Chapter

Cytokine Storm in Hypothyroidism in Infertile Women

Neha Sharma, Sanghapriya Mukherjee and Aparajita Kushwaha

Abstract

Thyroid dysfunction interferes with several aspects of reproduction along with pregnancy. Hypothyroidism in females leads to an elevated level of hormone prolactin which decreases levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and finally causes infertility. Obesity acts upon the reproductive cycle by decreasing oestrogen metabolism stimulating menstrual disturbance along with an ovulation. But till date, one of the most underestimated obstacles in fertility is inflammation. Hypothyroidism leads to inflammation in secondary epithelial cells of thyroid gland. This affects immune, nervous system and endocrinal functions of body. Inflammation contributes to oestrogen dominance, a hormonal state that consists of having too little progesterone in the body compared to oestrogen. This leads to progesterone resistance, prevention of progesterone hormone receptors from working properly. This condition also leads to infertility in hypothyroid females. Therefore, not only hormonal profile is sufficient to check up for reproductive problems in the female, but also inflammatory markers like IL-6 and CRP should be added to this profile.

Keywords: hypothyroid, cytokine storm, infertility, inflammation, inflammatory markers

1. Introduction

The risk of facing thyroid problems is nearly 10 times higher for women than for men. For the normal functioning of the ovaries and maturation of eggs, there is a correlation between reproductive hormones (oestrogen and progesterone) and thyroid hormones in females [1]. The balancing of thyroid hormones is thus essential for fertility in women (**Figure 1**). The function of reproductive hormones can be altered by hyper- or hypo-secretion of thyroid hormones and result in thyroid-related infertility [2].

Apart from thyroid hormone imbalance, infertility has a lot to do with the lifestyle of a woman. Hormones released by the thyroid gland can have a variety of effects on the reproductive systems like delay or early onset of puberty, amenorrhea, ovulation, miscarriage, premature birth, etc. Smoking, drinking, stress, consumption of fast food, depression, delayed conception and age are some of the other factors responsible for infertility.

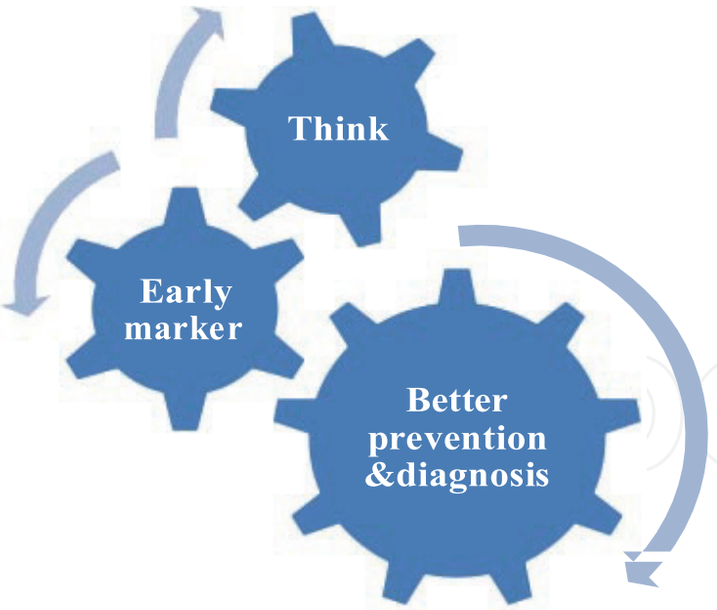

Figure 1.
Outline diagram for awareness. (Courtesy: Dr. Neha Sharma).

2. Hormonal regulation of menstrual cycle: oestrogen and progesterone

In females, usually most oestrogen and progesterone are released by ovarian follicles and corpus luteum, and by placenta at the time of pregnancy. The secretion reaches its peak in 7 days after ovulation and then declines if conception and implantation occur. Two types of oestrogen are produced: oestradiol and oestrone. Small amounts of oestrogen are produced by cells of corona radiata, theca interna and corpus luteum [3].

The main role of oestrogen is endometrial growth, follicle development or ovulation, increased proliferation of epithelial cells in vagina and uterus, stimulation of synthesis of proteins like contractile proteins in myometrial muscle fibres [3].

Other functions of oestrogen include promoting endometrial growth, increasing bone formation, increasing hepatic synthesis of binding proteins, increasing level of circulating coagulation factors II, VIII, IX, X, III and plasminogen and increasing adhesiveness of platelets.

Functions of progesterone are:

- It stimulates the secretary activity of uterine tubes, uterus and the vagina. This is responsible for pre-gestational changes in endometrium and along with oestrogen, it is responsible for the cyclic changes in cervix and vagina.

- Increases membrane potential of myometrial fibres.

