



## Association of Genetic and Reproductive Hormone with Infertility in Male

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### ABSTRACT

Infertility is an important medical and social problem in the world and male factor is responsible for about 8% to 15% of couples. A couple is said to be infertile if a female does not conceive after having unprotected sexual intercourse for one year. Variation have been observed in rates and etiology of infertility in terms of gender, sexual history, lifestyle, society, and cultural background this review summarizes current evidence regarding diagnosis and treatment of infertility.

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### Introduction

Infertility is defined as the failure to achieve pregnancy after 12 months of regular unprotected sexual intercourse. Approximately 85% of infertile couples have an identifiable cause. Male, female or both can contribute toward infertility [1-5]. Almost 30% of infertile males failed to show any causes of the dysfunction, however defective spermatogenesis was found to be responsible for 2-4% infertility cases. It is attributed to chronic infections, anti-sperm anti-bodies, and anatomical malformation as well as to socio-environmental and genetic factors [6]. An association between obesity and infertility has also been suggested [7].

Studies have shown that the association of various metabolic derangements are not only associated with excessive body weight but also they are hazardous for reproductive health. Studies shows an association between obesity and female infertility but a direct link between obesity and male infertility disorder are sparse. Although it has accepted for females. This is due to major focus of research on female infertility and its possible causes while not much attention has been paid to male infertility [8]. Current studies have also shown increased risk of erectile dysfunction, gall bladder diseases and disorders of bone in obese men [9-11]. Increased weight and obesity are the key factors that can lead to an altered reproductive hormonal profile which is characterized

by decreased T and sex hormone-binding globulin (SHBG) levels and increased estradiol levels in infertile males [12-14]. Recent published data has proved that defective spermatogenesis by Sertoli cells is related to overweight and obesity which can be observed by lower inhibin levels in infertile males. The extent of effects caused by hormonal changes on male reproductive potential is still not clearly determined [15].

The association of obesity or BMI with standard semen analysis parameters or male fertility has been recently examined in multiple studies with inconsistent results [16].

An intact hypothalamus pituitary testicular axis is required to initiate and maintain quantitative and qualitative normal spermatogenesis [17, 18]. Spermatogenesis and Steroidogenesis are two functions performed by testis. Both of these functions are influenced by genetic, hormonal, biochemical and environmental factors [19]. The endocrine control is exerted by the pituitary through the secretions of gonadotropins (FSH and LH). Both LH and FSH are required for initiation of spermatogenesis. The pituitary itself is under the control of hypothalamus via the gonadotropin releasing hormone (GnRH) Stimulation with LH (luteinizing hormone) resulted in bio synthesis and secretion of T from Leydig cells [11, 20, 21]. T secretion is regulated by feedback mechanism of LH. When Leydig cell are congenitally defective the testes remain intra—abdominal and there is lack of androgen dependent differentiation of the internal and external genitalia.

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Leydig cells make 95% of the total T concentration [22]. Leydig cells utilize cholesterol which is mainly a reservoir for T synthesis [23].

Steroidogenesis has been demonstrated in the human testis starting from the seventh week of gestation. The plasma T level in the male embryo rises until late pregnancy when it falls to the same level as in the female fetus. During the first three months after birth T level rises and then falls by one year remaining low until the onset of puberty. The plasma T level reaches its peak around 17 years of age. The level remains steady and at late middle age starts falling and after 70 years of age these are distinctly low. There are two pathways of T biosynthesis [24].

1. **Pathway:** This pathway leads to conversion of cholesterol to pregnenolone to progesterone to 17-hydroxyprogesterone to androstenedione which finally converts to T.
2. **Pathway:** This pathway leads to conversion of cholesterol to pregnenolone to 17 $\alpha$ -hydroxypregnenolone to dehydroepiandrosterone to androstenediol to T. The pathway is predominant in adrenals.

Sertoli cells convert T to estradiol or dihydroT (DOT). These cells do not synthesize T but produce androgen binding protein [6]. The T effects produce male secondary sexual characteristics and general anabolic effects [25].

### Metabolism of Testosterone

T once taken up by the cell may be

1. Aromatized to estradiol occurring in fat tissues as well as in liver, breasts or
  2. 5 $\alpha$ -reduced to DHT which is more potent than T. 5 $\alpha$ -reductase enzyme is involved in this process
1. 5 $\beta$ -reduced producing 5 $\beta$ DHT
  2. Metabolized in the liver which is then excreted in the bile or urine.

