HYPOTHYROIDISM AND FEMALE INFERTILITY

Essay

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LIST OF ABBREVIATIONS

OD	:	Ovulatory dysfunction
ART	:	Assisted reproductive technology
IVF	:	Invitro fertilization
ICSI	:	Intra cytoplasmic sperm injection
WHO	:	World health organization
AITD	:	Auto immune thyroid disease
TSH	:	Throid stomulating hormne
FT4	:	Free thyroxin
BMR	:	Basal metabolic rat
TNF	:	Tumor necrosis factor
IFN	:	Interferon
TSHR	:	Thyroid stimulating hormone receptor
TPO	:	Thyroid peroxidase antibodies
TSI	:	Thyroid stimulating inhibitory antibodies
IQ	:	Intelligent equation
RTH	:	Riedel's thyroditis
IRMAs	:	Immuno radiometric assay
THBR	:	Thyroid hormone binding ratio
HCG	:	Human chorionic gonadotrophin
ATA	:	Antithyroid antibodies
TAI	:	Thyroid auto immunity
LH	:	Luteinizing hormone
GNRH	:	Gonadotrophin releasing hormone
SH	:	Subclinical hypothyroidism
FSH	:	Follicle stimulating hormone
SHBG	:	Sex hormone binding globulin

E2	:	Estradiole
PRL	:	Prolactine
LT4	:	Levothyroxine
TRH	:	Thyroid releasing hormone
TSH-RIA	:	Thyroid stimulating hormone radio immune assay
PCOS	:	Polycystic ovarian syndrome
COH	:	Controlled ovarian hyper stimulation

INTRODUCTION

FEMALE INFERTILITY:

Difficulty to conceive or sub fertility constitutes a major psychological burden. Assisted reproductive technology (ART) changed significantly the outcome of couples faced with sub fertility. These techniques consequently increased tremendously our understanding of the mechanisms underlying reproductive failure and opened new perspectives for future interventions, not only to increase cumulative conception rates after ART, but also spontaneous pregnancy rates. Thyroid dysfunction adversely affects fertility.[1]

Many studies imply a role for immunology, including thyroid autoimmunity in conception failure. In this review we attempt to update the available information on the adverse effect of thyroid dysfunction and/or thyroid autoimmunity on sub fertility and we propose a rationale for testing and potential treatment options.[2]

Infertility is defined as the inability to conceive after 1 year of regular intercourse without contraception. The prevalence of infertility is estimated between 12 and 14% and has remained stable in recent years studies looking at the prevalence of sub fertility included primary infertility (inability to conceive) and secondary infertility (inability to conceive the desired number of children).[3]

Some authors distinguish sub fertility from infertility, the latter being the inability to conceive (absence of sperm, premature menopause, complete tubal obstruction). It thus represents a common condition, with important medical, economic and psychological implications.[4]

Medical and surgical services for the treatment of infertility have considerably increased in number throughout the last decade.[5]

This trend is probably the result of the tendency to delay childbearing age, the emergence of effective treatments of assisted reproduction and the increased public awareness of such treatments. In parallel, our understanding of the pathophysiological mechanisms underlying infertility has increased tremendously.[6]

Infertility evaluation usually indentifies different causes, including male infertility (30%), female infertility (35%), the combination of both (20%), and finally unexplained or 'idiopathic' infertility (15%).[7]

Female causes of infertility comprise endometriosis, tubal damage and ovulatory dysfunction (OD). According to WHO criteria OD is further subdivided in different categories:

Groups I: With hyperprolactinaemia.

Groups II: With low gonadotrophins.

Group III: Including primary ovarian failure.[8]

Male infertility is considered when identifiable female causes of infertility are excluded and semen quantity and quality fails to fulfill WHO criteria. 13 In the presence of a normal spermiogram and the absence of female infertility, couples are considered to have idiopathic infertility.[9]

As a first aid of reproduction, intrauterine insemination is proposed. When this procedure fails, assisted reproductive technology (ART) is applied. ART includes two techniques, in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). ICSI is the technique of choice in cases of male infertility. Excellent reviews on the subject have recently been published.[10]

Among negative prognostic factors influencing fertility, immunologic factors may play an important role in the reproduction processes of fertilization, implantation and fetal development.[11]

Different investigations support the association between reproductive failure and abnormal immunological test results, including anti-phospholipid, antinuclear antibodies and organ specific autoimmunity, among which the presence of antithyroid antibodies.[12]

Although an increased prevalence of immunological parameters has been linked to infertility, it remains controversial whether infertile women should undergo a complete immunological screening. It is indeed uncertain whether immunomodulatory treatment improves the outcome of infertility. Nevertheless, there is good evidence that the presence of thyroid autoimmunity (AITD) adversely affects the outcome of pregnancy, following the ART procedure.[13]

Thyroid dysfunction is a condition known to reduce the likelihood of pregnancy. Abnormal thyroid hormones disturb the normal menstrual pattern and treatment improves fertility. Frank hypo-and hyperthyroidism is readily treated and, if missed, is associated with an increased risk of miscarriage and possible long-term health consequences for the child.[14]

The impact of screening and treatment of subclinical thyroid disorders on infertility management has not extensively been documented in the literature. This review attempts to identify the impact of thyroid disease (AITD and thyroid dysfunction) on female infertility, and to propose guidelines for screening and treatment, when indicated according to the level of evidence.[15]

What is hypothyroidism:

Hypothyroidism is an underactive thyroid gland. Hypothyroidism means that the thyroid gland can't make enough thyroid hormone to keep the body running normally. People are hypothyroidism if they have too little thyroid hormone in the blood. Common causes are autoimmune disease, surgical removal of thyroid, and radiation treatment.

1. SYMPTOMS:

What are the symptoms:

When thyroid levels are too low, the body's cells can't get enough thyroid hormone and the body's processes start slowing down. As the body slows. You may notice that you feel colder. You tire more easily, your skin is getting drier. You're becoming forgetful and depressed, and you've started getting constipated. Because the symptoms are so variable, the only way to know for sure whether you have hypothyroidism is with blood tests.

2. CAUSES:

What causes hypothyroidism:

There can be many reasons why the cells in the thyroid gland can't make enough thyroid hormone. Here are the major causes, from the most to the least common.

- Autoimmune disease: In some people's bodies, the immune system that protects the body from invading infections can mistake thyroid gland cells and their enzymes for invaders and can attack them. Then there aren't enough thyroid cells and enzymes left to make enough thyroid hormone. This is more common in women than men. Autoimmune thyroiditis can begin suddenly or it can develop slowly over years. The most common forms are Hashimoto's thyroiditis and atrophic thyroiditis.
- Surgical removal of part or all of the thyroid gland. Some people with thyroid nodules, thyroid cancer, or Graves' disease need to have part or all of their thyroid removed. If the whole thyroid is removed people will definitely become hypothyroid.

If part of the gland is left it may be able to make enough thyroid hormone to keep blood levels normal.

- Radiation treatment. Some people with graves disease, nodular goiter, or thyroid cancer are treated with radioactive iodine (I-131) for the purpose of destroying their thyroid gland. Patients with Hodgkin's disease, lymphoma, or cancer of the head or neck are treated with radiation. All these patients can loose part or all their thyroid function.
- Congenital hypothyroidism: few babies are born without a thyroid or with only a partly formed one a few have part or all of their thyroid in the wrong place (ectopic thyroid).
- **Thyroiditis:** Thyroiditis is an inflammation of the thyroid gland. Usually caused by an autoimmune attack or by a viral infection. Thyroiditis can make the thyroid dump its whole supply of thyroid hormone into the blood at once, causing brief hypothyroidism (too much thyroid activity); then thyroid becomes underactive.
- Medicines: Medicines such as amiodarone, lithium, interferon alpha and interleukin-2 can prevent the thyroid gland from being able to make hormone normally. These are most likely to trigger hypothyroidism in patients who have a genetic tendency to autoimmune thyroid disease.
- Too much or too little iodine: The thyroid gland must have iodine to make thyroid hormone. Iodine comes into body in food and travels through the thyroid. Keeping thyroid hormone production in balance requires the right amount of iodine. Taking in too much iodine can cause or worsen hypothyroidism.
- Damage to the pituitary gland: The pituitary "master gland" tells the thyroid how much hormone to make. When the pituitary is damaged by a tumor, radiation, or surgery it may no longer be able to give the thyroid instructions and the thyroid may stop making enough hormone.
- Rare disorders that infiltrate the thyroid in a few people, diseases deposit abnormal substances in the thyroid and impair its ability to function. For example, amyloidosis can deposit amyloid protein, sarcoidosis can deposit granulomas, and hemochromatosis can deposit iron.