Oestradiol as well as progesterone both act on the endometrium: Oestradiol promotes the growth of constituents of the endometrium, while progesterone helps to change from a proliferative pattern into a secondary pattern. When the levels of oestrogen and progesterone fall, it leads to the end of the cycle as endometrium cannot be maintained further, and as a result menstruation occurs [4].

3. Gonadotropin releasing hormones (GnRH)

GnRH activates a surge of LH preceding ovulation [3]. Hypothalamic GnRH is released in an exciting manner by caudate nucleus of hypothalamus. GnRH

production is acted upon by oestradiol or catecholamine neurotransmitters. It reaches to anterior pituitary by hypothalamo-pituitary portal plexus.

Function of GnRH:

- Ovarian follicles act in response to pituitary gonadotrophin secretion by producing the main ovarian hormone oestradiol and progesterone.

- The production of LH and FSH from pituitary is caused by pulses of GnRH, which is produced by hypothalamus.

3.1 Prolactin

Prolactin is secreted through cells of adenohypophysis. The main function of prolactin is the initiation and maintenance of lactation. For ductal growth and development of breasts, prolactin is a must. This is required for synthesis of specific milk proteins (casein, gamma lactalbumin). Although the exact intracellular mechanism of prolactin action is yet not known, prolactin regulates transport of lipoproteins in adrenal gland, testis and ovary to ensure the continuous supply of LDL for steroid genesis. It also promotes synthesis of enzymes of androgen pathway, which facilitates the conversion of pregnenolone to dehydroepiandrosterone and/or dehydroepiandrosterone sulphate [5].

Release of prolactin is under a tonal inhibitory control through hypothalamus. This is also influenced through:

a. Oestradiol: Ovarian oestradiol augments prolactin secretion or action is responsible for the difference in concentrations of prolactin in adult, pre-pubertal or menopausal women)

b. Sleep: Moderate rise in prolactin concentrations at the time of sleep is seen.

c. Stress: Various types of stress, e.g., physical aggression, cold, surgery and heat are all known to raise prolactin levels.

d. Pharmacological agents: Tranquillisers may obstruct dopaminergic receptors, for example the phenothiazine derivatives, or slow down dopamine reuptake from inter-neuronal cleft, for example the tricyclic depressants [6]

Hyperprolactinemia is the most common in hypothalamic–pituitary disorder found in clinical endocrinology [1]. PRL concentration is also increased in women who have a problem in fertility like anovulation, with or without menstrual irregularity, amenorrhea and galactorrhoea. Causes of hyperprolactinemia include:

a. The presence of a prolactin-producing adenoma.

b. Tumour of the pituitary gland, which obstructs the inhibitory control of the hypothalamus.

c. In a few endocrine diseases such as primary hypothyroidism, anti-hypertensive polycystic ovarian syndrome.

d. Intake of antidepressants.

Hyperprolactinemia can interrupt ovarian physiology at various levels, including steroidogenesis, follicular maturation and ovulation, the process of luteinisation and corpus luteum function [7].

3.2 LH and FSH

The gonadotrophins FSH and LH are hormones that are protein in nature secreted by anterior pituitary [1]. LH and FSH are glycoproteins as they are made up of two peptide chains, alpha and specific beta subunit. Both hormones are glycosylated, which determines their bioactivity and half-life.

Secretion of gonadotrophins, LH, FSH is controlled by luliberin. This stimulates the emission of LH effectively than follitropin production, plasma levels of sex

