Reproductive endocrine disorders follow the typical pattern seen with other disorders in that they are classified as either hypofunction or hyperfunction at the primary, secondary or tertiary level. The table below summarizes this pattern for hypogonadism.

Disorder (site of injury)	Sex Steroids	FSH/LH	GnRH
Primary hypogonadism (testis, ovary)	↓	↑	↑
Seconday hypogonadism (pituitary)	↓	↓	↑
Tertiary hypogonadism (hypothalamus)	↓	↓	↓

The site of the reproductive endocrine disorder is often differentiated by dynamic tests.

I. Dynamic Testing - There are three stimulation tests that can be used to evaluate the hypothalamic/pituitary portion of the axis.

A. GnRH Stimulation Test. This test is used to evaluate the ability of the pituitary to produce LH and FSH.

1. Administration of GnRH stimulates secretion of LH and, to a lesser extent, FSH.
2. GnRH is given as a 100 μg intravenous bolus.
3. Serum LH is determined at baseline and 30 minutes post administration.
4. A LH increase of 2-3 times over basal with a minimal increase in FSH is normal.
5. There have been some concerns expressed regarding the GnRH stimulation test. Unfortunately, many normal individuals respond poorly to GnRH stimulation. In addition, in patients who are deficient in endogenous GnRH, the response to administered GnRH may be delayed or blunted because of the long-standing **underlying hypothalamic defect.**
6. The GnRH stimulation test is most often used to investigate menstrual disturbances and infertility in females and hypogonadotropic hypogonadism in males.

B. HCG Stimuation Test. Administration of HCG (which has similar actions to LH) tests the ability of Leydig cells to secrete testosterone.

1. A dose of 2000 U is given by intramuscular injection daily for four days.
2. A normal response is an increase in serum testosterone by 2 - 3 fold, or an increase of at least 200 ng/dL over baseline levels.

C. Clomiphene Stimulation. Clomiphene, an antiestrogen, has uses as a diagnostic and a therapeutic agent. It blocks the inhibitory effect of estrogen on the hypothalamus, thus nullifying the normal feedback on the hypothalamic/pituitary system. In women, this results in secretion of larger amounts of LH, FSH. The increase in FSH, in turn, induces follicular growth and initiates an ovulatory cycle.

1. A functioning hypothalamic/pituitary/ovarian axis is essential for successful therapy with clomiphene. Therefore, clomiphene is indicated in anovulatory women in whom there is evidence of follicular function and adequate estrogen production (in that they menstruate after administration of progesterone). Patients suspected of having polycystic ovaries may need progesterone along with clomiphene to create the proper environment.

2. Clomiphene citrate usually is given in a dosage of 50 to 100 mg daily for 5 to 10 days. Therapy is usually begun at the lower dose and duration, and if the patient fails to ovulate after two or three cycles, the dose or the length of therapy is increased. A convenient starting point is the fifth day of menstrual bleeding induced by progesterone administration.
3. A normal response is a significant increase in LH and FSH over baseline. The increase in FSH stimulates the growth and maturation of ovarian follicles preparing for ovulation. An abnormal test result would be an absence of the significant increase in LH and FSH.

II. Prolactin

A. Increased levels of prolactin (hyperprolactinemia) - result in hypogonadism because of the hormone's ability to inhibit LH and FSH release. As a result, estrogen levels are low in females and testosterone levels are decreased in males with hyperprolactinemia. The causes of increased serum prolactin can be physiological or nonphysiological. These causes are summarized below.

Physiological Causes of Increased Prolactin

1. **pregnancy**
2. **lactation**
3. **transient increase such as with stress, hypoglycemia, orgasm, nipple stimulation, exercise, seizure**

Non-Physiological Causes of Increased Prolactin

1. **pituitary tumor (70 - 80%)**
2. **hypothalamic disease**
3. **pituitary stalk compression (5 - 10%)**
4. **chronic renal failure**
5. **chest wall lesions such as trauma, herpes zoster, surgery**
6. **medications (5 - 10%) such as with phenothiazines, histamine blockers**

B. A prolactinoma - is a tumor that produces excessive amounts of prolactin.

1. Females with a prolactinoma present with amenorrhea, galactorrhea and infertility
2. Adult males exhibit impotence, decreased libido and infertility; symptoms are absent in many males with elevated prolactin.
3. Other symptoms, related to compression effects of the tumor's mass, include headache and visual disturbances.