3. DIAGNOSIS:

How is hypothyroidism diagnosed:

The correct diagnosis of hypothyroidism depends on the following.

- Symptoms. Hypothyroidism doesn't have any characteristic symptoms. There are no symptoms that people with hypothyroidism always have and many symptoms of hypothyroidism can occur in people with other diseases.
- Medical and family history. You should tell your doctor:
  - About changes in your health that suggest that your body is slowing down.
  - If you ever had thyroid surgery.
  - If you ever had radiation to your neck.
  - If you are taking any of medicines that can cause hypothyroidism.
  - Whether any of your family members have thyroid disease.

- Physical examination: The doctor will check your thyroid gland and look for changes such as dry skin, swelling, slower reflexes and a slower heart rate.
- Blood tests: There are tow blood tests that are used used in the diagnosis of hypothyroidism:

TSH (thyroid-stimulating hormone) test: This is the most important and sensitive test for hypothyroidism. It measures how much of the thyroid hormone thyroxin (T4) the thyroid gland is being asked to make. An abnormally high TSH means hypothyroidism: the thyroid gland is being to make more T4 because there isn't enough T4 in the blood.

T4 tests: Most of the T4 in the blood is attached to a protein called thyroxin-binding globulin. The bound T4 can't get into body cells. Only about 1%=2% of T4 in the blood is unattached ("free") and can gel into cells. The free T4 in the free T4 index are both simple blood tests that measure how much unattached T4 is in the blood and available to get into cells.

How is hypothyroidism treated:

Thyroxin (T4) replacement.

Hypothyroidism can not be cured but in almost every patient hypothyroidism can be controlled. It is treated by replacing the amount of hormone that your own thyroid can no longer make to bring your T4 and TSH back to normal levels. So even thyroid gland can work right. T4 replacement can restore your body's thyroid hormone levels and your body's function. Synthetic thyroxin pills contain hormone exactly like the T4 that the thyroid gland itself makes. All hypothyroid patients except those with severe myxedema can be treated as outpatients, not having to be admitted to the hospital.

Side effects and complications: The only dangers of thyroxin are caused by taking too little or too much. If you take too little, your hypothyroidism will continue. If you take too much you will develop the symptoms of hyperthyroidism-an overactive thyroid gland. The most common symptoms of too much thyroid hormone are fatigue but inability to sleep, greater appetite, nervousness, shakiness, feeling hot when other people are cold and trouble because of weak muscles shortness of breath. Patients who have hyperthyroid symptoms should have their TSH tested, if it is low indicating too much thyroid hormone their dose may need to be lowered.

Follow-up:

You will need to have your TSH checked about every 6 to 10 weeks after a thyroxin dose change. You may need tests more often you are pregnant or you are taking a medicine that interferes with your body's ability to use thyroxin the goal of treatment is to get and keep your TSH is the normal range.

AIM OF THE WORK

The present study was undertaken to assess the relation between hypothyroidism and female infertility.

Chapter (I)
FEMALE INFERTILITY

Difficulty to conceive or sub fertility constitutes a major psychological burden. Assisted reproductive technology (ART) changed significantly the outcome of couples faced with sub fertility. These techniques consequently increased tremendously our understanding of the mechanisms underlying reproductive failure and opened new perspectives for future interventions, not only to increase cumulative conception rates after ART, but also spontaneous pregnancy rates. Thyroid dysfunction adversely affects fertility.[1]

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Chapter (II)
HYPOTHYROIDISM

Adult hypothyroidism:

The onset of hypothyroidism is usually so insidious that the classic clinical manifestations may take months or years to appear and frequently go unnoticed by persons well acquainted with the patient. The gradual development of the hypothyroid state is due to a slow progression both of

Table (1): Symptoms of myxedema (77 cases)

Symptom	% of cases	Symptom	% of cases
Weakness	99	Constipation	61
Dry skin	97	Gain in weight	59
Coarse skin	97	Loss of hair	7
Lethargy	91	Pallor of lips	57
Slow speech	91	Dyspnea	55
Edema of eyelids	90	Peripheral edema	55
Sensation of cold	89	Hoarseness or aphonia	52
Decreased sweating	89	Anorexia	45
Cold skin	83	Nervousness	35
Thick tongue	82	Menorrhagia	32
Edema of face	79	Palpitation	31
Coarseness of hair	76	Deafness	30
Pallor of skin	67	Precordial pain	25
Memory impairment	66		

Data from Means JH the thyroid and its disease

thyroid hypo function and of the clinical manifestation after thyroid failure is complete. This course is in contrast to the more rapid development of the hypothyroid state that occurs when replacement therapy is discontinued in a patient with treated thyroprivic hypothyroidism or when the thyroid gland of a normal subject is surgically removed. In these circumstances the overall metabolic effect of thyroid hormone withdrawal can be judged from measurements of BMR and compared with the emergence of the classic clinical picture. The BMR decreases to about – 20% and symptoms of mild hypothyroidism appear within 3 weeks. After 6 weeks, the BMR has decreased to – 30% and manifestations of frank hypothyroidism are present; by 3 months, full – blown myxedema is usually evident.[17]

The early symptoms of hypothyroidism are variable and nonspecific.[18]

Tiredness and lethargy are common and lead to difficulty in performing a full day's work. Constipation may develop or, if present, become worse. Sensitivity to cold may be an early manifestation; its presence is often suggested by the use of more blankets on the bed or a preference for warm weather. Women may complain of menstrual disturbance especially menorrhagia, or difficulty in conceiving because of anovulatory cycles. Loss of libido occasionally occurs in both men and women. At this stage of the disease the BMR is moderately decreased. With progression of the disease the BMR falls to its minimal value usually between – 35 and – 45%, but the clinical picture continues to evolve slowly. Drowsiness and slowing of intellectual and motor activity appear. The patient becomes apathetic and loses interest in work and environment. Women frequently complain of hair loss, brittle nails, and dry skin.[19]

Despite a reduction in appetite, modest weight gain often occurs. The voice becomes husky, which may be attributed to laryngitis. Orbital puffiness may be present. Mucus collects in the eyes, and lids are often stuck together when the patient awakes in the morning. Stiffness and aching of muscles are sometimes prominent and may be attributed to "rheumatism". Numbness and tingling of the fingers may occur. Progressive deafness may lead the patient to seek medical advice.[20]

Eventually, the picture of full-blown myxedema results, with thickened features, enlarged tongue, hoarseness, no pitting edema, and extreme mental and physical lethargy.[21]

Mild hypothermia may call the physician's attention to the diagnosis. Many structural and functional manifestations become evident, but occasionally those arising in a particular organ predominance. The patient, if untreated, may remain in this state for years, finally developing myxedema in these circumstances, rapid repletion of the peripheral hormone pool is necessary. This can be accomplished by a single intravenous dose of 500μg of levothyroxine in the average adult. Alternatively, by virtue of its rapid onset of action, levothyroxine (25μg orally every 8h) can be used if the patient is able to take medication by mouth as an intravenous preparation is not available. With both regimens, the initial effect is achieved within several hours. Oral therapy with levothyroxine is instituted as soon as possible, as outlined earlier.