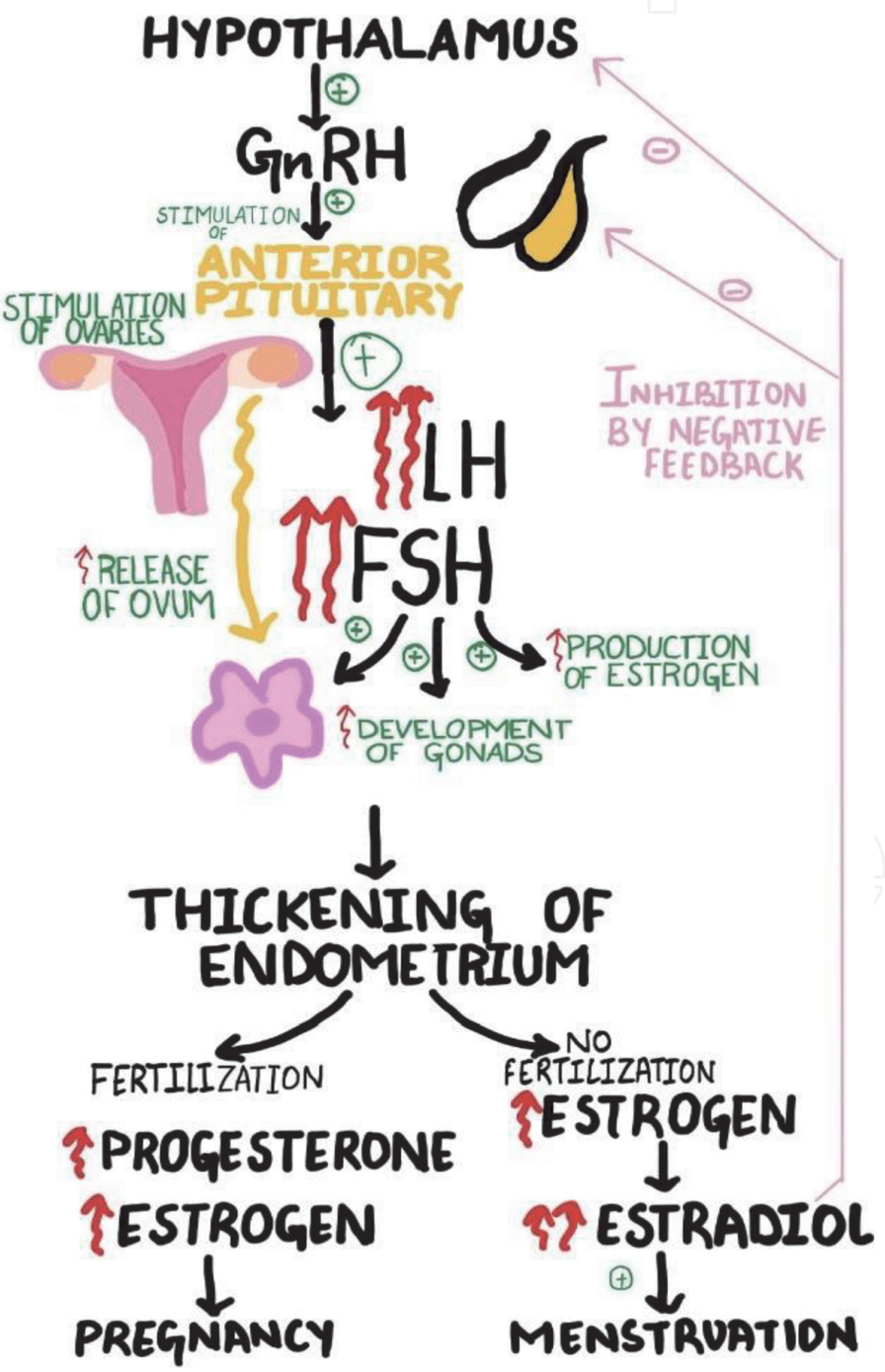

Figure 2.
Hormonal regulation of menstrual cycle. (Courtesy- Ms. Aparajita Kushwaha, Ms. Sanghapriya Mukherjee).

hormone by positive and negative feedback. It is also controlled by hormone Inhibin, which is produced by the Graafian follicles [3].

FSH and LH work on gonads to trigger gametogenesis and synthesis of hormones associated with it. At the follicular stage, FSH and LH trigger oestrogen production by the developing follicle.

LH and FSH have significant actions on the ovary:

a. The major effect of FSH is to trigger growth and development of Graafian follicles, while on the other hand, LH leads to ovulation.

b. Ovarian steroids are produced by actions on FSH and LH.

When Graafian follicle enlarges, it increases the amount of oestrogen and oestradiol production. Within mid-cycle, surge of LH is seen, so ovulation takes place and the Graafian follicle is changed into corpus luteum by progesterone activity [4].

FSH also reaches its peak at the end of the follicular stages, a part of the surge of pre-ovulatory gonadotrophin (**Figure 2**) [6].

4. Thyroid stimulating hormone (TSH)

The thyroid stimulating hormone, also called thyrotropin, is secreted from adenohypophysis in reaction to thyroid releasing hormone (TRH). It is a glycoprotein in nature, containing 209 amino acids [3]. It is chiefly associated with the growth of thyroid gland and stimulation of its hormonal activity [5].

Functions of TSH.

1. It has a wide range of activity on the follicular cells:

    a. TSH acts directly on the thyroid gland to raise the secretion of thyroid hormones and help in formation of follicular cells (cuboidal and columnar shaped).

    b. Increase the number of follicular cells, also known as hyperplasia.

    c. TSH decreases the volume of follicular colloid, thereby increasing vascularity of the gland.

    d. Other effects of TSH on follicular cell activity include:

        - Increases oxygen consumption.
        - Increased glucose utilisation.
        - Increased carbon dioxide production.
        - Increased formation of phospholipids.
        - Increased synthesis of RNA and protein [8, 9].

2. TSH stimulation leads to the secretion of the stored thyroid hormone from the follicular colloid.

3. TSH promotes the production of thyroid hormone by increasing the transportation of iodine into the follicular cells or by enhancing organic

binding of iodine to thyroxine as well as subsequent coupling to form thyroid hormone on the surface of thyroglobulin molecules [10].