Approximately 6mg/d of T is produced by the Leydig cells in a normal young person. T is bound to SHBG and human serum albumin (HAS). The secretion of T is pulsatile hence the serum concentrations may fluctuate between 0.3 to 1.2 $\mu$ g/dl. T is converted into dihydroT (DHT) by 5 $\alpha$ -reductase, which is nearly three times as potent but has a tight binding to plasma proteins. T can either be aromatized to estradiol which occurs in the brain, breast, liver and other tissues. As there is large mass of adipose tissue, aromatization became an important step that causes extra glandular synthesis of estrogen in the body. Approximately 20% of estradiol is produced by the aromatase activity of Leydig cells themselves [26, 27]. For proper functioning of reproductive organs an appropriate milieu of male reproductive hormones must exist for the normal sperm production and survival [28].

Hypogonadotropic hypogonadism which is a failure of the pituitary gland to produce adequate amount of FSH and LH, can lead to decreased sperm counts and a state of infertility [29]. Normal serum concentration of PRL have been shown to exert permissive roles in the male reproductive tract but excessive serum PRL concentration is correlated with infertility, hypogonadism, impotence and galactorrhea [30]. The changes in LH and FSH may be the reason that causes the dysfunction of spermatogenesis and sperm maturation in patients with idiopathic azoospermia and oligospermia [31].

T is metabolized in peripheral tissues to the potent androgen dihydrotestosterone (DHT) or the potent estrogen estradiol. These androgens and estrogens act independently to modulate LH secretion. The mechanism of feedback control of FSH is regulated by a product from Sertoli cells called inhibin. Decrease in spermatogenesis is accompanied by decreased production of inhibin and this reduction by negative feedback is associated with reciprocal elevation of FSH levels. Isolated increased levels of FSH constitute an important, sensitive marker of the state of the germinal epithelium [32-34]. Reduced level of T is shown in overweight individual. Excessive visceral body fat has a link with decreased serum T levels. This decrease reproductive hormone level is proportional to degree of excessive body fat [8]. Various causative factors explain the origin of hypogonadotropism in obese males. Obesity has a link with adipocytes quantity and quality as both the number and size of these cells are found to be increased in obese male [35]. High levels of estrogen appear to be primary cause of hypogonadotropism. Reduced total T and T/estradiol ratio is also a consequence of reduced SHBG in fatty individual [14]. Both the estrone and estradiol are increased in obese male [36].

Aromatization of T & androstenedione in obese male has an essential role in increased estrogen synthesis as compared to healthy fertile male. Aromatase enzyme is present on CYP19 gene and is responsible for reduction in T/estrogen ratio in obese men having BMI>35 seeking infertility treatment [37, 38]. It is believed that higher serum estrogen levels in overweight persons cause raised aromatase enzyme in adipose tissue [39]. High levels of estrogens in obese males result from the increased conversion of androgens into estrogens owing to the high bioavailability of these aromatase enzymes. Altered levels of sex hormones can cause great changes in both spermatogenesis and reproductive hormone level of obese male [40, 41].

### Historical Perspective

The most primitive bear witness of understanding the problem of infertility goes back to Egyptians, nearly thousands of years ago. Endocrine function of testicles was first documented by Berthold (1803-1861). Bernard and Zondek and Ashheim are well known for the discovery of FSH and LH. The advancement in technology coincides with the discovery of new product which results in rapid progress in field of reproductive biology. Infertility is defined as inability of couple to achieve pregnancy after one year of unprotected intercourse [4]. Male factors alone constitute 40% - 50% of all infertile study group of infertility and they contribute to another 30% in combination with female factors [42]. Known etiologies of male infertility include cryptorchidism, testicular torsion or trauma, varicocele, seminal tract infections, antisperm antibodies, Hypogonadotropic hypogonadism, gonadal dysgenesis, environmental factors, and obstruction of the reproductive channels and cannot neglect genetic factors as well [3, 43]. Most causes of male infertility results in defective spermatogenesis [41]. Obesity is proposed for addition to this list obesity is a well-recognized risk factor for female infertility [33].

The dilemma of infertility has its societal impacts on affected couples in terms of mental stress and depression [44]. The prevalence of infertility in Pakistan is 21.9% [45]. In conservative South Asian culture, a child brings prestige and security to a woman and the desire of having a child is much more intense in Asian

part of the world [46, 47].