C. Serum prolactin is used clinically to assess infertility and to diagnose and monitor prolactinomas.

1. **Normal prolactin** is typcially <15 ng/mL in males and <20-25 ng/mL in females, except during pregnancy or lactation.
2. **Prolactin > 200 ng/mL** is highly specific for prolactinoma. In patients with prolactin of 100 - 200 ng/mL, 80 - 90% are due to prolactinoma. Lesser elevations of prolactin can occur in small prolactinomas, but are more likely to be due to other causes.
3. Serum prolactin is most commonly measured by immunoassay.

III. Male Reproductive Endocrine Disorders

A. **Hypergonadism** may be seen in two circumstances:

1. In adrenogenital syndrome where there is an increased production of testosterone primarily in the adrenal cortex.

2. In carcinoma of the adrenals or testes.

B. **Hypogonadism** - A decreased level of androgens in the male. The main goal of the clinical laboratory is to assist in distinguishing between primary and secondary hypogonadism.

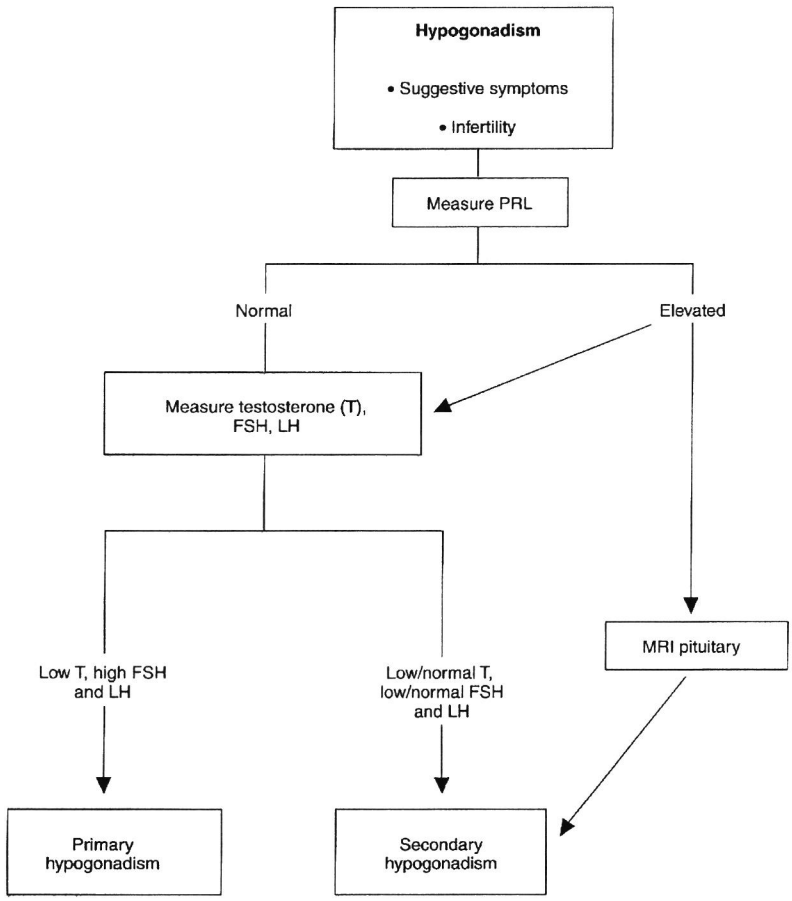
1. **Primary hypogonadism** - is due to testicular dysfunction and is characterized by low serum testosterone concentrations in conjunction with high gonadotropin levels (LH and FSH), reflecting the absence of negative feedback on the hypothalamic-pituitary axis.
   - **a.** Abnormal testicular function may result from a genetic disorder, from defects in testosterone synthesis or metabolism, from abnormalities in the androgen receptor, or from direct gonadal damage.
     - **1)** The most common genetic disorder causing primary hypogonadism in men is Klinefelter's syndrome. Klinefelter's syndrome occurs in about 1 in 400 men.
   - **b.** Primary hypogonadism occurring after puberty is frequently the result of testicular damage. Men who are infected with the mumps virus during or after puberty have about a 50% chance of developing testicular problems, and as many as 60% of these will be infertile because of extensive seminiferous tubule damage.
2. **Secondary hypogonadism** (also known as hypogonadotropic hygogonadism) is characterized by low testosterone concentrations in association with gonadotropin (LH and FSH) levels that are subnormal or within the reference range. This combination indicates failure of the pituitary to respond normally to a lack of **negative feedback.**
   - **a.** Secondary hypogonadism may be caused by congenital or acquired defects.
3. **Tertiary hypogonadism** may also be congenital.
   - **a.** The classical example of congenital tertiary hypogonadism is Kallmann syndrome, which is a defect in hypothalamic GnRH.