Because of the possibility that acute increases in metabolic rate will exist pituitary–adrenocortical reserve, supplemental glucocorticoid should be administered. Finally, in view of the tendency of hypothyroid patients to retain water, intravenous fluids should be given with caution.[22]

When hypothyroidism results from administration of iodine or drugs with antithyroid activity, withdrawal of the offending agent usually suffices to relieve both the hypothyroidism and the accompanying goiter.[23]

Infants and children:

In the cretin the critical factor determining eventual intellectual attainment is the age at which adequate treatment with thyroid hormone was begun. The initiation of treatment for infants with congenital hypothyroidism should consists of raising the serum T4 level to greater than 130nmol/L (10μg/dL) as rapidly as possible and maintaining it here for the first 3 to 4 years of life. This is usually accomplished by administering an initial levothyroxine dose of 50μg/d, which is considerably higher than the adult dose on a weight basis and accords with the higher metabolic clearance of the hormone in the infant.[24]

The serum TSH concentration may not normalize completely on this high dose because of an apparent residual rest of the pituitary feedback mechanism. After age 1 to 2, a TSH result in the normal range may be used as an index for optimal therapy in infants and in children as it is in adults.[25]

Speical aspects of hypothyroidism:

Subclinical hypothyroidism: The term subclinical hypothyroidism designates a situation in which an asymptomatic patient has normal free thyroid hormone indices but a slightly elevated TSH level. Other synonyms for this common condition are mild hypothyroidism, preclinical hypothyroidism, biochemical hypothyroidism, and decreased thyroid reserve. There is a modest elevation of the TSH level in such patients between 5.5 and 15mU/L. this syndrome is most often seen in patients with Hashimoto disease or with Graves disease after treatment with surgery or radioactive iodine. It is also observed in patients with no evidence of autoimmune thyroid diseases other than circulating antithyroid antibodies.[26]

Patients with type I diabetes mellitus, primary biliary cirrhosis, and vitiligo are prone to develop subclinical or frank hypothyroidism, as are patients with pernicious anemia and progressive systemic sclerosis.[27]

A number of studies have evaluated the utility of thyroid hormone treatment in such patients. Physiological end points used to judge its effects include measurements of various serum enzymes, systolic time intervals, and psychometric testing, and the effects have been variable. In the most carefully controlled studies, one or another of the physiological or psychological parameters has responded in a positive fashion in about 25% of such patients.[28]

In one study that employed a double – blind crossover approach, the 4 of 17 women who improved could be differentiated only be somewhat lower serum free T3 concentration at the start of the study.[29]

Thus, when confronted with this clinical situation, there is no clearly correct approach. It is of interest vies the issue of the relative roles of T4 and T3 in the regulation of TSH in humans that in virtually all such studies, levothyroxine treatment causes an increase in the free T4 level, the serum free T3 level remains constant, and the serum TSH level is suppressed to normal. This is consistent with expectations based on animal studies discussed earlier and on studies of human iodine deficiency and hypothyroidism.[30]

In the authors opinion, one factor favoring institution of levothyroxine therapy is the presence of antithyroid microsomal antibodies in significant titers (>1/1600) or the presence of goiter. There is a risk of progression of thyroid dysfunction in patients with Hashimoto disease and, depending on the clinical circumstances, this premonitory sign of thyroid failure may be sufficient justification for initiation therapy.[31]

To be weighted against this are the expense and bother of daily medication, not acceptable to many patients, as well as the possibility that over dosage with levothyroxine may aggravate osteoporosis. If a therapeutic trial is performed, the TSH concentration should be monitored carefully and not be permitted to fall below normal. If no therapy is given, patients should be monitored at intervals of 6 to 12 months.[32]

Classification: Autoimmune hypothyroidism may be associated with a goiter (Hashimoto's, or goitrus thyroiditis) or, at the later stages of the disease, minimal residual thyroid tissue (atrophic thyroiditis). Because the autoimmune process gradually reduces thyroid function, there is a phase of compensation when normal thyroid hormone levels are maintained by a rise in TSH. Through some patients may have minor

symptoms, this state is called subclinical hypothyroidism or mild hypothyroidism. Later, free T4 levels fall and TSH levels rise further; symptoms become more readily apparent at this stage (usually TSH > 10mU/L), which is referred to as clinical hypothyroidism or overt hypothyroidism.[33]

Prevalence: The mean annual incidence rate of autoimmune hypothyroidism is up to 4 per 1000 women and 1 per 1000 men. It is more common in certain populations, such as the Japanese, probably because of genetic factors and chronic exposure to a high-iodine diet. The mean age at diagnosis is 60 years, and the prevalence of overt hypothyroidism increases with age. Subclinical hypothyroidism is found in 6 to 8% of women (10% over the age of 60) and 3% of men. The annual risk of developing clinical hypothyroidism is about 4%when subclinical hypothyroidism is associated with positive TPO antibodies.[34]

Pathogenesis: In Hashimoto's thyroiditis, there is a marked lymphocytic infiltration of the thyroid with germinal center formation, atrophy of the thyroid follicles accompanied by oxyphil metaplasia, absence of colloid, and mild to moderate fibrosis. In atrophic thyroiditis, the fibrosis is much more extensive, lymphocyte infiltration is less pronounced, and thyroid follicles are almost completely absent. Atrophic thyroiditis likely represents the end stage of Hashimoto's thyroiditis rather than a distinct disorder.[35]

As with most autoimmune disorders, susceptibility to autoimmune hypothyroidism is determined by a combination of genetic and environmental factors, and the risk of either autoimmune hypothyroidism or Graves' disease is increased among sibling. HLA-DR polymorphisms are the best documented genetic risk factors for autoimmune hypothyroidism, especially HLA-DR3, -DR4, and – DR5 in Caucasians. A week association also exists between polymorphisms in CTLA-4, a T cell –regulating gene, and autoimmune hypothyroidism.[36]

Both of these genetic associations are shared by other autoimmune diseases, which may explain the relationship between autoimmune hypothyroidism and other autoimmune disease, especially type 1 diabetes mellitus, Addison disease, pernicious anemia, and vitiligo. HLA-DR and CTLA-4 polymorphisms account for approximately half of the genetic susceptibility to autoimmune hypothyroidism. The other contributory loci remain to be identified.[37]

A gene on chromosome 21 may be responsible for the association between autoimmune hypothyroidism and Down syndrome. The female

preponderance of thyroid autoimmunity is most likely due to the effects of sex steroids on the immune response but an X chromosome-related genetic factor is also possible, which may account for the high frequency of autoimmune hypothyroidism in Turner syndrome. Environmental susceptibility factors are also poorly defined at present.[38]

The thyroid lymphocytic infiltrate in autoimmune hypothyroidism is composed of activated CD4+ and CD8+ T cells, as well as B cells. Thyroid cell destruction is believed to be primarily mediated by the CD8+ cytotoxic T cells, which destroy their targets by either perforin-induced cell necrosis or granzyme B- induced apoptosis. In addition, local T cell production of cytokines, such as tumor necrosis factor (TNF), IL-1, and interferon (IFN) γ, may render thyroid cells more susceptible to apoptosis mediated by death receptors, such as Fas, which are activated by their respective legends on T cells. These cytokines also impair thyroid cell function directly, and induce the expression of other pro inflammatory molecules by the thyroid cells them selves, such as cytokines, HLA class I and class II molecules, adhesion molecules, CD40, and nitric oxide. Administration of high concentration of cytokines for therapeutic purposes (especially IFN-α) is associated with increased autoimmune thyroid disease, possibly through mechanisms similar to those in sporadic disease.[40]

Antibodies to Tg and TPO are clinically useful markers of thyroid autoimmunity, but any pathogenic effect is restricted to secondary role in amplifying an ongoing autoimmune response. TPO antibodies fix complement, and complement membrane attack complexes are present in the thyroid in autoimmune hypothyroidism. However, trans placental passage of Tg or TPO antibodies has no effect on the fetal thyroid, which suggests that T cell- mediated injury is required to initiate autoimmune damage to the thyroid. Up to 20% of patients with autoimmune hypothyroidism have antibodies against the TSH-R which, in contrast to TSI, do not stimulate the receptor but prevent the binding of TSH. These TSH-R-blocking antibodies against the TSH-R which, in contrast to TSI, do not stimulate the receptor but prevent the binding of TSH. These TSH-R-blocking antibodies therefore cause hypothyroidism and, especially in Asian patient, thyroid atrophy. Their trans placental passage may induce transient neonatal hypothyroidism. Rarely, patients have a mixture of TSI- and TSH-R-blocking antibodies, and thyroid function can oscillate between hyperthyroidism and hypothyroidism as one or the other antibody becomes dominant. Predicting the course of disease in such individuals is difficult, and they require close monitoring of thyroid function. Bioassays can be used to document that TSH-R- blocking antibodies reduce the cyclic AMP-inducing effect of TSH on cultured

TSH-R-expressing cells but these assays are difficult to perform. Assays that measure the binding of antibodies to the receptor by competition with radio labeled TSH [TSH-binding inhibiting immunoglobulins (TBII)] do not distinguish between TSI-and TSH-R- blocking antibodies, but a positive result in a patient with spontaneous hypothyroidism is strong evidence for the presence of blocking antibodies. The use of these assays does not generally alter clinical management, although they may be useful to confirm the cause of transient neonatal hypothyroidism.[42]