Similar to women a sex hormone imbalance may affect reproduction in men, and excess weight can affect male hormone levels [48]. Obese males usually express a characteristic hormonal profile described as “hyperestrogenic hypogonadotropic hypogonadism” [49]. In fact, both total and free blood T levels are shown to be decreased in obese men. Total body fat has been associated with low levels of total and free T. It appears that central obesity, in particular, is associated with a decrease in circulating androgen levels. The decrease in androgen levels is proportional to the degree of obesity [50]. In obese males, adrenal androgens are diminished as well. A significantly reduced T to estradiol ratio has been observed among overweight or obese men. Body mass index (BMI) has been demonstrated to affect female fertility; however, little information is available on the impact of BMI on male fertility or semen parameters. Body mass index is associated with alterations in sperm parameters in several reports [51]. Previously investigating factors associated with semen quality among couples who visited an assisted reproduction clinic, the prevalence of obesity among men with infertility was 3 times greater than among male partners of couples with idiopathic or female factors [52]. Kort et al described the relationship between sperm parameters and BMI in overweight subjects [53]. Hinz et al. by his study concluded that obese men presenting having BMI greater than 25 kg/m<sup>2</sup> shows defective quality of sperm [54].

Tsai et al (2004) has concluded that low sex hormone binding globulin and T levels, together with low gonadotropins, are frequently observed in diabetic men with severe obesity [55]. Outcomes of assisted fertilization greatly influence by excessive body fat in female [56]. Conclusion of various studies has also been shown that also female reproductive health is influence by BMI [57].

#### Prevalence and Geographical Distribution of Primary and Secondary Infertility

The prevalence and causation of infertility vary from area to area and it can be due to male and female factor or both [58].

Problem of infertility is the same in Pakistan as in the rest of the world but the desire of having a child is much more intense in this part of the world [6].

According to WHO-DHS comparative reports (2004) one in four married women of reproductive age in most developing countries are infertile because of primary or secondary causes [59].

**Table 1: Distribution of Diagnosis for Male Infertility**

Diagnosis	Percentage (%)
Idiopathic	48.5
Idiopathic abnormal semen analysis	26.4
Varicocele	12.3
Infection	6.6
Immunologic factor	3.1
Other abnormalities	3.0
Acquired factors	2.6
Congenital anomaly	2.1
Coital factors	1.7
Endocrine abnormalities	0.6

**Source:** Adopted from EAU guidelines on male infertility 2005(World Health Organization; n=7,057)

#### Causes of Infertility

Male infertility can occur due to variety of causes and qualitative abnormalities in semen analysis. The causes are divided into four categories. Infertility affects about 8% to 15% of the world’s population and in about half of the infertile study group men are either the single cause of, or contribute to, the couple’s infertility [60].

- The female factor
- The male factor
- Combined factor
- Unexplained Infertility

In 20-25% of infertile study group the problem is due to the male partner and in 30-40% the problem is predominantly female, in approximately 30% of infertile study group abnormalities were found in both partners, and in 15% no specific factor could be identified [58]. Common causes of infertility vary from area to area which include anatomopathologic and physio pathologic anomalies like hormonal abnormalities, genital infections and varicocele [61]. Common causes are summarized in Table 2.

Table 2: Abnormality of Sperm Count

<p>A. Azoospermia – extreme oligospermia</p> <p>B. Central</p> <ol style="list-style-type: none"> <li>1. Hypogonad, hypogonadism</li> <li>2. Panhypopituitarism</li> <li>3. Hyperprolactinemia</li> <li>4. Hypothalamic and pituitary sarcoidosis</li> <li>5. Hemochromatosis</li> </ol> <p>C. Genetic</p> <ol style="list-style-type: none"> <li>1. Klinefelter's syndrome and variants</li> <li>2. Noonan's syndrome (XX male)</li> <li>3. Ring Y chromosome mechanism</li> </ol> <p>D. Testicular</p> <ol style="list-style-type: none"> <li>1. Anorchia</li> <li>2. Cryptorchidism</li> <li>3. Primary hypogonadism due to orchids             <ol style="list-style-type: none"> <li>a. Selective germinal cell dysfunction</li> <li>b. Germinal cell aplasia</li> <li>c. chemotherapy</li> <li>d. Androgen resistance syndrome</li> <li>e. Sertoli-cell-only syndrome</li> </ol> </li> </ol> <p>E. Obstruction or aplasia of ductal system</p> <ol style="list-style-type: none"> <li>1. Congenital             <ol style="list-style-type: none"> <li>a. Alplasia of vas deferens</li> <li>b. Alplasia of epididymis</li> </ol> </li> <li>2. Acquired             <ol style="list-style-type: none"> <li>a. Preepididymal</li> <li>b. Epididymal</li> <li>c. Postepididymal</li> </ol> </li> <li>3. Vas deferens occlusion             <ol style="list-style-type: none"> <li>a. Vasectomy</li> <li>b. Young's syndrome</li> </ol> </li> </ol> <p>F. Retrograde ejaculation</p> <ol style="list-style-type: none"> <li>1. Autonomic insufficiency</li> <li>2. Ganglionic blocker</li> </ol>	<p>II. Oligospermia</p> <ol style="list-style-type: none"> <li>1. Hypogonadotropic hypogonadism</li> <li>2. Panhypopituitarism</li> <li>3. Hyperprolactinemia</li> <li>4. Hypothalamic and pituitary sarcoidosis</li> <li>5. Hemochromatosis</li> <li>6. Selective and germinal cells dysfunction</li> <li>7. Germinal cell aplasia</li> <li>8. Chemotherapy</li> <li>9. Radiotherapy</li> <li>10. Androgen resistance syndrome</li> <li>11. Sertoli-cell-only syndrome</li> <li>12. Varicocele</li> <li>13. Idiopathic</li> </ol>	<p>III. Normospermia</p> <ol style="list-style-type: none"> <li>A. Immunologic infertility</li> <li>B. Varicocele</li> <li>C. Unrecognized female factor</li> <li>D. Normal but infertile</li> </ol>
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(Ref: Arey LB. Developmental anatomy. 7 ed. Philadelphia W B Saunders 1965)

