University of Papua New Guinea
School of Medicine and Health Sciences
Division of Basic Medical Sciences
Discipline of Biochemistry and Molecular Biology

PBL SEMINAR: SEX HORMONES PART II – An overview

What are the functions of male gonads?

- Testes secrete Testosterone and produces Spermatozoa
- LH influences development of Leydig cells and their secretion of Testosterone
- FSH influences Sertoli cell function
- FSH and LH are required for stimulation and maintenance of Spermatogenesis (**Fig. 1**)
- 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.

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 and LH or only LH may be absent in Hypogonadotrophic Hypogonadism
- Generalized failure of Pituitary function may occur

What are some of the causes 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?

- 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 the functions of female sex hormone (Estradiol)?

- Estradiol:
  - Responsible for Female secondary sex characteristics
  - Stimulation of follicular growth
  - Development of the Endometrium

What Axis is involved in regulation the female sex hormone?

- Hypothalamus-Anterior Pituitary Ovarian Axis (HPO-Axis) See **Fig. 2**

TAKE NOTE:

- Estradiol secretion is low before puberty,
- At puberty Estradiol secretion rise rapidly and fluctuate cyclically throughout reproductive life
- After Menopause, plasma Estradiol concentrations fall despite high circulating concentrations of Gonadotropins

What hormones influence the menstrual cycle?

- Menstrual cycle is influences by cyclic variations of hormones produced by Hypothalamus (Gn-RH), Anterior Pituitary (FSH & LH) and Ovary (Estradiol and Progesterone)
- **Figs 3a & 3b** shows changes in plasma concentrations 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 Oestrone;
  - Both are metabolized to a third Estrogen called Estriol
- After Ovulation, Corpus Luteum secretes Progesterone as well as Estrogens
- Changes in Uterus are determined by Ovarian Steroid output
  - Changes are modified if pregnancy occurs
- Progesterone acts on Uterus and is essential for maintenance of early pregnancy
- Estradiol-17β may stimulate or inhibit secretion of Gonadotrophins, depending on its concentration in plasma;
  - Stimulating effect of Estradiol-17β can be prevented by high plasma concentration of Progesterone

What are some of the disorders related to female sex hormones?

- **Subfertility**, **Amenorrhoea, Oligomenorrhoea**
- **Hirsutism**:
  - Increase in body hair with male pattern distribution
  - Majority of cases (termed idiopathic) it is genetic in origin and benign
  - Commonest pathological cause is Polycystic Ovarian Disease
  - Essential to exclude serious disease when investigating Hirsute women

- **Virilism**:
  - Testosterone concentrations are usually markedly elevated
  - Evidence of excessive Androgen action such as:
    - Clitoral Enlargement, Hair Growth in a male pattern, Deepening of Voice Breast Atrophy
  - Tumours of Ovary or Adrenal are the likely cause

Oligomenorrhoea and Amenorrhoea:

- Women with Oligomenorrhoea or Amenorrhoea may present because of concerns they have regarding their:
  - 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), thus abnormal development may be the likely cause, or
  - Secondary to various causes as listed in Table below

- Summary of some endocrine causes of infertility that may have to be considered, especially if there are menstrual abnormalities also

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 (may be 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?

- Measurement of plasma concentrations of hormones that affect HPO-axis
  - FSH, LH, Estradiol-17β, Prolactin, TSH, and FT4

- If Hirsutism or Virilization is present, measure:
  - Plasma Testosterone, Androstenedione and Dehydroepiandrosterone Sulphate (DHAS)

What is the Androgen Screen in Female and how is it interpreted?
(Fig. 4)

- Observation of Elevated Testosterone in a female must be Investigated further
- Androgen screen test is to identify the source of the Testosterone
- A decrease SHBG concentration is evidence of Elevated Androgen (**Why?**)
    - Because Testosterone inhibits synthesis of SHBG in the Liver
- Source of Testosterone may be either the Ovary or Adrenal Cortex
- By measuring concentration of other Androgens such as Androstenedione and DHA Sulphate (an "Androgen screen"), the source of Testosterone can be identified (**Fig. 4**)
- An elevated DHA sulphate suggests that Adrenal or an Adrenal tumor is overproducing Androgens
- If the Ovary is the source then only Androstenedione will be raised

