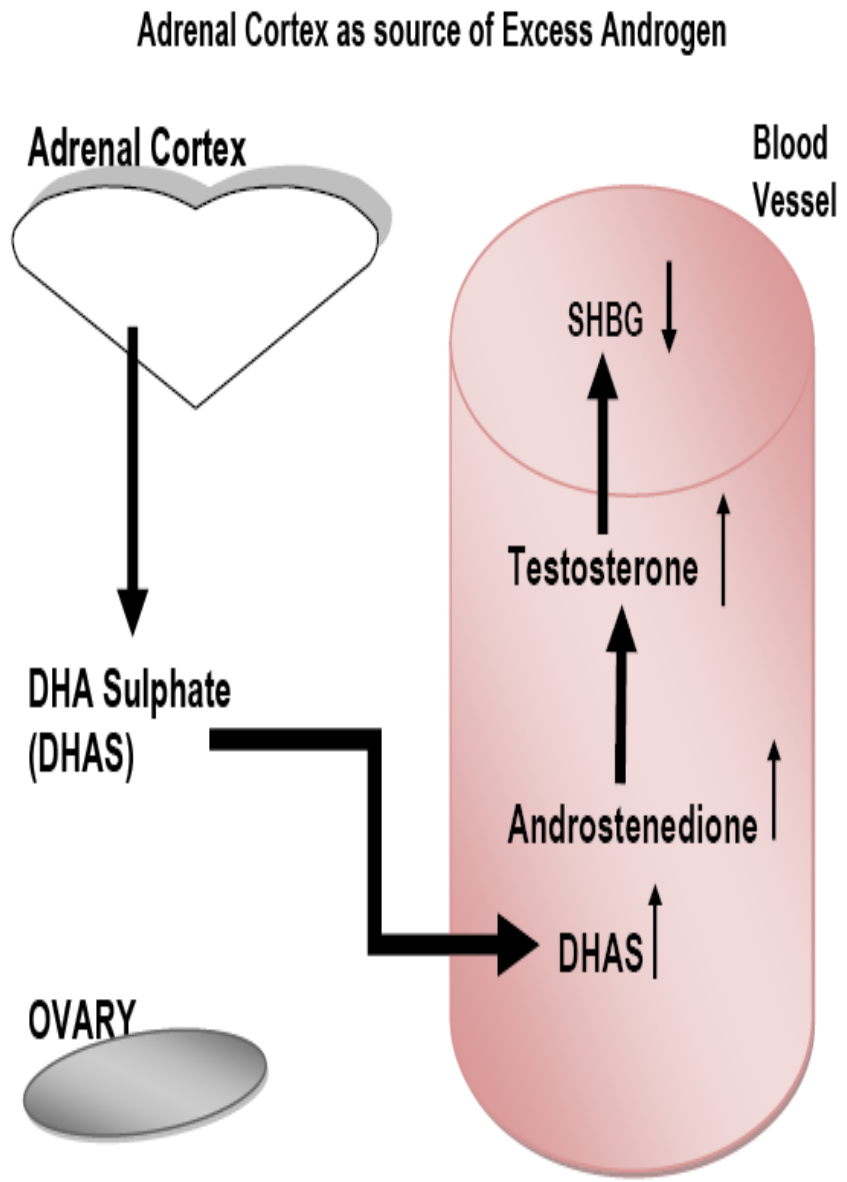