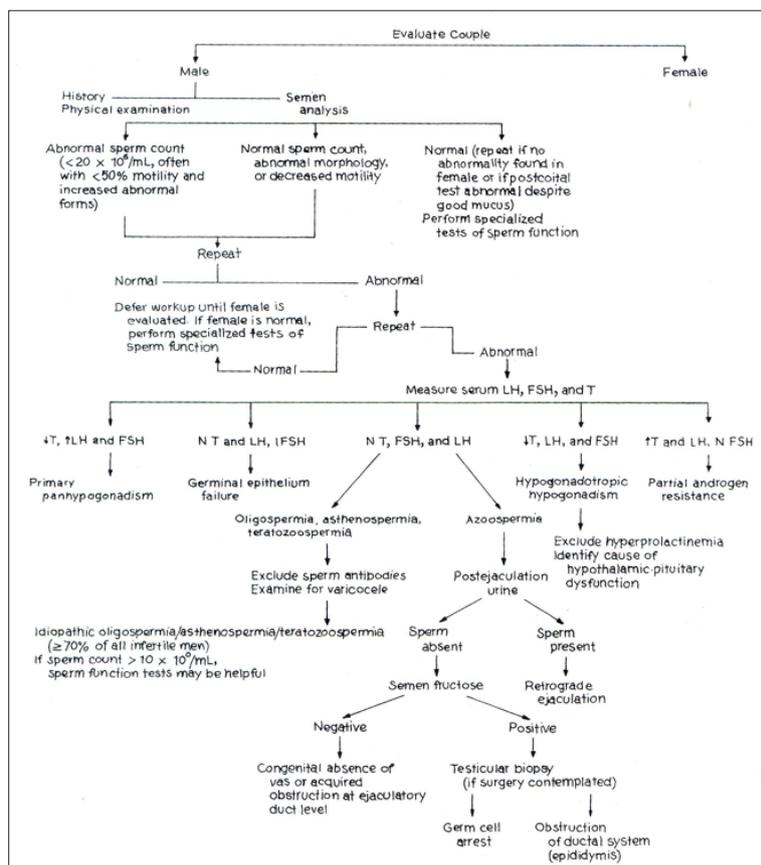


Figure 1: Schematic Diagram Showing Steps and Evaluation of an Infertile Male

The causes of male infertility can be classified as pre-testicular, testicular and post-testicular which are discussed [62].

**Pretesticular Causes:** The causes relating to the effect on reproductive hormones secreted from the hypothalamus and Pituitary gland or use of any drugs which directly or indirectly affect the function of the testes or an injury to the head disturbing the function of the pituitary gland) include

- (a) condition in which the pituitary secretes very low quantities of FSH and LH
- (b) there is a tumor in the pituitary gland which increases PRL secretion.
- (c) injury to the pituitary gland and
- (d) use of corticosteroids and high doses of T. Adjustment of the steroid reproductive hormone improve sperm quality [62].

**Testicular Causes**

**Include**

- (a) some genetic problems such as Klinefelter’s syndrome,
- (b) exposure of testes to some toxic substances,
- (c) failure of descent of the testis from the abdominal cavity into their correct position which is inside the scrotum,
- (d) mumps infection causing swelling of the testis and
- (e) draining blood from the testicles [63].