4. TSH along with T3 and T4 plays an important role in regulation, synthesis, development, metabolism and overall growth of the body. The functions include:

    a. Strengthening metabolism of carbohydrates, proteins and lipids.

    b. Reinforcement of growth and development.

    c. Regulation and transportation of water and electrolytes.

    d. Stimulation of the cardiovascular system.

    e. Stimulation of the Central Nervous System [11].

5. Hypothyroidism

Hypothyroidism is a condition characterised by elevated serum thyroid stimulating hormone level and decreased serum levels of T3 and T4 due to under activity of the thyroid gland. According to NHANES (National Health and Nutrition Examination Survey), in the last 6 years, the prevalence of hypothyroidism is 4.6% [12]. Thyroid disorders, hypothyroidism or hyperthyroidism are more common in females than in males.

5.1 Causes of hypothyroidism

The causes of hypothyroidism are divided into six categories:

- Hypothyroidism through compensatory thyroid enlargement owing to transient and progressive destruction by hormone biosynthesis, for example, goitrous hypothyroidism.
- Permanent loss and atrophy of tissue of thyroid gland, for example atrophic thyroidism.
- Transient Hypothyroidism, i.e., transient deficiency of thyroid hormones a few days prior to birth.
- Central hypothyroidism due to insufficient stimulation of thyroid gland as a result of hypothalamic or pituitary disease.
- Resistance to thyroid hormone (RTH), which is a deficiency of thyroid hormone [13].

Symptoms of hypothyroidism include cold intolerance, fatigue, lethargy, decreased metabolism, weight gain, brittle nails and dry skin.

5.2 Consequences of hypothyroidism

Thyroid disease is associated with a wide range of metabolic abnormalities, owing to the fact that thyroid hormones act on majority of the metabolic pathways.

6. Infertility

What is infertility?

Infertility is defined as an inability to conceive after 1 year of regular intercourse without contraception. WHO defined infertility as 'a disease of the reproductive system which is explained by inability to achieve pregnancy after twelve months or more of regular unprotected intercourse' [14].

6.1 Types of infertility

First degree or primary infertility.

When a couple is not able to conceive even having unprotected intercourse over a period of minimum 1 year, it is defined as the first degree or primary infertility [15].

Second degree or secondary infertility.

Secondary infertility occurs when a couple cannot conceive for the second time even after regular intercourse without any contraceptives. To count as secondary infertility, the first childbirth should not have occurred with the help of any kind of fertility medication or procedures like IVF [15].

6.2 Causes of infertility

Problems of infertility start from hormonal dysfunction of the hypothalamic pituitary gonadal axis. The major cause of infertility is a disorder of oocyte production, ovulation, healthy sperm production, fallopian tube dysfunction, and lastly, improper implantation of the embryo in the uterine wall.

Sexually transmitted diseases like gonorrhoea and syphilis may also lead to infertility.

PCOD, obesity, thyroid issues and imbalanced hormones of the menstrual cycle can also lead to infertility through a surge in the cytokine levels of the body (cytokine storm).

Multiple studies show that cigarette smoking, narcotics and drugs have been established to impair fertility in both males and females (**Figure 3**). Smoking has unfavourable effects on tubal function, secretion of hormones and cervical mucus production [16].

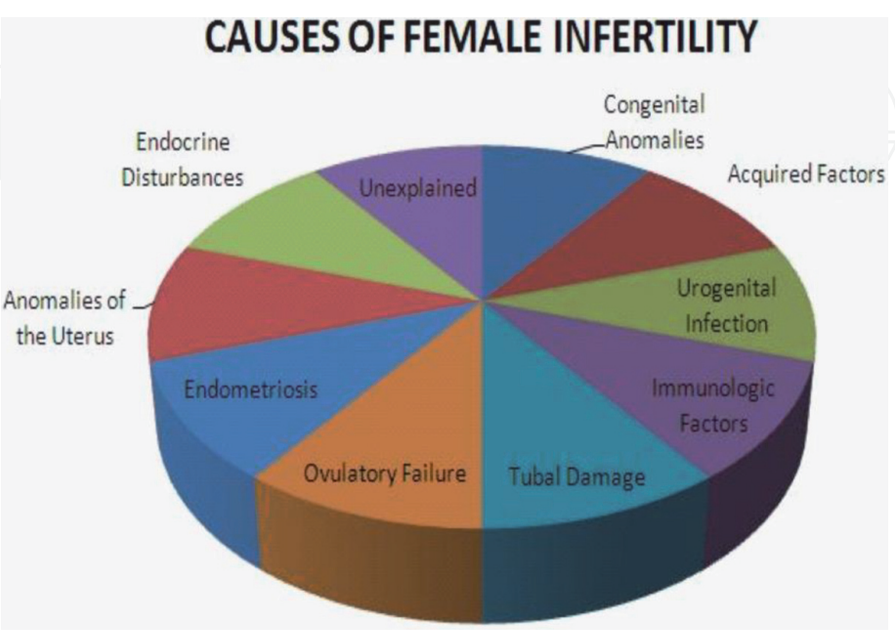

Figure 3.
Causes of infertility (Courtesy – Dr. Neha Sharma).