***Clinical manifestations*:** The onset is usually insidious, and the patient may become aware of symptoms only when euthyroidism is restored. Patients with Hashimoto's thyroiditis may present because of goiter rather than symptoms of hypothyroidism. The goiter may not be large but is usually irregular and firm in consistency. It is often possible to palpate a pyramidal lobe, normally a vestigial remnant of the thyroglossal duct. Rarely, uncomplicated Hashimoto's thyroiditis is associated with pain.[43]

Patients with atrophic thyroiditis, or the late stage of Hashimoto's thyroiditis, present with symptoms and signs of hypothyroidism. The skin is dry, and there is decreased sweating, thinning of the epidermis, and hyperkeratosis of the stratum cornea. Increased dermal glucoseaminoglycan content traps water, giving rise to skin thickening without pitting (myxedema). Typical features include a puffy face with edematous eyelids and non pitting pretibial edema. There is pallor, often with a yellow ting to the skin due to carotene accumulation. Nail growth is retarded, and hair is dry, brittle, difficult to manage, and falls out easily. In addition to diffuse alopecia, there is thinning of the outer third of the eyebrows, although this is not a specific sign of hypothyroidism.[44]

Other common features include constipation and weight gain (despite a poor appetite). In contrast to popular perception, the weight gain is usually modest and due mainly to fluid retention in the myxedematous tissue. Libido is decreased in both sexes, and there may be oligomenorrhea or amenorrhea in long-standing disease, but menorrhagia is also common. Fertility is reduced and the incidence of miscarriage is increased. Prolactin levels are often modestly increased and may contribute to alterations in libido and fertility and cause galactorrhea.[45]

Myocardial contractility and pulse rate are reduced, leading to a TSI antibodies that stimulate the TSH-R in Graves' disease. They can be measured in bioassays or indirectly in assays that detect antibody binding

to the receptor. The main use of these assays is to predict neonatal thyrotoxicosis caused by high maternal levels of TSI in the last trimester of pregnancy.[46]

Causes of Hypothyroidism:

Iodine deficiency remains the most common cause of hypothyroidism worldwide. In areas of iodine sufficiency, autoimmune disease (Hashimoto's thyroiditis) and iatrogenic causes (treatment of hyperthyroidism) are most common.[47]

Congenital hypothyroidism: *Prevalence*, Hypothyroidism occurs in about 1 in 4000 newborns. It may be transient, especially if the mother has TSH-R blocking antibodies or has received antithyroid drugs, but permanent hypothyroidism occurs in the majority. Neonatal hypothyroidism is due to thyroid gland dysgenesis in 80 to 85%, inborn errors of thyroid hormone synthesis in 10 to 15%, and is TSH- R antibody mediated in 5% of affected newborns. The development abnormalities are twice as common in girls. Mutations that cause congenital hypothyroidism are being increasingly recognized, but the vast majority remain idiopathic.[48]

Table: (2) shows causes of hypothyroidism:[(49)]

Primary: Autoimmune hypothyroidism: Hashimoto's thyroids, atrophic thyroditis.
Iatrogenic: ^{131}I treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer.
Drugs: Iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs, β-amino salicylic acid, interferon-α and other cytokines aminoglutethimide.
Congenital hypothyroidism: Absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation. Iodine deficiency.
Infiltrative disorders: Amyloidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroditis. Over expression of type 3 deoiodinase in infantile hemangioma Transient Silent thyroiditis, including postpartum thyroiditis. Sub acute thyroditis. Withdrawal of thyroxin treatment in individuals with an intact thyroid After ^{131} I treatment or subtotal thyroidectomy for Graves' disease.
Secondary: Hypopituitarism: Tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of combined pituitary hormone deficiencies. Isolated TSH deficiency or inactivity. Bexarotene treatment Hypothalamic disease: Tumors, trauma, infiltrative disorders, idiopathic.

Clinical manifestations: The majority of infants appears normal at birth, and < 10% are diagnosed based on clinical features, which include prolonged jaundice, feeding problems, hypotonia, enlarged tongue, delayed bone maturation, and umbilical hernia. Importantly, permanent neurologic damage results if treatment is delayed. Typical features of adult hypothyroidism may also be present. Other congenital

malformations, especially cardiac, are four times more common in congenital hypothyroidism.[50]

Diagnosis and treatment: Because of the severe neurologic consequences of untreated congenital hypothyroidism, neonatal screening programs have been established in developed countries. These are generally based on measurement of TSH or T4 levels in heel-prick blood specimens. When the diagnosis is confirmed, T4 is instituted at a dose of 10 to 15 μg/kg per day and the dosage is adjusted by close monitoring of TSH levels. T4 requirements are relatively great during the first year of life, and a high circulating T4 level is usually needed to normalize TSH. Early treatment with T4 results in normal IQ levels, but subtle neurodevelopment abnormalities may occur in those with the most severe hypothyroidism at diagnosis or when treatment is suboptimal.[51]

Table: (3) Signs and symptoms of hypothyroidism (Descending order of frequency).[52]

Symptoms:	Signs:
- Tiredness, weakness - Dry skin - Feeling cold - Hair loss - Difficult concentrating and poor memory - Constipation - Weight gain with poor appetite - Dyspnea - Hoarse voice - Menorrhagia (later oligomenorrhea or amenorrhea) - Parathesia - Impaired hearing	- Dry coarse skin; cool peripheral extremities - Puffy face, hands, and feet (myxedema) - Diffuse alopecia - Bradycardia - Peripheral edema - Delayed tendon reflex relaxation - Carpal tunnel syndrome - Serous cavity effusions

As "dominant negative" activity, explains the autosomal dominant mode of transmission. The diagnosis is suspected when unbound thyroid hormone levels are increased without suppression of TSH. Similar hormonal abnormalities are found in other affected family members. Although the TRβ mutation arises de novo in about 20% of patients. DNA sequence analysis of the TRβ gene provides a definitive diagnosis. RTH must be distinguished from other causes of euthyroid hyperthyroixinemia (e.g., FDH) and inappropriate secretion of TSH by

TSH- secreting pituitary adenomas. In most patients, no treatment is indicated; the importance of making the diagnosis is to avoid inappropriate treatment of mistaken hyperthyroidism and to provide genetic counseling.[53]

Physical examination:

In addition to the examination of the thyroid itself, the physical examination should include a search for signs of abnormal thyroid function and the extra thyroidal features of ophthalmopathy and dermopathy (see below). Examination of the neck begins by inspecting the seated patient from the front and side, and noting any surgical scars, obvious masses, or distended vein. The thyroid can be palpated with both hands from behind or while facing the patient, using the thumbs to palpate each lobe. It is best to use a combination of these methods, especially when the nodules are small. The patient's neck should be slightly flexed to relax the neck muscles. After locating the cricoid cartilage, the isthmus can be identified and following laterally to locate either lobe (normally the right lobe is slightly large than the left). By asking the patient to swallow sips of water, thyroid consistency can be better appreciated as the gland moves beneath the examiner's fingers.[54]

Features to be noted include thyroid size, consistency, nodularity, and any tenderness or fixation. An estimate of thyroid size (normally 12 to 20g) should be made, and a drawing is often the best way to record findings. However, ultrasound is the method of choice when it is important to determine thyroid size accurately. The size, location, and consistency of any nodules should also be defined. A bruit over the gland indicates increased vascularity, as occurs in hyperthyroidism. If the lower borders of the thyroid lobes are not clearly felt, a goiter may be retrosternal. Large retrosternal goiters can cause venous distention over the neck and difficulty breathing, especially when the arms are raised (Pemberton's sign). With any central mass above the thyroid, the tongue should be extended, as thyroglossal cysts then move upward. The thyroid examination is not complete without assessment for lymphadenopathy in the supraclavicular and cervical regions of the neck.[55]

Laboratory evaluation:

Measurement of thyroid hormones: The enhanced sensitivity and specificity of TSH assays have greatly improved laboratory assessment of thyroid function. Because TSH levels change dynamically in response to alterations of T4 and T3, a logical approach to thyroid testing is to first determine whether TSH is suppressed, normal or elevated. With rare exceptions, a normal TSH level excludes a primary abnormality of

thyroid function. This strategy depends on the use of immunoradiomertic assays (IRMAs) for TSH that are sensitive enough to discriminate between the lower limit of the reference range and the suppressed values that occur with thyrotoxicosis.[56]