<u>Endocrine Investigation in the Subfertile Female</u>: (**Fig. 5**)

- Investigation of Infertile female depends on Phase of Menstrual Cycle
- Female presenting with Regular Menstrual Cycle:
    - Measure Serum Progesterone in the Middle of Luteal Phase (day 21)
        - If Progesterone is High (> 30 nmol/L), Ovulated has occurred 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

- Female presenting with Irregular or Absent Menstruation (Oligomenorrhoea or Amenorrhoea) or who are not Ovulating,
    - Hormone measurements may be Diagnostic
    - Protocols for investigation are shown in **Figs. 5**, **6, 7, and 8**

- Measurement of Estradiol and Gonadotrophin concentrations may detect:
    - Primary Ovarian Failure or Polycystic Ovarian Disease

- Measurement of Prolactin, and Androgens may also assist

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

- **Primary Ovarian Failure**:
    - Indicated by elevated Gonadotropins and Low Estradiol concentration (a post-menopausal pattern)
    - Hormone replacement therapy assists libido and prevents osteoporosis, but does not restore fertility

- **Polycystic Ovarian Disease**:
    - Indicated by Elevated LH and normal FSH
    - Estradiol measurements are often unhelpful
    - Hirsutism, a feature of this condition, is associated with raised Testosterone and subnormal sex hormone binding protein concentrations

- **Hypogonadotrophic Hypogonadism**:
  - Subnormal Gonadotrophin and Estradiol concentrations suggests the presence of a Hypothalamic-Pituitary Lesion such as interferences from a Pituitary Tumour
  - Mechanism responsible for Amenorrhoea or Oligomenorrhoea in female with Normal Gonadotrophin and Estradiol concentrations is not clear

- **Hyperprolactinaemia**:
  - Prolactin acts directly on Mammary Glands to control lactation
  - Gonadal function is impaired by elevated circulation of Prolactin
  - Hyperprolactinaemia is common and can cause infertility in both sexes
  - Early indication in women is Amenorrhoea and Galactorrhoea

  - **Some causes of Hyperprolactinaemia**:
    - Stress;
    - Drugs (e.g., estrogens, phenothiazines, alpha-methyl dopa, metoclopramide);
    - Primary Hypothyroidism (Prolactin is stimulated by the raised TRH);
    - Pituitary diseases

Interpretation of Fig. 6 (Investigation of Oligomenorrhoea and Amenorrhoea)

- Fig. 6 summarizes the interpretation of investigations commonly performed in patients with menstrual abnormalities

- ***Plasma level of Prolactin High***:
  - Result needs to be confirmed by repeating the investigation
  - Even then, it must be interpreted with caution, since stress, certain drugs, Hypothyroidism and Chronic Renal Failure can all lead to elevation in plasma concentration of Prolactin

- ***Plasma level of Prolactin Normal:***
- Three possible scenarios:

- **High plasma levels of FSH and LH; Low plasma level of Estradiol-17β**
  - Indicates Primary Ovarian Failure,
  - May be due to Chromosomal Abnormality, Chemotherapy or Auto-immune disease, or it may be Idiopathic due to Premature Menopause

- **High Plasma level of LH, Plasma levels of FSH and Estradiol-17β Low or at Lower limit of Normal**
  - May indicate Polycystic Ovarian Syndrome

- **Plasma level of FSH, LH and Oestradiol-17β are all low, or at lower limits of reference ranges**
  - May indicate Hypothalamic, Pituitary or other endocrine disease
  - Before this possibility is investigated, a Progesterone challenge test should be performed

How is the Progesterone challenge carried out and interpreted?