Ingestion of alcohol has also been shown as a reason to decrease gonadotrophin levels or irregularities in ovulation.

6.3 Factors affecting infertility

Fertility of a couple is defined as fertility of both the partners. High fertility of one partner, to some extent, can balance the low fertility in the other partner. Low fertility in both partners can however lead to first- or second-degree infertility [17].

Another significant factor influencing fertility is the age of the female partner. Fertility in both males and females is at its peak in the mid-twenties. In females, it starts to decline sharply after 30 years [2]. As many couples do not conceive a child at an early age, postponement of pregnancy decreases the number as well as the quality of egg, reducing the chances of getting pregnant. Females also go through an unwanted sequel of circumstances such as endometriosis, pelvic inflammatory disease (PID) and uterine fibrinoids. All these complications lead to the release of cytokines in the form of interleukins and C-reactive proteins, which further contribute to the already existing infertility in females [15].

It is not easy to determine the exact cause of infertility as there are many factors that bias. The cause can be recognised only after proper investigations.

6.4 Association of female infertility with hypothyroidism

Hypothyroidism is common in males and females. A range of reproductive disorders ranging from abnormal sexual growth to menstrual cycle irregularities or infertility have been connected to thyroid disorders. Morphological changes of follicles in hypothyroidism may be an outcome of higher prolactin production that blocks both secretion as well as action of gonadotropins [4]. Enough supplementation of thyroid hormone restores prolactin and normalises ovulatory function [3]. Hypothyroidism itself possibly will contribute to infertility because thyroid hormones may be necessary for maximum production of both oestradiol and progesterone hormones (**Figure 4**).

7. Obesity

Obesity represents excess body fat or is defined by a basal metabolic rate of more than 30 ky/m^2. Elevated levels of TSH; hypothyroidism does not always result in weight problems but may cause obesity in some cases.

Subclinical hypothyroidism, marked by elevated TSH concentration with normal concentration of peripheral thyroid hormones (T3 andT4) has been consistently found in obese individuals. Lipid profile findings of obese individuals show marked dyslipidemia, involving high levels of serum TG, LDL, TC and low serum HDL level [14]. A recent report from coronary artery risk development in young adults (CARDIA) shows that among physiologically infertile women, probability of infertility is twice in African and American women as compared to others [15]. Economic problems have led to limited access to diagnosis and treatment of various diseases, resulting in selective underestimation of thyroid dysfunctions and hypothyroidism related infertility [18].

Thyroid affects various aspects of reproduction; especially pregnancy is adversely affected by thyroid dysfunction [19].

An understanding of the implications of obesity and hormonal balance and fertility may help couples facing challenges in conception to give the reproductive health and better opportunity and take steps to improve the reproductive capacity and probability of a healthy pregnancy.