Extremely sensitive (Fourth generation) assays can detect TSH levels $\leq$ 0.004 mU/L, but the practical purposes assays sensitive to $\leq$ 0.1 mU/L are sufficient. The widespread availability of the TSH IRMA has rendered the TRH stimulation test obsolete, as the failure of TSH to rise after an intravenous bolus of 200 to 400 μg TRH has the same implications as a suppressed basal TSH has the same implications as a suppressed basal TSH measured by IRMA.[57]

The finding of an abnormal TSH level must be followed by measurements of circulating thyroid hormone levels to confirm the diagnosis of hyperthyroidism (suppressed TSH) or hypothyroidism (elevated TSH).[58]

Radioimmunoassay are widely available for serum total T4 and total T3, T4 and T3 are highly protein-bound, and numerous factors (illness, medications, genetic factors) can influence protein bindings.[59]

It is useful, therefore, to measure the free, or unbound, hormone levels, which correspond to the biologically available hormone pool. Two direct methods are used to measure unbound thyroid hormones:

- Unbound thyroid hormone competition with radio labeled T4 (or an analogue) for binding to a solid-phase antibody.
- Physical separation of the unbound hormone fraction by ultracentrifugation or equilibrium dialysis.[60]

Though early unbound hormone immunoassays suffered from artifacts, newer assays correlate well with the results of the more technically demanding and expensive physical separation methods. An indirect method to estimate unbound thyroid hormone levels is to calculate the free T3 or free T4 index from the total T4 or T3 concentration and the thyroid hormone binding ratio (THBR). The latter is derived from the T3-resin uptake test, which determines the distribution of radio labeled T3 between an absorbent resin and the unoccupied thyroid hormone binding proteins in the sample. The binding of the labeled T3 to the resin is increased when there is reduced unoccupied protein binding sites (e.g., TBG deficiency) or increased total thyroid hormone in the sample; it is decreased under the opposite circumstances. The product of THBR and total T3 or T3 provides the free

T3 or T4 index. In effect, the index corrects for anomalous total hormone value caused by abnormalities in hormone-protein binding.[61]

Total thyroid hormone levels are elevated when TBG is increased due to estrogens (pregnancy, oral contraceptives, hormone replacement therapy, tamoxifen), and decreased when TBG binding is reduced (androgens, the nephritic syndrome).[62]

Genetic disorders and acute illness can also cause abnormalities in thyroid hormone binding proteins, and various drugs (phenytoin, carbamazepine, salicylates, and non steroidal anti-inflammatory drugs) can interfere with thyroid hormone binding. Because unbound thyroid hormone levels are normal and the patients is euthyroid in all of these circumstances, assays that measure unbound hormone are preferable to those for total thyroid hormones.[63]

From most purposes, the unbound T4 levels sufficient to confirm thyrotoxicosis, but 2 to 5% of patients have only an elevated T3 level (T3 toxicities). Thus, unbound T3 levels should be measured in patients with a suppressed TSH but normal unbound T4 levels.[64]

There are several clinical conditions in which the use of TSH as a screening test may be misleading, particularly without simultaneous unbound T4 determinations. Any severe non thyroidal illness can cause abnormal TSH levels. Although hypothyroidism is the most common cause of an elevated TSH level, rare causes include a TSH-secreting pituitary tumor, thyroid hormone resistance, and assay artifact. Conversely, a suppressed TSH level, particularly < 0.1 mU/L, usually indicates thyrotoxicosis but may also bee seen during the first trimester of pregnancy (due to HCG secretion), after treatment of hyperthyroidism (because TSH remains suppressed for several weeks), and in response to certain medications (e.g., high doses of glucocorticoids or dopamine). Importantly, secondary hypothyroidism, caused by hypothalamic-pituitary disease, is associated with a variable (low to high – normal) TSH level, which is inappropriate for the low T4 level. Thus, TSH should not be used to assess thyroid function in patients with suspected or known pituitary diseases.[65]

Tests for the end- organ effects of thyroid hormone excess or depletion, such as estimation of basal metabolic rate, tendon reflex relaxation rates, or serum cholesterol, are not useful as clinical determinants of thyroid function.[66]

Tests to determine the etiology of thyroid dysfunction: Autoimmune thyroid disease is detected most easily by measuring circulating anti-bodies against TPO and Tg. As antibodies to Tg aloe are uncommon, it is reasonable to measure only TPO antibodies. About 5 to 15% of euthyroid women and up to 2% of euthyroid men have thyroid antibodies; such individuals are at increased risk of developing thyroid dysfunction. Almost all patients with autoimmune hypothyroidism and up to 80% of those with Graves' disease, have TPO antibodies, usually at high levels.(67)

Deiodinases: T4 may be thought of as a precursor for the more potent T3, T4 is converted to T3 by the deiodinase enzymes. Type I deiodinase, which is located primarily in thyroid, liver, and kidney, has a relatively low affinity for T4. Type II deiodinase has a higher affinity for T4 and is found primarily in the pituitary gland, brain, brown fat, and thyroid gland. The presence of the type II deiodinase allows it to regulate T3 concentrations locally, a property that may be important in the context of levothyroxine (T4) replacement. Type II deiodinase is also regulated by thyroid hormone-hypothyroidism induces the enzyme, resulting in enhanced T4 $\rightarrow$ T3 conversion in tissues such as brain and pituitary. T4 $\rightarrow$ T3 conversion is impaired by fasting, systemic illness or acute trauma, oral contrast agents, and a variety of medications (e.g., propylthiouracil, propranolol, amiodarone, glucocorticoids). Type III deiodinase inactivates T4 and T3 and is the most important source of reverse T3 (rT3). Massive hemangiomas that express type III deiodinase are a rare cause of hypothyroidism in infants.(68)

Chapter (III)
INFERTILITY AND THYROID DISORDERS

Introduction:

Thyroid disorder are quite prevalent in the population of reproductive age,[71] four to five times more frequent in women than men. Both hyper and hypothyroidism may result in menstrual disturbances, an increased risk of miscarriage, possible long-term health effects in the offspring and spermatogenic abnormalities.[72]

Thyroid autoimmunity (TAI) is more prevalent in infertile women, especially in those with endometriosis, but the conception rate does not seem to be affected by the presence of antibodies nor by thyroxin treatment.[73]

TAI is associated with an increased miscarriage rate but thyroxin treatment does not appear to play a protective role. Sufficient data on subclinical hyperthyroidism, hypothyroidism and isolated TAI in infertility are lacking. A review of current information on the relation of thyroid disorders and infertility seems relevant and timely in order to review recent knowledge, as well as to highlight areas, where evidence is not yet sufficient. Since radioiodine continuous to be used widely in hyperthyroidism and thyroid cancer, its updated role in infertility is also included in this review.[74]

Hypothyroidism, female reproductive axis and female infertility:

Hypothyroidism is caused by reduced secretion of thyroid hormones often mediated by an autoimmune process (autoimmune or hashimoto thyroiditis), and sometimes following thyroid surgery or treatment with radioactive iodine. Subclinical hypothyroidism resulting from mild thyroid failure is defined as an elevated serum thyroid stimulating hormone (TSH) concentration with free T4 in the refrence range.[75]

Overt hypothyroidism is seen in about 0.5-0.7% of women of reproductive age and subclinical hypothyroidism in 2-4%.[76]

The prevalence of increased TSH in women with infertility is reported to range from 0.7 to 4% but the studies performed are limited in number.[77]

The effects of hypothyroidism on female reproductive hormones include a decrease in sex hormone binding globulin (SHBG), decrease in total estradiol and increase in the unbound fraction of testosterone and estradiol.[78]

The metabolic clearance of esterone and androstenodione is decreased.[79]

These changes may lead to alteration of the pituitary ovarian axis. Luteinizing hormone (LH) may increase but still within the normal range[80] and pulsatile Gonadotrophin releasing hormone (GnRH) secretion required form normal follicular development and ovulation is impaired.[81]

Hyperprolactinemia is a well known finding in hypothyroidism especially when thyroid under activity is profound.[82]