**The Post Testicular Causes**

(a) blockage of the tubes which carry the sperm from the tests to the outside world or absence of these tubes by birth. There are other conditions in this group such as chronic infection of the epididymis (a tubular structure which stores and matures the sperm produced from the testes or Young’s syndrome in which plugs of mucus block the tubes. Vasectomy which is tying off the tube for male contraception [64].

**Table 3: Showing Various Causes of Infertility in Relation to Testis**

Etiology of male infertility in relation to testis		
I. Pretesticular	II. Testicular	III. Posttesticular
A. Central	A. Genetic	A. Genetic
1. Hypothalamic hypogonadotropism	1. Klinefelter’s syndrome (XXY)	1. Congenital aplasi of
2. Pituitary gland	2. Noonan’s syndrome (XX male)	a. Seminal vesicles
3. Hyperprolactinemia	3. XYY syndrome	b. Vas deferens
4. Isolated FSH deficiency	B. Acquired	c. Epididymis
5. FSH-secreting pituitary adenoma	1. Cryptorchidism	B. Acquired
B. Peripheral hormonal dysfunction	2. Torsion of the testis	1. Varicocele
1. Hyperthyroidism	3. Viral orchitis	2. Immunology infertility
2. Hypothyroidism	4. Maturation arrest	3. Young’s syndrome
3. Estrogen excess – cirrhosis	5. Hypo spermatogenesis	4. Epidymitis
4. Cushing’s syndrome	6. Sertoli-cell only syndrome	5. Immotile-cilia syndrome
C. Pharmacologic	7. Radiation	C. Iatrogenic
1. Corticosteroid excess (treatment for ulcerative colitis or arthritis)	8. Chemotherapy	1. Vasectomy
2. Anabolic steroid abuse (for athletes)		2. Immunologic infertility after
3. Androgens inhibitors		3. Vasovasostomy
a. Spironolactone		
b. Cimetidine		

## Male Infertility Pathophysiology

The male accessory reproductive organs consist of epididymis, vas Deferens, seminal vesicles, prostate glands and Cowper's glands [64]. The secretion of the accessory organs has a crucial role in the reproductive function of the male. Defect in any one of these organs can cause malfunction resulting in infertility or sexual disorders.

### Epididymis

There are two types of cells lining the epididymis

- 1) Principle cells
- 2) Basal cells

Spermatozoa after being produced by testis travel through this elongated structure [64]. It not only provides a passage and store house for spermatozoa, its secretory protein/ hormones play a role in maturation of spermatozoa and acquiring sperm fertilizing capacity [65].

### Biochemical Reaction/ Secretion in Epididymis

#### a) Glyceryl Phosphoryl Choline (GPC)

It is mainly secreted by the epididymis as shown by studies performed on vasectomy, vasoepididymostomy and testicular fluid specimen. Prostate also produces a small amount of GPC. Serum T and semen GPC levels show a feeble relationship. Some workers have found significant correlations between GPC levels and spermatozoal progression [66]. The role of GPC is however unclear. It acting with other compound may maintain osmotic pressure of fluid surrounding the sperm. It may also play some role in maintaining the epididymal pH. It also inhibits phospholipase A 2 activity [67].

#### (b) Carnitine

Spermatozoa are dependent on fatty acid metabolism. Carnitine has a significant role in the oxidation of the palmitic acid and maintaining the viability of sperm. It may also play a role in the maintenance of osmotic pressure and may stimulate motility. Reduced levels of carnitine in semen are found in men with hypogonadism which increases after HCG administration [68]. Carnitine level in seminal plasma is an important biochemical marker for the sperm quality.

#### (c) Proteins

Two specific proteins galactosyl transferase and lactalbumin are found in the epididymis. These proteins contribute to the glycosylation of sperm [68].

#### (d) Lipids

These constitute nearly 1% of the total weight of the epididymis. Phospholipids, cholesterol and glycosides constitute 64%, 12%, and 24% of the total lipids in the epididymis respectively [68].

#### (e) Steroids

There are certain enzymes present in the epididymal tissue which are involved in steroidogenesis. T and dihydroepiandrosterone are produced. The blood supply to the epididymis provides steroids. The epididymal tissue may also supply some amount of androgens [67].