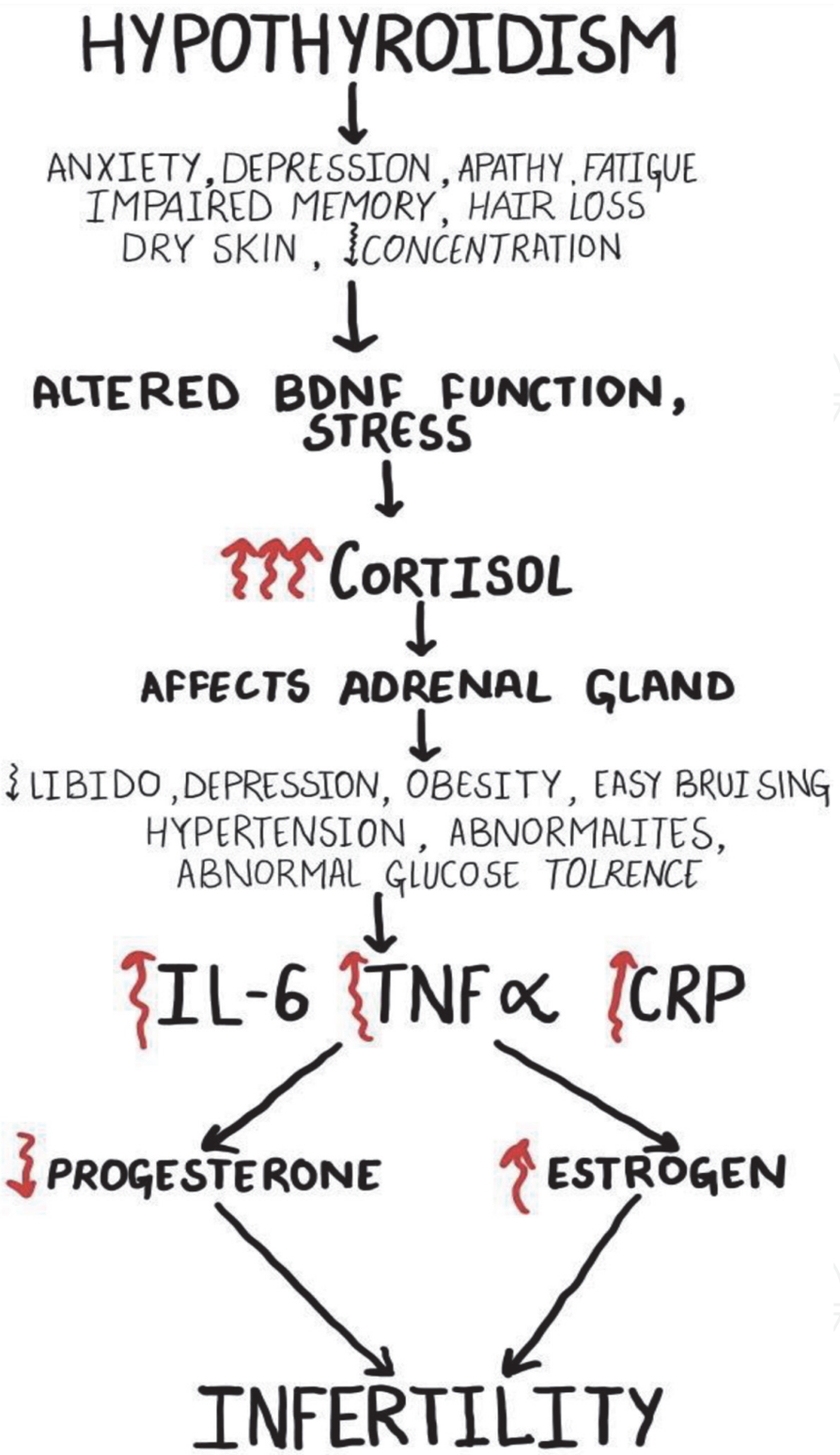

Figure 4.
Hypothyroidism and infertility. (Courtesy – Ms. Aparajita Kushwaha, Ms. Sanghapriya Mukherjee).

Consequences of obesity on ovarian function.

- Changed oestrogen metabolism.
- Insulin resistance.
- High androgen levels.

- Slim women are oestrogen deficient while obese women have an excess of oestrogen but have irregular cycles [20].

- BMI – more than 30 kg/m^2.

- Body fat affects the onset of puberty.

Obese adipocytes act as secretary cells and release adipose cytokines, chemokines and cytokines. The secretion of inflammatory agents like IL-6 and TNF-@ is considerably increased in obese individuals. These contribute towards producing a low-grade chronic systemic inflammation. Thyroid hormones can affect the metabolism of cholesterol and triglycerides, where depression of cholesterol concentrations caused due to an increase in hepatic LDL levels, or decreased LDL clearance can be seen. As a result, total cholesterol or LDL levels are increased in hypothyroid individuals.

Obesity is not only associated with infertility but also with various other health problems including hypertension, cardiovascular diseases, diabetes and hormonal imbalances. The effects of obesity expand across conception, gestation, parturition and also post-parturition. Excess weight gain negatively impacts efficacy of treatment and results of served reproductive techniques. Therefore, high body fat and obesity cause a rise in oestrogen production that body perceives as birth control confining the chances of acquiring pregnancy (**Figure 5**).

8. Stress

Stress is most common in women. Stress is normally underestimated because of dysfunction in reproduction. Stress-induced anovulation (SIA) usually termed