In adult women hypothyroidism results in changes in cycle length and amount of bleeding.[83] Oligomenorrhea or amenorrhea and menorrhagia reflecting probably estrogen breakthrough bleeding because of anovulation are frequent findings.[84] Proliferative endometrium on endometrial biopsy is also common and reflects anovulatory state.[85] Ovulation and conception however, can still occur in mild hypothyroidism.[86]

Treatment of hypothyroidism with thyroxin usually restores a normal menstrual pattern and reverses hormonal alterations.[87] Hypothyroidism has also been reported in association with ovarian hyper stimulation syndrome.[88] In a recent study women with infertility and particularly those with ovulatory dysfunction had higher mean basal TSH in comparison to controls.[89] Thyrotrophic and thyroid hormone receptors have been reported in human granulosa cells and both T3 and T4 have been found in follicular fluid.[90]

T4 enhances the action of gonadotropins on lutenization and progestin secretion by granulosa cells in vitro.[91] Thus, inadequate thyroid hormone concentration at the level of the ovary may contribute significantly to the gonadal dysfunction. The role of thyroid hormones on oocyte physiology is supported by the evidence that TSH is possibly an important predictor of fertilization failure in women undergoing in vitro fertilization (IVF).[92]

Subclinical Hypothyroidism and Female Infertility:

Subclinical hypothyroidism may be associated with ovulatory dysfunction.[93] The impact of treatment of subclinical hypothyroidism on infertility has not been evaluated prospectively. In a selected group of infertility patients with subclinical hypothyroidism a possible benefit in time of conception and conception rates has been shown with fine-tuning thyroxin dose.[94] Negative effect of subclinical hypothyroidism on prolactin regulation with restoration to normal with TSH-guided levothyroxine treatment has recently been demonstrated.[95]

Since in addition to a possible effect on fertility, subclinical hypothyroidism adversely affects pregnancy outcomes, early detection and treatment of hypothyroidism of any degree in women seeking treatment for infertility is advised.[96]

Hypothyroidism, male reproductive axis and male infertility:

Hypothyroidism is less common in men compared to women [97] and has less clear-cut effect on the reproductive system.[98] In hypothyroid males LH response to GnRH appears to be blunted.[100].

Hypergonadotrophic, hypogonadotrophic and normal serum LH and follicular stimulating hormone (FSH) states have been reported.[101] Serum free testosterone and SHBG are normal or low [102] and the 5a: 5b ratio of the metabolites of androsterone and androstenodione are markedly decreased.[103] Prolactin might be elevated and improves with adequate T4 replacement.[104]

Hypothyroidism is associated with hypoactive sexual desire, erectile dysfunction, and delayed ejaculation.[105] However, little is known about the effects of hypothyroidism on human spermatogenesis and fertility since the reports are scare.[106]

Variations in testis size and histology have been noted in autopsy material.[107] Short term post pubertal hypothyroidism although might decrease semen volume and sperm forward motility, does not appear to cause seminal alterations sufficiently intense to impair male fertility.[108] Subclinical hypothyroidism does not impact semen density, motility or morphology.[109]

Thyroid autoimmunity and infertility:

Immunologic factors play an important role in the reproductive processes of fertilization, implantation and placental development. Reproductive failure is associated with organ specific autoimmunity, including TAI.[110]

Autoimmune disorders tend to occur during the reproductive years in women, thereby affecting fecundity and pregnancy outcome.[111] TAI is the most frequent autoimmune disorder in humans affecting 5 to 10% of females of childbearing age.[112]

TAI is characterized by the presence of Anti-Thyroid antibodies (ATA), which includes thyroglobulin antibodies (TG-Abs) and thyroid peroxidase antibodies TPO-Abs). The prevalence of ATA in normal pregnant women is estimated at 15 to 20%, in women with a history of recurrent miscarriages at 20-25% and in women undergoing IVF at 20%.[113]

The clinical significance of TAI in infertility is still controversial. A number of retrospective studies have attempted to associate the presence of TAI with infertility. Although individual studies did not yield convincing results, when the data were pooled, a significant association between TAI and infertility was found (RR 1.95).[114]

The question whether TAI is associated with a particular cause of infertility is still not answered. There is no correlation between pregnancy rate after assisted reproductive technology (ART) and thyroid antibodies. Women in couples with female-factor sub fertility, when compared to controls, have a higher prevalence of positive TPO-Abs and particularly those with endometriosis, a fact that strengthens the hypothesis of an altered immunity in this disease. In couples with male-factor infertility or unexplained infertility, women had similar to control frequency of positive TPO-Abs.[115] Thyroid dysfunction is more frequent in women with positive TPO-Abs and may interfere with normal ovarian function.[116]

The association between recurrent IVF failure and presence of TAI is still unclear. Although the prevalence of ATA is not increased in patients undergoing ART, higher concentration of ATA was found in women with three or more failed IVF cycles, suggesting that the level of ATA might be a useful indicator of reproductive failure in IVF.[117] In a recent study, thyroxin treatment in euthyroid TPO-Abs positive women

did not improve pregnancy rates during controlled ovarian stimulation therapy when compared to a similar group without thyroxin support and to TPO-Abs negative controls. The miscarriage rate however, was higher in TPO positive women (RR: 2.01) and did not decrease by thyroxin treatment.[118]

The association between TAI and pregnancy loss remains unclear because of poorly understood mechanisms and conflicting data. Independent association between TAI and miscarriage has been suggested and explained by autoimmunity affecting the fetal allograft, where ATA are markers of this process.[119] The presence of ATA carried a significant increased risk for miscarriage in women, who became pregnant following an ART procedure, where no effect was observed on pregnancy rate. Therefore determining the presence of ATA before embryo transfer may be useful in identifying women at risk for miscarriage[120] Women with TAI treated with thyroid replacement therapy had a lower rate of miscarriage compared to a similar group treated with IV immunoglobulins suggesting that mild thyroid insufficiency may be present in the early stages of pregnancy.[121]

Data on the role of TAI in male infertility are scare. The prevalence of TAI in men with infertility was found to be 7.5% and the elevated titers of ATA were correlated with semen abnormalities such as athenospermia and pathozoospermia.[122]

In conclusion TAI may be a marker for other autoimmune disease or may simply identify a subgroup of women who may not meet the increased demand for thyroid hormones in early pregnancy. Whether the presence of TAI represents an epiphenomenon or is an actual marker of the underlying immune disorder still cannot be determined.

Hyperthyroidism, female reproductive axis and female infertility:

Overt hyperthyroidism is characterized by suppression of pituitary TSH and increase of serum FT4, FT3 or both. When TSH alone is suppressed in the presence of normal serum thyroxin (T4) and triiodothyroxine (T3), the state is called subclinical hyperthyroidism. The prevalence of hyperthyroidism in the general population is around 1.5%.[123] In thyrotoxic females, SHBG production is significantly increased, bound and total estradiol (E2) is 2-3 times higher than normal and free E2 is at the lower end of the normal range. The conversion of androgen to estrogen is increased. Baseline LH is frequently elevated and mid-cycle LH peak is blunted, possibly interfering with ovulation.

Menstrual disturbances are quite frequent in thyrotoxicosis. The most recent study was in 1994 by Krassas et al.,[124] who observed a 21.5% rate (46/214) in hyperthyroidism compared to 8.4% in controls. An earlier study reported a 64.7% rate of menstrual irregularities in hyperthyroidism compared to 17.2% in controls. Various factors in combination or alone, can contribute to the menstrual flow abnormalities noted in thyrotoxicosis.[125]

Treatment of hyperthyroidism usually corrects the biochemical and clinical changes. No data exist on the effect of treatment of subclinical hyperthyroidism.

The prevalence of hyperthyroidism in infertility was studied prospectively by Poppe et al., in 2002,[126] who found that 2.3% of women of infertile couples had suppressed TSH, but none of them had ovulatory dysfunction. However, only 17% of these patients had overt hyperthyroidism. Joshi et al., 1993,[127] reported a 5.8% rate of primary and secondary infertility in 53 hyperthyroid patients. The exact role of thyrotoxicosis in infertility remains undefined,[128]

Hyperthyroidism male reproductive axis and male infertility:

In thyrotoxic males SHBG is elevated, total and bound testosterone (T) is increased, free T is transiently reduced or normal and mean basal bio-available T is decreased.[129]

The metabolic clearance rate of T is reduced and circulating E2 levels are increased. An increased production rate of the estrogen and an enhanced peripheral conversion of androgen to estrogen have been observed in some men.[130] These changes can cause gynecomastia (24%), decreased libido (70%), erectile dysfunction (56%), spider angiomas and spermatogenic dysfunction.[131]

Basal serum LH and FSH may be slightly increased or normal. Correction of thyrotoxicosis reverses these hormonal changes.