- Progesterone challenge test is carried out by given the patient a certain amount of Progesterone (Medroxy-progesterone) daily for 5 days
- Menstrual bleeding in the week following Progesterone withdrawal indicates that there has been adequate Priming of the Endometrium by Estrogens;
- Polycystic Ovary Syndrome may be the diagnosis in these patients

Interpretation of Fig. 7 (Investigation of Female Infertility with Normal Menstruation)

- In patients who menstruate normally it is important to establish whether the cycles are Ovulatory or Anovulatory
- Measure Serum level of Progesterone on one occasion between days 19 and 23 of the cycle,
- Monitor response in three separate cycles
- Ovulatory cycle is indicated if serum level of Progesterone is greater than 30nmol/L
- Anovulatory cycles is strongly indicated if Progesterone level is less that 10 nmol/L
- In patients with serum concentration of Progesterone between 10 and 30 nmol/L, the cycles may be Ovulatory, but there may be a defect in the Luteal Phase leading to decreased fertility

Interpretation of Fig. 8 (Investigation of Hirsutism in females):

- Scheme for investigation of female Hirsutism (Fig. 8)
- Measure serum level of Testosterone and Dehydroepiandrosterone sulphate (DHAS)
- DHAS is a specific Adrenal product in females
- Hirsutism is usually idiopathic in women with normal levels of DHAS
- Detailed investigation, may reveal evidence of Adrenal excess due:
    - To low plasma concentration of SHBG accompanied by increased serum concentration of Free Androgens, or
    - To increased conversion of Testosterone to 5α-Dihydrotestosterone (5α-DHT) in the skin

- **A second group** of Hirsute women have moderate increased serum concentration of Testosterone, secondary to increased production by the Ovaries or Adrenals, and often associated with Menstrual Irregularity
- If the underlying cause is Late-Onset Congenital Adrenal Hyperplasia due to Partial deficiency of 21-hydorxylase this can be confirmed by injecting 250 mg Synacthen, Intramuscularly and then measure the serum concentration of 17α-Hydroxyprogesterone one hour later
- In a patient with CAH, there will be an increase in serum concentration of this compound to more than twice the upper reference value
- Polycystic Ovarian Syndrome (Stein-Leventhal syndrome) is a more common cause of Hirsutism, with patients often having Irregular Menses, moderately increased serum Testosterone levels and serum DHAS with increased plasma concentration of LH

- **Third group** of Hirsute women have considerably increased serum concentrations of Testosterone and DHAS, and may be excluded as should rarer causes of abnormalities, e.g., ovarian or adrenal tumours