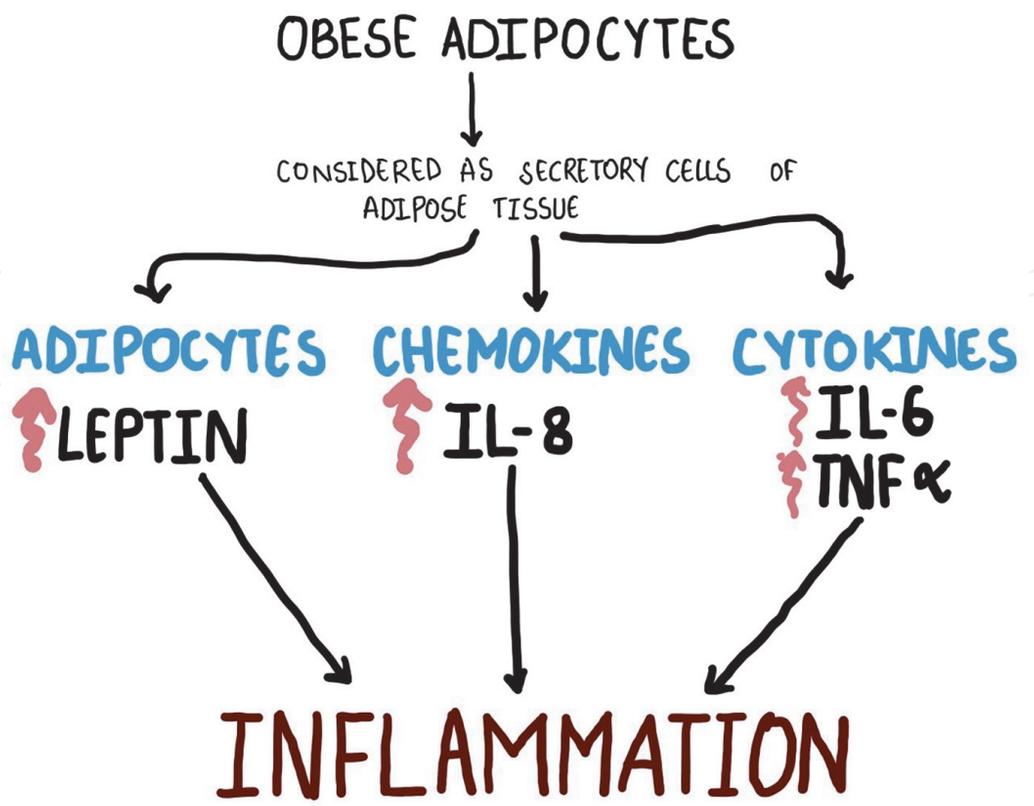

Figure 5.
Relationship between obesity and inflammation. (Courtesy – Ms. Aparajita Kushwaha, Ms. Sanghapriya Mukherjee).

functional hypothalamic amenorrhea (FHA) and functional chronic hypothalamic anovulation, which causes infertility, increases acute and chronic health burden in women of all ages.

Chronic psychological and physical stress is common among hypothyroid individuals. This causes an elevated production of cortisol which aggravates release of IL-6incirculation [21].

Increased level of IL-6 tends to suppress immune system and endocrine system. This is responsible for production of acute phase protein, i.e., CRP.

Effects of IL-6 are mediated through regression of BDNF (Brain-Derived Neurotropic Factor). Downregulation of BDNF causes decreased connectivity in between anterior singulating cortex and several limbic areas like hippocampus. Increased level of IL-6 in stress causes FHA (functional hypothalamic amenorrhea). This leads to defects in the mechanism operating the anterior pituitary gland resulting in delayed ovum maturation, decreased FSH and decreased LH, which results in infertility.

IL-6 synthesis through peripheral blood mononuclear cultures of chronically stressed individuals has been reported to be higher than that of cultures from control subjects when stimulated by LPS, in a study conducted on older adults [22].

IL6 is a multifunctional cytokine with essential roles in inflammatory response or in leading T-cell differentiation in acquired immunity. IL-6 is broadly expressed in reproductive tract or gestational tissues of women, as well as maintains a regulatory role in embryo implantation or placental development, and immune adaptations are required for tolerating pregnancy. Elevated IL-6 is recurrently evident in altered cytokine profiles, feature of unexplained infertility, recurrent miscarriage, preterm delivery and preeclampsia. Especially, there is undeniable evidence representing altered IL-6 trans-signalling in female prone to recurrent miscarriage, with higher IL-6 bioavailability potentially suppressing generation of CD4 cells and T-cells, regulatory cells necessary for tolerance of pregnancy.

Inadequate local IL-6 may also lead to fetal loss since IL-6 appearance is reduced in the endometrium of females due to recurrent miscarriage [23].

CRP is an acute phase response protein synthesised by liver. Small levels of CRP are present normally in blood but increase rapidly in response to inflammatory conditions [22]. Hypothyroidism can increase chronic subclinical inflammation which raises IL-6 levels, resulting in raised levels of CRP. Hypothyroidism is associated with relatively increased inflammatory marker levels [24]. Psychological stress causes a rise in CRP, which can lead to a poor prognosis as well as pregnancy complications [25].

Stress, eating habit and infertility:

Infertility often results in immense pressure leading to a lot of stress and anxiety. Depression tends to induce unhealthy eating habits. Due to excessive consumption of unhealthy food, it paves way to obesity and an increase in the level of the

Figure 6.
Cytokine storm in hypothyroid subjects. Courtesy: Ms. Sanghapriya Mukherjee, Ms. Aparajita Kushwaha.