Very few studies exist on the effect of overt hyperthyroidism on semen quality and none regarding the effects of subclinical hyperthyroidism. In 1992, Hudson and Edwards studies the spermograms of 16 thyrotoxic males and found that the sperm density was lower than cotnrols, but not statistically significant. In a later report 21 thyrotoxic patients, who were studied 62-87% had motility problems and 43% oligospermia. Krassas et al. in 2002.[132] Reported a prospective study of 23 thyrotoxic males and 15 healthy controls. The semen volume was

unchanged; sperm density and morphology tended to be lower but not statistically significant, while mean sperm motility was significantly lower. At 5 months post treatment, motility and semen volume normalized but not morphology. Semen fructose, zinc and magnesium were not altered by the correction of hyperthyroidism.

Radioactive iodine (I^{131}) therapy and infertility:

Radioactive iodine (I^{131}) is widely employed in the treatment of hyperthyroidism and well differentiated thyroid cancer. For patients of reproductive age, there are concerns that radiation may affect the gonads with consequent effect on fertility, genetic malformations in the offspring and appearance of secondary tumors.

In hyperthyroidism, the dose of (I^{131}) used is around 10mCi (370MBq), while in thyroid cancer the amount is 10-100 times higher, exposing the gonads to a higher radiation dosage.

In thyrotoxic women treated with 10mCi of (I^{131}) the genetic risk is negligible; additionally the reproductive health of the treated patients and the general health of the pregnant women is normal.(133)

Therefore, the use of I^{131} in hyperthyroidism bears no significant effect on the gonads. In thyroid cancer patients, the radiation to the gonads has the following effects:

- Effect on fertility: Temporary amenorrhea with elevated FSH and LH values in 17-82% of women, starting some time after (I^{131}) intake, and lasting 6 – 12 months at most. No permanent ovarian failure was observed but premature menopause could occur.(134) The fertility rate (live births per 1000 fertile women per year) in treated women was not reduced. Conception is recommended after 1 year from (I^{131}) treatment, because of increased miscarriage risk (40%) in the first 12 months.(135)
- In males, the radiation effects of (I^{131}) are more pronounced because of increased testicular sensitivity. Transient suppression of spermatogenesis or, even complete azospermia, have been noted, lasting up to 3 years in the patients that received the higher dose. Transient FSH elevations and inhibin B suppression can happen, starting at 3-6 months post I^{131} and lasting up to 18 months. Sperm cryopreservation before (I^{131}) should be addressed in all young men, especially those likely to receive higher and/or cumulative (I^{131}) doses.(136)

- The genetic risks in the offspring of women and men treated with ablative doses were not significantly increased, nor was the incidence of thyroid disease and malignancy.[137]

Hypothyroidism and female infertility:

The prevalence of hypothyroidism in the population of reproductive age is defined as an abnormally elevated TSH concentration, ranges from 2 to 4%.[138] Several factors may affect the prevalence, including age and dietary iodine status. In women of fertile age, AITD is the most common cause of hypothyroidism and in most patients thyroid peroxidase antibodies are found.[139] Other, though, rarer causes of hypothyroidism, include post-131I, post-thyroiditis and drug-induced hypothyroidism. Hypothyroidism is associated with a broad spectrum of reproductive disorders ranging from abnormal sexual development to menstrual irregularities and infertility.

- In the first decade of life, hypothyroidism leads to a delay in sexual maturity. Occasionally, precocious puberty, galactorrhea and a delay in pubic hair growth are associated with juvenile hypothyroidism. These manifestations reverse after thyroid hormone supplementation.
- In adult women, more common ovulatory disorders including galactorrhea, hirsutism, amenorrhea and menorrhagia have been reported.[140]

The impact of hypothyroidism on the menstrual cycle has been known since 1950.23 Hypothyroidism in adult women often results in changes in cycle length and blood flow. In older series, menorrhagia (increased blood flow) was the most prevalent symptom and occurred in 60% of overt hypothyroid women. In India, Joshi et al found 68.2% of menstrual abnormalities in hypothyroid women (15/22) compared with 12.2% of healthy controls (6/49).[141]

The menstrual abnormality may precede clinical symptoms and signs of hypothyroidism. In a more recent study by Krassas et al., the frequency of menstrual irregularities was 23.4% among 171 hypothyroid patients and was significantly higher than the 8% in 214 normal controls. Moreover, the most common manifestation was oligomenorrhea. None of the control had amenorrhea, compared with 12% in the hypothyroid group. One of the most likely explanations for the discrepancies was that thyroid disease was diagnosed earlier in the Greek study. In the study by Karassas there was a tendency to have more menstrual abnormalities with higher TSH. Hypothyroidism is commonly associated with failure of

ovulation, but ovulation and conception can occur in milder hypothyroidism. The impact of hypothyroidism on menstrual function and ovulation is related to numerous interactions of thyroid hormones with the female reproductive system.[142]

Hyperprolactinemia resulting from increased production of TRH has been implicated in ovulatory dysfunction and in 1-3% of cases, with galactorrhea. 27 An alternative hypothesis is that diminished synthesis and secretion of dopamine in the hypothalamus could account for loss of dopaminergic inhibitory influences on PRL, TSH and also LH.28 in favor of this hypothesis is the rapid decline of LH, TSH and PRL to normal levels during dopaminergic infusion in a young woman with severe hypothyroidism.[143]

Hypothyroidism interferers with normal physiological pulsatile GnRH secretion, a prerequisite for normal follicular development and ovulation. A delay in LH response may lead to inadequate corpus luteum progesterone secretion.[144] Disturbances in normal pulsatile release of LH and hyperprolactinaemia can result in menstrual dysfunction, ranging from anovulatory cycles with menorrhagia, oligomenorrhea or amenorrhea.[141]

Thyroid hormone receptors are expressed in human oocytes, cumulus cells and granulosa cells.[142] At the cellular level, thyroid hormones synergize with FSH to exert direct stimulatory effects on granulosa cell functions, including morphological differentiation. Thyroid hormones facilitate FSH-mediated LH/HCG receptor induction and progesterone secretion. Hence, the occurrence of gonadal dysfunction may further result from inadequate thyroid hormone availability at the level of the ovary.[144]

Moreover, both gonadotrophins and thyroxin appear to be necessary to achieve maximum fertilization rates and blastocyst development. Recently, Gramer et al. showed that TSH is a significant predictor of fertilization failure in women undergoing IVF. These data support the important role of thyroid hormones in oocyte physiology.[143]

Hypothyroidism also results in altered peripheral estrogen metabolism. Decreases in SHBG and its binding activity, together with an altered peripheral metabolism of estrogen may result in abnormal feedback at the pituitary level. In the presence of anovulation, ovarian androgen production increases with higher biologically active androgens (low SHBG). These changes further contribute to anovulation and an

increased incidence of hirsutism. Independent of hormonal changes menorrhagia can results from defects in hemostasis, involving decreased levels of factors VII, VIII, IX and XI.[144]

Studies that examine the incidence of infertility in hypothyroid patients are scare. Ideally, this should be evaluated prospectively determining the incidence of infertility in patients with hypothyroidism compared with the incidence in a matched control group. Such data are not available, and most studies deal with the prevalence of infertility in a cross-sectional design of hypothyroid patients or evaluated the prevalence of hypothyroidism in selected populations presenting at fertility clinics.[140]

Joshi et al., detected primary and secondary infertility in 6.2% of 16 overtly hypothyroid women. This prevalence was comparable to 4.8% in normal control women (without goiter, but unknown thyroid function). The number of patients was small, the thyroid antibody status unknown and the control population not clearly defined.[145]

In another study serum TSH levels was determined in 704 infertile women without previous thyroid disorders, 2.3% had increased serum TSH (both overt and subclinical hypothyroidism). No control population was available, but the percentage was comparable to that in the general (female) population of reproductive age. In 2000 Arojoki et al investigated retrospectively the prevalence of hypothyroidism in 299 women with different causes of infertility. Overall 4% of the women had an increased TSH and 2.3% an overt hypothyroidism. The highest percentage of women with increased TSH was found in the group with OD (6.3%) compared with 4.8% in the idiopathic group, 2.6% in the tubal infertility group and none in the endometriosis group. No statistical differences were obtained when comparing the frequency of hypothyroidism between the different groups of infertility. It is generally accepted that because of the low yield of overt hypothyroidism, screening for hypothyroidism is not warranted.[142]