The epididymis is regulated by hormones which arrive from the circulation and from the rete testis [67]. Circulating T undergoes 5 $\alpha$  reduction and binds to specific receptors to induce gene acti-

vation and to maintain epididymal function. PRL is also required for epididymal growth, as it helps in the uptake of T. PRL acts synergistically with DHT (DHT). Fluid absorption is also androgen dependent. Aldosterone has no effect. LH, FSH, vasopressin and epinephrine have stimulatory effects. High concentration of salicylic acid has effect on the acrosome of maturing spermatozoa. There one certain enzyme involved in steroidogenesis present in epididymis. T and DHT are produced. Inhibin has a negative feedback effect on FSH from the pituitary gland hence thus reabsorption may play a role in controlling FSH this has been questioned by many workers [69].

Obesity is a metabolic disorder in which LDL and HDL ratio are disturbed and high levels of cholesterol also produce hormonal abnormalities and also cause accumulation of arachidonic acid or lipid metabolites, studies shown that product of arachidonic acid affect spermatogenesis [70]. All three lipoprotein produced concentration related inhibition of prostaglandin biosynthesis [71].

### Vas Deferens

The vas deferens is a 35-45 cm long tube which extends from the caudal epididymis to the neck of the seminal vesicles. There are three different types of epithelial cells. These are

- 1) principal cells
- 2) pencil cells
- 3) mitochondria rich cells.

The principal cells contain stereocilia on their apical surfaces. Small coated vesicles and vacuoles are present which may be responsible for the uptake of the material from the lumen. The principal cells are highly irregular and contain intranuclear granules which speak for their active metabolic role. The mitochondria rich cells may be involved in acidification of the seminal plasma or transport of electrolytes and water across the mucosa. The vas deferens from many animals has been studied extensively with regard to use of obstruction for the purpose of male contraception. The human vas converts T to DHT and thus the functions of the vas deferens are androgen dependent [71].

### Seminal Vesicles

Nearly two third amount of the ejaculate is contributed from the seminal vesicles. The first part of the ejaculate is rich in sperm while the second part contains very few sperm and is secreted mainly from the seminal vesicle. Fructose is the primary sugar which is secreted by the seminal vesicles into the semen. Its measure around 315 mg/100 ml and is taken as a marker for the function of the seminal vesicles [72]. If fructose is absent in the seminal fluid it implies that seminal vesicles and the vas deferens (as both have same embryonic origin) are not present. The level of fructose is androgen controlled and age, nutritional status, length of storage, frequency of ejaculation and blood glucose concentration are some factors which have an effect on the concentration of fructose in the seminal fluid. The epithelium of seminal vesicles metabolizes T which is reduced to 5 $\alpha$ -dihydroT. PRL may also have some role in the control of the seminal vesicles. It has synergistic action with T. Estrogens too have been shown to affect the function of the seminal vesicles [73].

### Prostate

The prostate secretes 0.5 to 1.5 ml of thin milky fluid per day and form 15-30% of total ejaculate. The human prostatic fluid contains no of constituents, significant are acid phosphatase, citric acid,

polyamines and bivalent cations Ca<sup>2+</sup>, Zn<sup>2+</sup>, and Mg<sup>2+</sup>. Polyamines are synthesized in the body from arginine via ornithine, catalyzed by ornithine decarboxylase. This enzyme is controlled by T [74]. Endocrine and neural factors are responsible for regulating the function of the male accessory sex organs. The androgen-dependent tissues such as the prostate gland show the control of carbohydrate metabolizing enzymes by T.

### Factors Affecting Fertility

#### Reproductive Hormonal Levels

#### Prolactin

PRL is a hormone which is produced by the pituitary gland due to the deficiency of its controlling factor which is called dopamine. PRL as the name suggests is the milk making hormone which sharply increases in pregnant women to enable them to lactate. However this hormone can be secreted excessively in women without a pregnancy and also in men. The high levels of PRL affect the normal functioning of the testes and indirectly responsible for defective spermatogenesis [75]. Hyperprolactinemia in men is responsible for lack of libido. The rise in the level of PRL may be due to several factors including the use of drugs such as anti-depressants, tranquilizers and anti-vomiting agents. Another cause of high PRL is the presence of small tumors in the pituitary gland which can be detected by CT scan or MRI. Normally treatment with bromocriptine restores normal levels of PRL. In case the tumor in the pituitary gland is large, surgical removal of the growth is carried out. PRL is determined in subject with galactorrhea and androgen deficiency and loss of libido [76].

High levels of PRL interfere with the production of FSH and LH which in turn will affect the testicular function. In men high PRL concentration causes decrease in sexual impotence. The treatment is usually carried out by the administration of bromocriptine. When the tumor in the pituitary gland is large and not responding to medical treatment, surgical removal of the tumor is the only treatment hyperprolactinemia can cause both reproductive and sexual dysfunction [76].