Fig. 1: HYPOTHALAMUS-ANTERIOR PITUITARY-TESTICULAR AXIS (HPT-AXIS) IN MALES

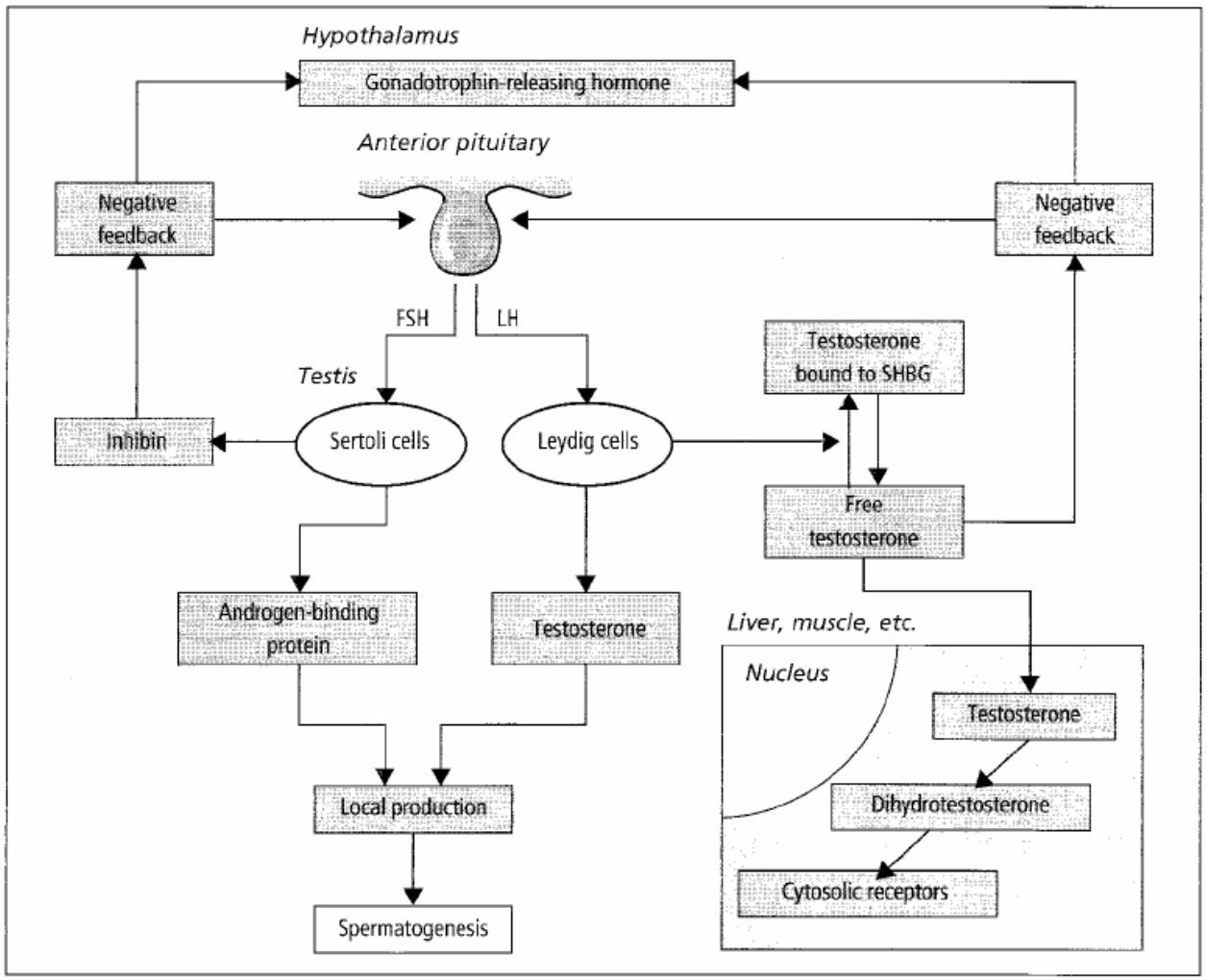


Figure 17.1 The hypothalamic–pituitary–testicular axis. SHBG: sex hormone-binding globulin. Activin from Sertoli cells stimulates FSH release.

NOTE: **5-α-Reductase catalyzes the conversion of Testosterone to Dihydrotestosterone**

Fig. 2: HYPOTHALAMUS-ANTERIOR PITUITARY OVARIAN AXIS (HPO-AXIS) IN FEMALES

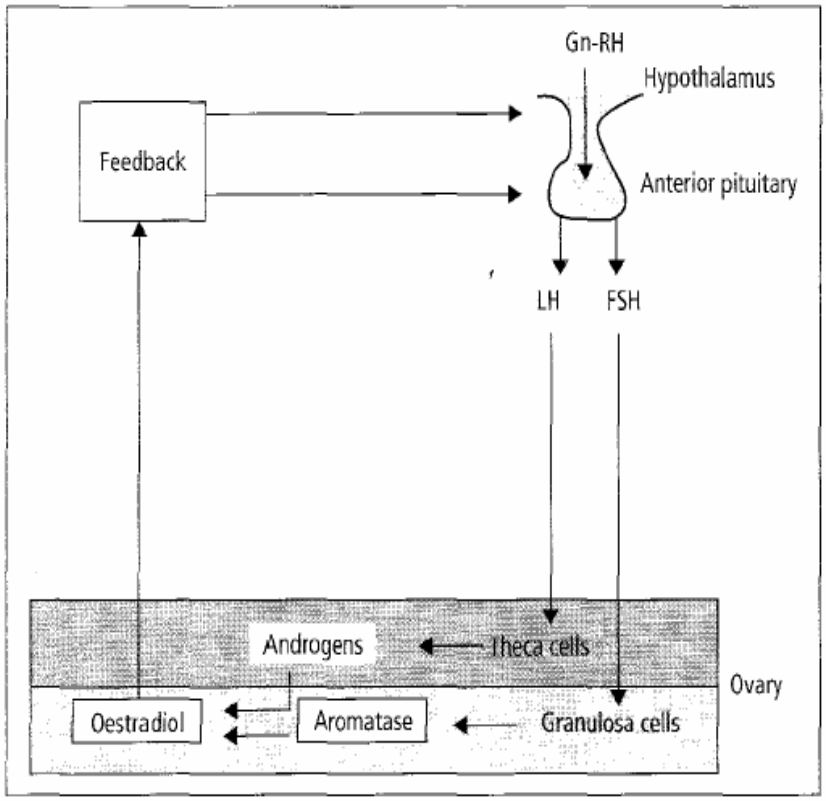


Figure 17.3 The hypothalamic–pituitary–ovarian axis. Activins, inhibins and progesterone also have a role in regulating the cycle.