C. **Gynecomastia** is an increase in tissue of the male breast. As the estrogen:androgen ratio increases, breast tissue increases. Alterations in the concentration of SHBG can also be a source of gynecomastia. Other causes of gynecomastia include:

1. cirrhosis
2. medications (estrogens, digitalis)
3. hyperthyroidism
4. rapid weight gain
5. primary testicular failure
6. hypogonadotropic hypogonadism
7. estrogen or HCG secreting tumor

Evaluation of gynecomastia involves testing serum levels of LH, FSH, testosterone, prolactin, and HCG. Sometimes, particularly when gynecomastia is accompanied by testicular atrophy (suggesting Kleinfelter's syndrome), chromosome analysis may be required.

The following diagram illustrates the clinical approach to the investigation of male hypogonadism. In the diagram, the first step is to measure prolactin levels. Prolactin secreting pituitary tumors can cause hypogonadism.



D. **Impotence**. - In men, the clinical presentation of gonadal failure is impotence and/or infertility. Only 15 - 20% of impotence is hormonal in etiology. Assessment of hormone-related impotence is done by total testosterone. In early gonadal failure, total testosterone is often normal because of increased SHBG whereas free testosterone is low. Addition of serum prolactin identifies those men with impotence secondary to hyperprolactinemia, virtually 100% of these also have low testosterone, suggesting that using prolactin for screening would not be cost-effective.

IV. Female Reproductive Endocrine Disorders

A. Hypogonadism - A decreased level of estrogens in the female. The main goal of the clinical laboratory is to assist in distinguishing between primary and secondary hypogonadism.

1. **primary hypogonadism** - The clinical presentation of female hypogonadism depends both on age of onset and the degree of estrogen deficiency. The defect in female is caused by primary ovarian hypofunction. Typically, LH and FSH are increased while estradiol is decreased. Some of the causes of primary hypogonadism in females include:
   a. androgen insensitivity (phenotypic female, genetically male)
   b. olycystic ovary syndrome
   c. ovarian failure (menopause, premature menopause)
2. **Secondary hypogonadism** refers to pituitary dysfunction. Usually, estradiol, progesterone, LH and FSH are all decreased. Some of the causes of secondary hypogonadism in females include:
   a. hypothyroidism
   b. functional (anorexia nervosa, stress, intense physical training, severe weight **loss, malnutrition)**
3. **Tertiary hypogonadism** is rare in females.

B. Hypergonadism -

1. **primary hypergonadism** - Estrogen-secreting tumors are the primary cause of female **primary hypergonadism**. Laboratory results include increased estradiol levels with decreased levels of LH and FSH.
2. **secondary hypergonadism** - Precocious puberty (puberty at an earlier age than normal) and premature maturation of the CNS are the major causes of female **secondary hypergonadism**. Estradiol, LH, and FSH are all inappropriately increased for the age of the child.