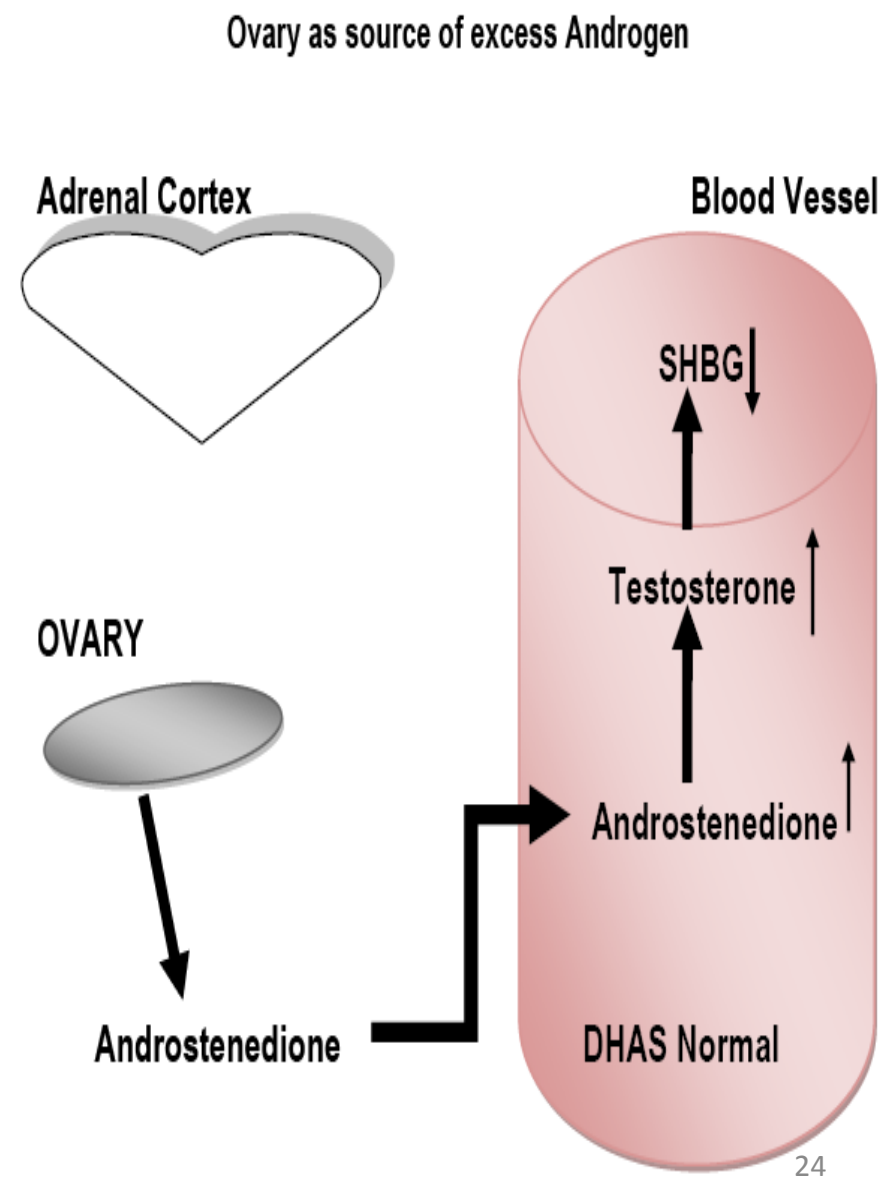