#### Male Hormone Testosterone

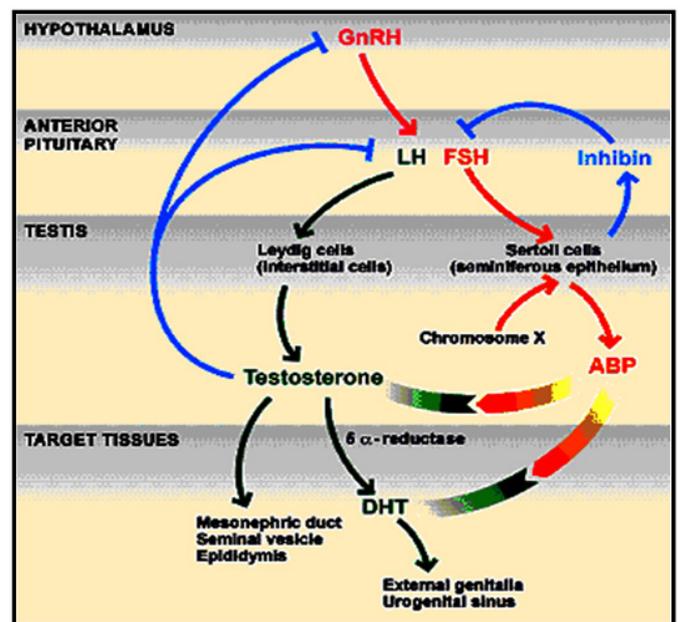
Testes produce T which plays a significant role in the process of spermatogenesis. If the quantity of this hormone is low then the process of spermatogenesis is bound to be defective. Decrease in intratesticular concentrations of T or other local factors are important for spermatogenesis [77]. Obesity decreases the feeling of general wellbeing. Most of the signs and symptoms have a multifactorial origin. Nevertheless, androgen (T) substitution generally improves symptoms like increasing muscle mass and strength, improving libido and sexual activity, decreasing abdominal fat and improving insulin sensitivity as well as the sense of wellbeing, effects which suggest a role of androgen deficiency in their genesis. Low T is associated not only with loss of muscle and bone, but an increase in body fat, which tends to be associated with decreased insulin sensitivity. Giving T replacement therapy decreases abdominal fat and improved insulin sensitivity [78]. Low serum T level is one of the predictors of increased visceral fat in Japanese-American men [79].

#### FSH and LH

These hormones are secreted from the pituitary gland which receives signals from the hypothalamus and which in turn receives signals from the testes in the form of male hormone and if this

signal is lacking the pituitary gland will be geared up in producing more FSH and LH to stimulate the cells in the testes. If these two hormones reach a level which is much higher than the normal level, testes will have stop functioning which is described as testicular failure [80].

Sperm production depends on the concerted action of FSH and LH on the testis. The action of LH is mediated through production of T by the Leydig cells. Since male germ cells possess neither FSH nor androgen receptor, the action of FSH and T occurs through Sertoli cells. Although precise function of two hormones remain elusive the existing evidence suggest that both hormones stimulate spermatogenesis [81]. If the levels of FSH and LH are low, the pituitary gland is not producing enough hormones due to some more complex problems. This situation is amenable to treatment by stimulating the hypothalamus or by injecting the same hormones. Isolated FSH deficiency is extremely uncommon, whereas abnormal FSH level is rarely seen with normal spermatogenesis [82].



**Figure 2:** Schematic Diagram of Hypothalamic Pituitary Hormone (Ref: Arey LB. Developmental anatomy. 7 ed. Philadelphia W B Saunders 1965)

#### Leptin

Leptin is a 16 – kd protein secreted primarily by adipose tissue. Other proteins secreted by white adipocytes are angiotensinogen, resistin, adipsin, acylation stimulating protein, adiponectin. Adipose derived hormones and proteins like leptin level are elevated as compare to normal healthy individual as well as altered reproductive hormone might be a cause of raised prevalence of infertility [83]. Leptin may have role in modulation of fertility and its potential use in artificial reproductive technique (ART) has been considered and reviewed [84].

#### Estrogen

Estrogen is more potent than T. Small change in the levels of circulating estrogen can, therefore, elicit large downstream effects and can increase the potential for abnormal estrogen activity in the testes, whereas the complete absence of any estrogen in the testes has a direct deleterious impact on sperm production and maturation and steroidogenesis, abnormally high levels are detri-

mental to male reproductive potential. High estrogen levels have been shown to lead to adverse effects on spermatogenesis [85].