C. **Menstrual irregularities**, usually due to an imbalance in sex steroid levels, are defined as follows:

1. **menorrhagia** - heavy periods
2. **metrorrhagia** - irregular periods

B. **Amenorrhea -** is caused by the absence of normal cyclic estrogen production. Serum estradiol levels are decreased. Common causes of amenorrhea include:

1. **pregnancy**
2. **polycystic ovary syndrome**
3. **menopause**
4. **primary, secondary or tertiary hypogonadism**
5. **hyperprolactinemia**
6. **hypothalamic/pituitary dysfunction**

7. The clinical assessment of amenorrhea is dependent upon the woman's age and her symptoms.
   a. In older women, initial assessment is limited to FSH; greatly increased FSH is consistent with menopause.
   b. In women of childbearing age, serum HCG is the test of first choice. An elevated HCG level is consistent with pregnancy or HCG-secreting tumor. A negative/normal HCG is followed by serum prolactin to evaluate for

hyperprolactinemia as the cause of amenorrhea. With a normal prolactin, additional assessment includes serum LH and FSH. Decreased levels of LH and FSH with decreased sex steroid levels are consistent with hypogonadotropic hypogonadism (i.e., the defect is at the level of the pituitary or hypothalamus). When LH is abnormally elevated relative to FSH, polycystic ovary syndrome is the most likely cause of amenorrhea.

D. **Hirsutism** - has previously been considered when discussing the adrenal cortex. Hirsutism is mentioned here as it relates to reproductive endocrinology. Hirsutism is an abnormal androgen effect defined as excessive hair growth in females in androgen-responsive skin zones typically considering being masculine in distribution. This excessive hair growth is caused by production of androgens locally at the hair follicle. The source of this is often familial. Familial hyperandrogenemia may have as its source the ovaries, adrenals, or peripheral tissues. The major causes of hirsutism include:

1. **Cushing's Syndrome**
2. **congenital adrenal hyperplasia**

E. **Polycystic ovaries** - are characterized by a serum LH:FSH ratio > 3:1. With congenital adrenal hyperplasia, steroid precursors are elevated. Testing to elucidate the androgen source includes total and free testosterone, dehydroepiandrosterone sulfate (DHEA-S, the sulfated conjugate of DHEA that is produced predominately by the adrenals), LH, and FSH. Increased DHEA-S levels point to the adrenals as the source of excess androgens while an increased testosterone implicates the ovaries. If virilization (i.e., masculine characteristics in the female), a tumor is suspected as the androgen source.

F. **Infertility**. In most couples, multiple factors contribute to inability to conceive. The most common causes include abnormal sperm production, fallopian tube disease and low progesterone.

Summary

The following table summarizes the laboratory values associated with the laboratory assessment of reproductive function.

Laboratory Assessment of Reproductive Function

Female Normal Function	
Pregnancy	↑ HCG, progesterone, & estrogens, ↓ LH and FSH
Menopause	↓ estradiol & progesterone, ↑ LH & FSH, FSH:LH >1.0
Female Hypogonadism	
Primary	↓ estradiol, ↑ LH & FSH
Secondary	↓ estradiol, LH, FSH, & progesterone
Female Hypergonadism	
Primary	↑ estradiol, ↓ LH & FSH
Secondary	↑ estradiol, LH, & FSH
Male Hypogonadism	
Primary	↓ testosterone, ↑ LH & FSH
Secondary	↓ testosterone, LH, & FSH
Miscellaneous Disorders	
Ectopic Pregnancy	↓ HCG
Gynecomastia	↑ estrogen:androgen ratio
Hirsutism	↑ DHEA-S and/or ↑ testosterone
Luteal-Phase Defect	↓ progesterone
Non-Viable Pregnancy	↓ HCG & progesterone
Polycystic Ovary Disease	LH:FSH >2.0
Precocious Puberty	↑ estradiol or testosterone, LH, & FSH
Prolactinoma	↑ prolactin, ↓ LH, FSH, & estradiol or testosterone
Virilization	↑ DHEA-S and/or ↑ testosterone