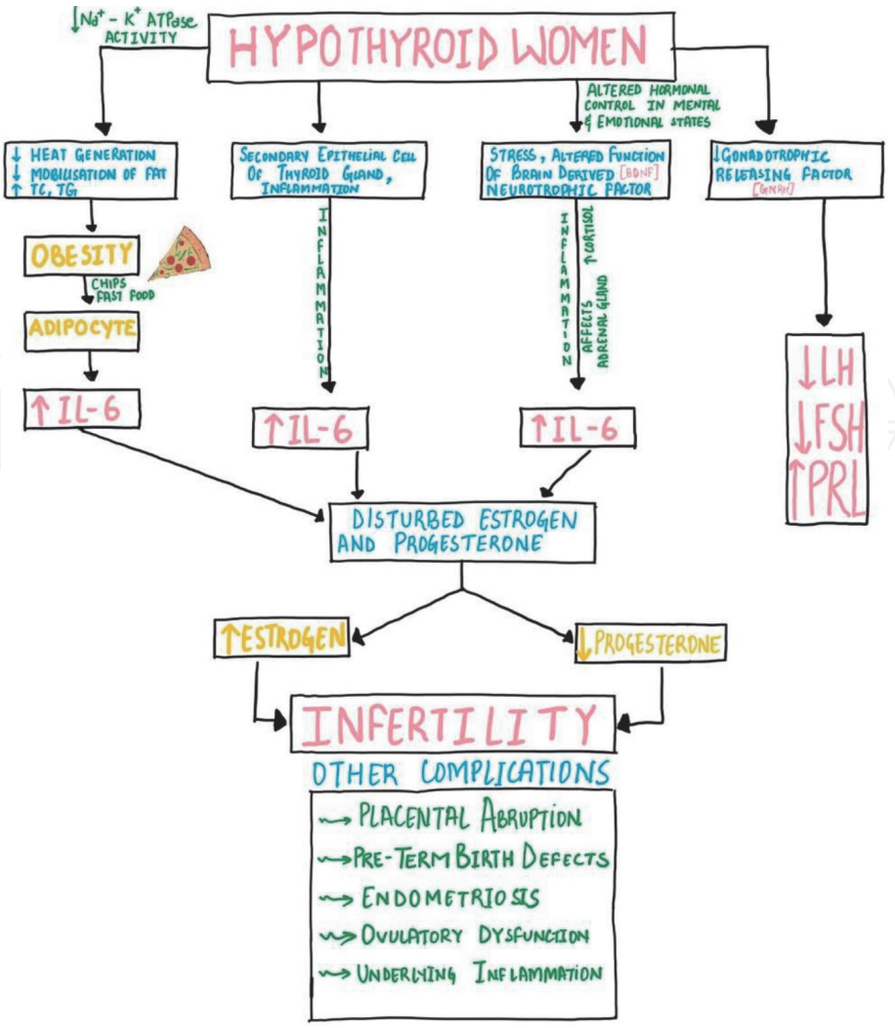

Figure 7.
Summary: hypothyroidism and infertility. (Picture courtesy: Dr. Neha Sharma).

inflammatory markers (cytokine storm), and finally resulting in probability of conception to almost zero (**Figures 6** and 7).

9. Conclusion

In women of reproductive age, hypothyroidism poses a great risk to their fertility. Hypothyroidism triggers a cascade of physiological irregularities and also makes women more prone to diseases.

Though obesity is not necessarily a part of symptoms and effect of hypothyroidism, it is not uncommon for hypothyroid women to be obese. Various factors contribute towards excess weight gain in hypothyroid women, mainly, hypothyroidism-induced depression and hormonal changes, which usually results in unhealthy eating habits and eventually weight gain. The accumulation of fat cells or obese adipocytes acts as secretary cells and secrete IL-8, IL-6 and TNF-α (inflammatory agents) causing a low-grade inflammatory response.

Hypothyroid women also suffer from chronic physiological and mental stress. Chronic stress causes elevated levels of cortisol which triggers increased secretion of inflammatory agents like IL-6 and CRP.

Hypothyroidism induces obesity, stress, anxiety and depression, thus cumulatively causes inflammation in the body, which leads to difficulty in conception, frequent miscarriages and infertility in severe cases.

Abbreviations

BDNF	Brain derived neurotropic factor
BMI	Body Mass Index
CARDIA	Coronary artery risk development in young adults
CD-4	Cluster of differentiation-4
CRP	C reactive protein
FHA	Functional hypothalamic amenorrhoea
FSH	Follicle stimulating hormone
GnRH	Gonadotropin releasing hormone
HDL	High density lipoprotein
IL-6	Interleukin-6
IVF	In vitro fertilisation
LH	Luteinizing hormone
LPS	Luteal phase ovarian stimulation
PCOD	Poly-cystic ovarian disease
PID	Pelvic inflammatory disease
SIA	Stress induced anovulation
TC	Total cholesterol
TG	Triglycerides
TNF	Tumour necrosis factor
TSH	Thyroid stimulating hormone
WHO	World Health Organisation

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