Studies on animal models show that presence of estrogen receptors on the male hypothalamus has indicated that it might contribute to hunker down T levels through a negative feedback mechanism [86]. Estrogen acts on the hypothalamus to negatively regulate the release of pulses of gonadotropin releasing hormone (GnRH) as well as the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary gland, and estrogen agonists have been shown to have an inhibitory effect on androgen biosynthesis [82]. Study concluded that estrogens might have a part in regulating the Hypothalamic Pituitary gonadal axis, indicative of defective spermatogenesis [87]. Infertile men may have low serum T to estradiol ratio and on treatment with an aromatase inhibitor; there occurs increase in ratio in association with increased semen parameters [88].

#### **Male Hormone Excess**

Many men complaining of impotence and lack of libido are wrongly treated by large doses of the male hormone, T by some inexperienced doctors. The cause of sexual impotence is not always lack of the male hormone. When this hormone is administered excessively, the internal hormonal system gets badly affected and quite often a man who is producing normal number of sperm becomes azoospermic after the excessive use of T. There are some bad effects of male hormone therapy on the prostate gland [89].

Many athletes and men addicted to excessive exercise sometimes use T to enhance performance. They run a risk of damaging their testes [90].

#### **Malnutrition**

Protein malnutrition interferes with the normal production of GnRH from the hypothalamus particularly in women who thus stop menstruating [89].

#### **Acute or Chronic Illness**

Acute or chronic illness, psychiatric disorders, cancers, burns, chronic liver, kidney or lung disease such as tuberculosis (TB) suppress GnRH production (from the hypothalamus) causing testicular dysfunction [91].

#### **Resistance to Male Hormone**

Some men have a birth defect of not responding to the effect of the male hormone on their cells. This occurs because of the absence of special points on the cell surface which react to the signal of the male hormone. If these points which are called receptors are absent or not reactive then obviously the hormone will not have any effect. The result is the body manifests the signs of the deficiency of the male hormone even though it may be present in sufficient quantity. Consequently feminine features start appearing such as enlargement of breasts and undescended testes etc. Sperm production is very scanty or absent. There is no treatment for this condition [92].

#### **Liver and Kidney Failure**

These conditions may cause impairment in both sperm and male hormone production. Liver damage may occur in men who consume alcohol excessively. Liver infection with hepatitis-B virus may cause severe damage to the liver [93]. When the liver is damaged the female hormone estrogen is increased in the body

causing gynaecomastia in men [94]. Kidney failure of long standing may also impair sperm production and male hormone levels. Successful kidney transplantation improves the function of the testes [95].

#### **Syndrome Associated with Obesity**

Various syndromes are associated with obesity and infertility.

#### **Laurence-Moon-Bardet-Biedel Syndrome**

It is an autosomal recessive trait. Clinical features are obesity, mental retardation, retinitis pigmentosa, polydactyly and hypogonadism. The hypogonadism is present in most of prepubertal patients. These syndromes are due to a defect in hypothalamic secretion of GnRH [96].

#### **Kallmann's Syndrome**

It is a disorder present at birth due to deficiency in the production of gonadotropin releasing hormone (GnRH) from the hypothalamus which is responsible for the production of FSH and LH from the pituitary gland. Due to the absence of these hormones testes stop producing the male hormone, T as well as sperm [97, 98]. It is second to Klinefelter's syndrome as a cause of hypogonadism. The syndrome is often associated with anosmia, congenital deafness, hair lip, cleft palate, craniofacial asymmetry, renal abnormalities, and color blindness. If exogenous GnRH is administered, both LH and FSH are released from the pituitary [98, 99]. Except for the gonadotropin deficiency, anterior pituitary function is intact. Infertility in Kallmann's syndrome is potentially treatable by the administration of GnRH therapy or replacement of FSH and LH hormones. The syndrome appears to be inherited either as an autosomal recessive trait or an autosomal dominant trait with incomplete penetrance [100, 101].

#### **Prader-Willi syndrome**

An inherited disorder which is associated with adult onset diabetes mellitus, hypogonadism, hypomentia, hypotonia at birth and obesity. Low FSH and low LH levels are present in blood and in urine. Defect on chromosome 16 is noticed in 15% of patient [101].

#### **Conclusion**

Infertility is a global health problem affecting one in seven couples. In half of these cases, male factor is, in part, responsible. As a general obstetrician and gynecologist, it is important to be aware of modifiable lifestyle factors that provide opportunities for therapeutic intervention, as well as available sperm assessment and selection tests, including genetic tests, because these could alter clinical management in the not-so-distant future.

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