Fig. 3A: Hormonal changes in the menstrual cycle

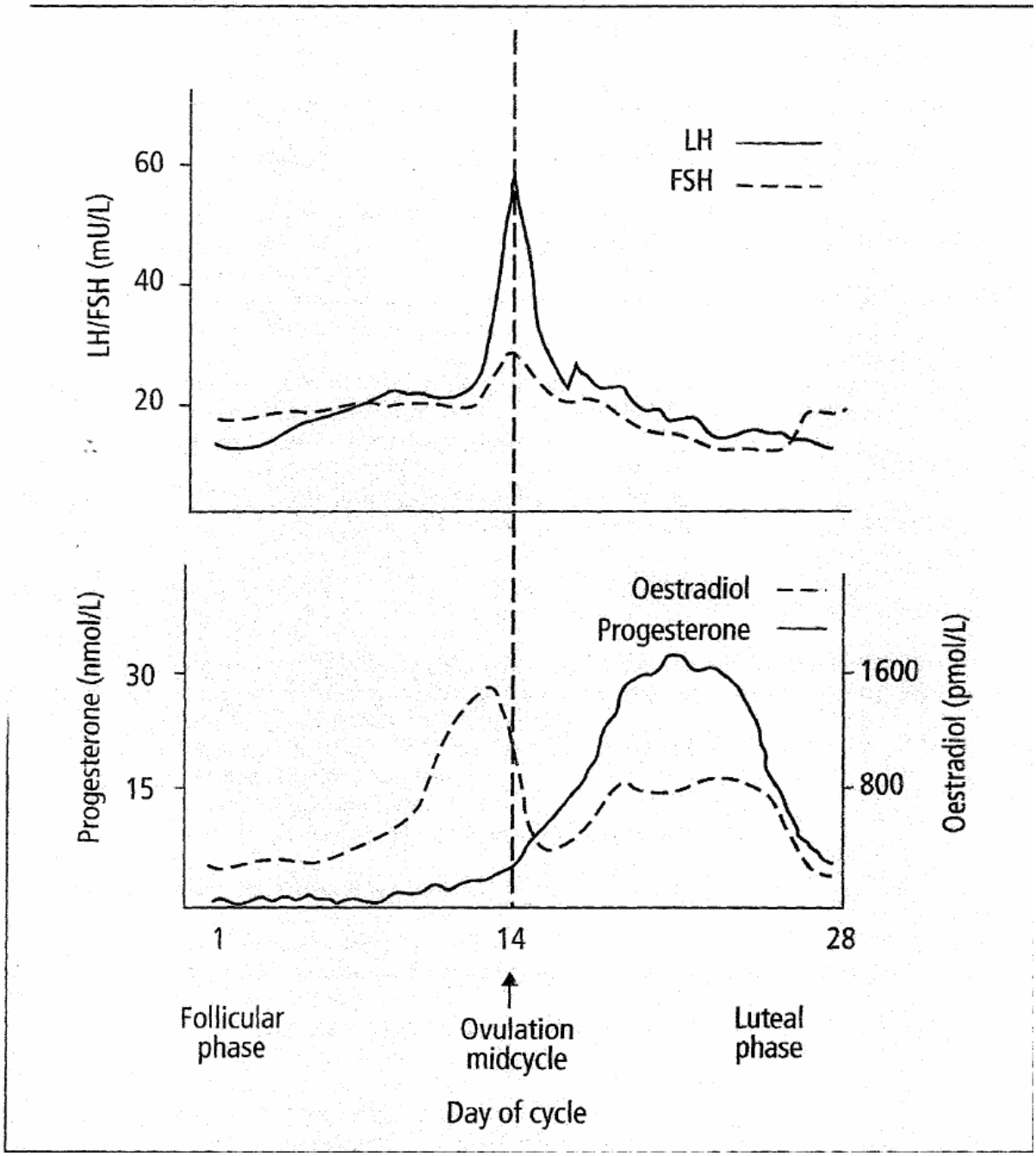
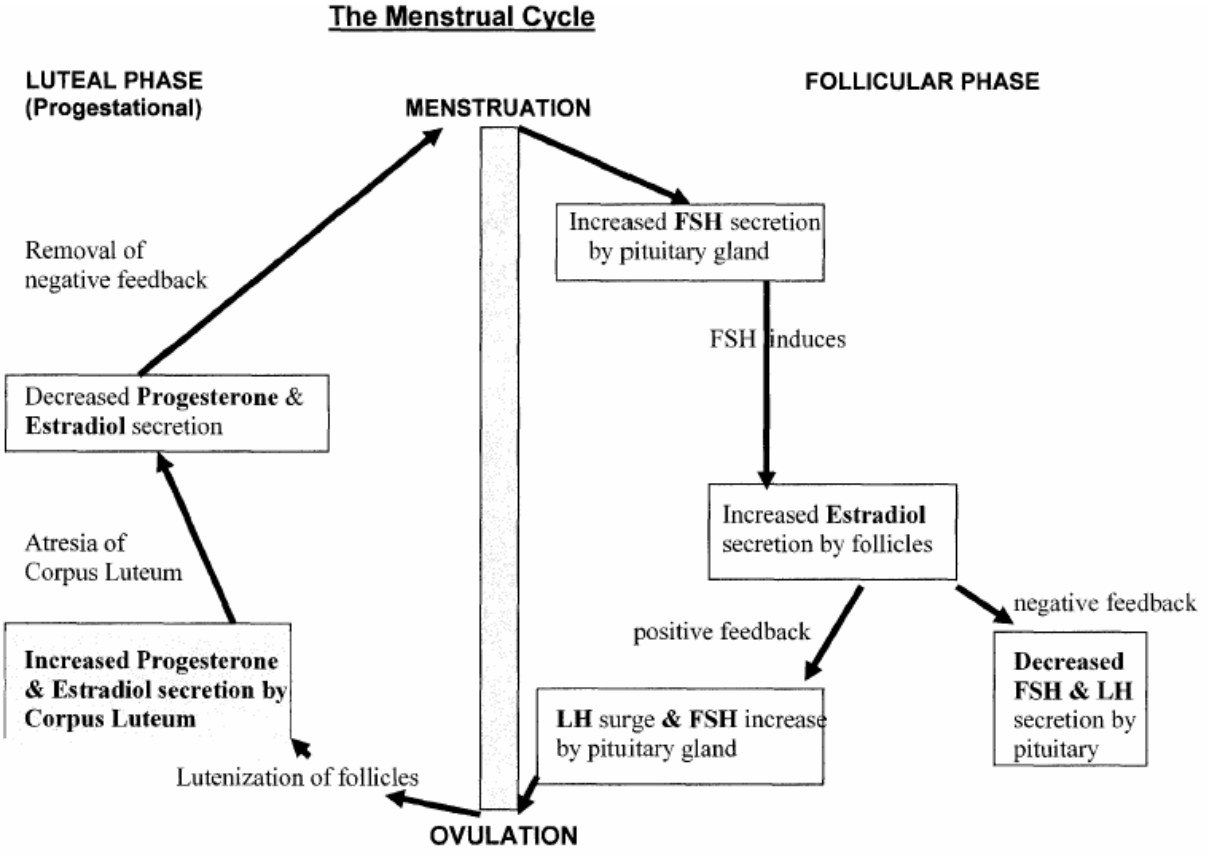


Fig. 3b: Hormonal changes in Menstrual cycle showing positive and negative feedback effects of Estradiol



CHECK THE HANDOUTS GIVEN TO YOU IN CLASS FOR ALL THE OTHER DIAGRAMS (FIGURES: 4 to 8).