Fig. 4b



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 Amenorrhoea)** 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;

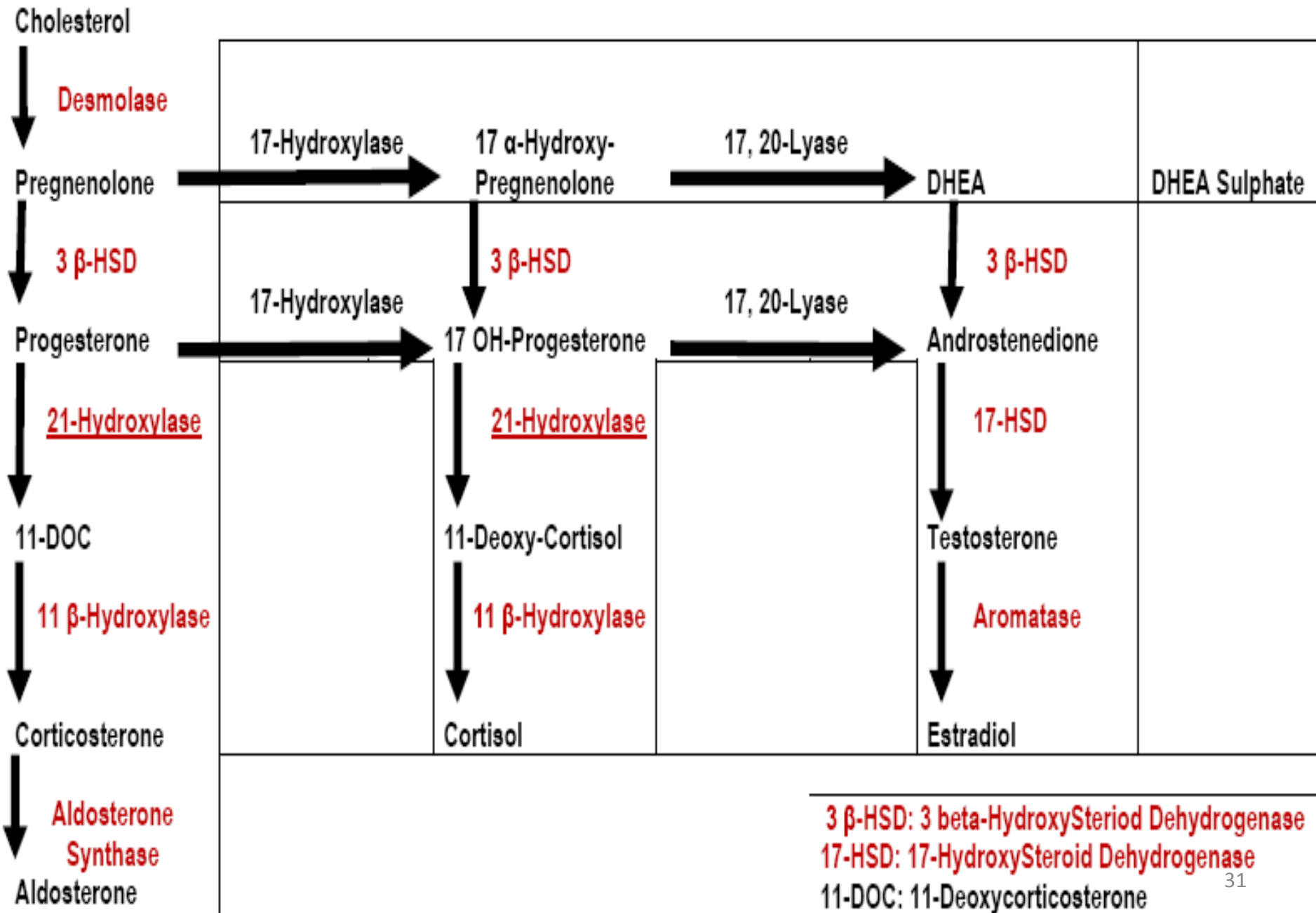
What are some of the Endocrine causes of Subfertility in females?

- **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 Amenorrhoea and Galactorrhoea;
- **Some causes of Hyperprolactinaemia:**
 - Stress;
 - Drugs (e.g. Estrogens, Phenothiazines, α -Methyl Dopa)
 - Primary Hypothyroidism (TRH can stimulate Prolactin);
 - Pituitary diseases;

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



REFERENCES

- Textbook of Biochemistry with Clinical Correlations 4th Edition. Edited by Thomas M. Delvin. Chapter on Steroid Hormone.
- Harper's Illustrated Biochemistry 26th Edition; 2003; Ed. By R. K. Murray et. al.
- Biochemistry, By V. L. Davidson & D. B. Sittman. 3rd Edition.
- Hames BD, Hooper NM, JD Houghton; Instant Notes in Biochemistry, Bios Scientific Pub, Springer; UK.
- VJ Temple Biochemistry 1001: Review and Viva Voce Questions and Answers Approach; Sterling Publishers Private Limited, 2012, New Delhi-110 – 020.
- G Beckett, S Walker, P Rae, P Ashby, Lecture Notes: Clinical Biochemistry 7th Ed. 2008, Blackwell Publishing, Australia.
- WWW.postgradmed.com/ Which tests are appropriate for screening? By Stefan Hasinski, MD VOL 104 / NO 7 / JULY 1998 / POSTGRADUATE MEDICINE
- WWW.emedicine.com/emerg