However it is difficult to form a clear interpretation from the available data. Patients with overt thyroid failure are probably detected before referral to infertility treatment clinics, thereby introducing a bias in the estimated prevalence in infertility disorders.[143]

Treatment with levothyroxine (LT4) is straight forward and has been shown to normalize PRL levels, to restore normal LH responses to

its releasing hormone, to overt menstrual disturbances to prevalences comparable in euthyroids women, and increases spontaneous fertility. Given the potential implications of hypothyroidism on ovulatory function, screening is certainly indicated in the presence of OD.[145]

Subclinical hypothyroidism and infertility:

Subclinical hypothyroidism (sh) is defined as elevated serum TSH in the presence of free thyroxin (fT4) concentrations within the normal references range. Recent data indicated that variations of fT4 in the individual are narrower than variations within the reference range for the population. These data may indicate that normal fT4 (for the population reference range) could reflect an abnormal fT4 for the individual patient with increased serum TSH.[143]

After the introduction of third-generation assays for serum TSH, Sh is more often detected. sh results from the same causes as overt hypothyroidism and the evolution to overt hypothyroidism depends on a number of factors, including the presence of thyroid antibodies.[146]

The association between sh and infertility was evaluated in different studies. Most studies are uncontrolled and retrospective. In 1981 Bohnet et al performed TRH tests in 185 infertile women with an age range between 25 and 34 years. Infertile women with an exaggerated TSH response to TRH (0.20 mU/ml), were considered sub clinically hypothyroid. Twenty women (20/185) or 11% had sh, the causes of infertility were not specified. The authors stated that sh is an infertility factor. Eleven of the 20 women were treated with 50 mg LT4 and normalized their mid-progesterone secretion and two women became pregnant.[145]

In a subsequent small study, Bals-Pratsch was unable to confirm that corpus luteum insufficiency in female infertility was linked to sh nor did this change with LT4 for fertility reasons.[147]

Some elements of this study design were the subject of different controversies. Gerhard et al showed a positive correlation between basal TSH and LH and testosterone in the early follicular phase. Women with high stimulated TSH had lower pregnancy rates than women with normal or low stimulated TSH (TSH stim. 20mU/L). Only one patient out of 185 infertile women had an elevated TSH RIA value of 6 mU/L, thus presenting with sh. Shalev et al., looked retrospectively at the prevalence

of sh in 444 infertile women. Thyroid function was evaluated by measuring plasma free thyroxin and TSH. Only three out of the 444 (0.23%) women had increased TSH levels and all these women had ovulatory dysfunction.[140]

Grassi et al., included 129 women from infertile couples. The etiology of infertility was related to a male factor, OD and unexplained infertility. Six patients (4.6%) had serum TSH levels. 4.5mU/L and five of these had AITD. The mean duration of infertility was significantly longer for patients with thyroid abnormalities (including abnormal TSH and /or AITD). In the latter study, patients with tubal or pelvic factors including endometriosis (13.4% of the original cohort) were excluded. This can explain the higher prevalence of sh compared with other studies. Another uncontrolled retrospective study (Arojoki et al) revealed an elevated TSH level (5.5 mU/L) in 12 out of 299 women presenting for the first time with infertility (4%). The prevalence of increased TSH was highest in the group with OD (63%) and lowest in patients with tubal damage.[146]

Prior to enrolment in infertility examination, 10 out of 299 women had used thyroxin substitution for primary hypothyroidism. The incidental finding of elevated TSH in patients with infertility is therefore reduced to two out of 299 women (0,1%) and the same as in the general population in Finland (1-2%). We recently undertook a controlled prospective study in 438 women with various causes of infertility, with the aim of assessing the prevalence of AITD and undisclosed alterations of thyroid function. Overall, median TSH was significantly higher in patients with female infertility compared with controls. Serum TSH above normal (4.2 mU/L) was not more prevalent infertile women than in the controls. Only one patient in the OD and one in the idiopathic infertility group had sh with anovulatorly prevalence of 0.5%. both patients had positive thyroid antibodies (TPO-Abs). In the 100 fertile women the prevalence was 1% in accordance with the data of Arajoki et al. in the Finish study two spontaneous pregnancies occurred in the group after adjustment of thyroxin substitution dose, and two after initiation of thyroxin treatment for sh, compared with none in the levothyroxine treatment group.[148]

Studies looking at the association of sh and infertility are poorly controlled. Considering the largest cohorts published, the prevalence of sh in infertility ranges from 1 to 4% and most cases of sh are associated with ovarian dysfunction.[143]

The impact of treatment of sh in infertility has not been evaluated prospectively in the general infertility population. Recently however, pregnancy rate was assessed prospectively in a cohort of 283 'selected' infertile patients, referred to an endocrine clinic and followed up to 5 years. In this study, 34% of patients had sh (gynecological definition: TSH stimulated after TRH 0.20m U/L) which mirrors the specific referral pattern. At the time of pregnancy, 0.25% of these patients till had sh.(144)

Women who never achieved a basal TSH 2.5mU/l, or a TRH-stimulated TSH, 0.20 mU/L were observed more frequently among patients who did not become pregnant than among those who did. Subsequent abortions occurred with increased frequency with higher basal TSH, independent of the presence of AITD. These data point to the benefit of fine-tuning LT4 treatment in patients with TRH-induced TSH rise above the mean of a healthy population.(145)

Subclinical-overt hyperthyroidism and infertility:

A suppressed serum TSH and increased FT4, FT3 or both characterize hyperthyroidism. The most common cause of hyperthyroidism women of reproductive age in Graves' disease; other causes are toxic goiter and thyroiditis. The prevalence in the general population is around 1.5%.(144)

Menstrual disturbances in hyperthyroidism have already been described by Von Basedow in 1840 and confirmed by other groups.(149)

Joshi et al., found menstrual irregularities in 64.7% of hyperthyroid women, compared with 17.2% of healthy controls. More recently, Krassas et al observed irregular cycles in only 46 of 214 hyperthyroid women (21.5%). 24 women had hypo menorrhea, 15 polymenorrhea, 5 oligomenorrhea, 2 hyper menorrhea and none had amenorrhea. The prevalence of menstrual abnormalities was two-and-a-half times higher than in the control population (8.4%). Despite these findings, most hyperthyroid women remain ovulatory, according to endometrial biopsies.(148)

In contrast to the hypothyroid state, SHBG production is increased. Estrogen metabolism is altered and conversion of androgens to estrogens increased. Hyperthyroxinemia augments gonadotropin response to GnRH and baseline gonadotropin concentrations are frequently elevated. The decrease in menstrual flow may also relate to effects on haemostatic factors, including the synthesis of factor VIII. Usually, treatment corrects

cycle changes observed with hyperthyroidism. The exact impact of hyperthyroidism on fertility remains ill-defined.[149]

As for hypothyroidism, most studies on the prevalence of hyperthyroidism in infertility are derived from uncontrolled, retrospective cohort studies. One study showed that out of 53 hyperthyroid patients, 5.8% had primary and secondary infertility. In our prospective cohort study the prevalence of suppressed TSH (0.1 mU/l) in 438 women of infertile couples was 2.3%, of whom 40% had positive thyroid antibodies; 83% of these patients had normal free hormone levels (subclinical hyperthyroidism). None of the women with suppressed TSH had OD. Treatment of overt hyperthyroidism normalizes menstrual pattern. Data on the impact of treatment of subclinical hyperthyroidism are not available. Krassas et al reviewed the impact of radioiodine in the management of hyperthyroidism in patients of reproductive age. Fertility is not disturbed in the long term and ^{131}I is not contraindicated in hyperthyroid patients because of the risk of infertility.[140]

Thyroid autoimmunity and infertility:

Autoimmune abnormalities have been investigated for possible associations with reproductive failure. The particularity of thyroid autoimmunity (AITD) is two-fold. AITD is the most common autoimmune disorder in the female population, affecting 5-10% of women of childbearing age and secondly it is the most frequent cause of thyroid failure (subclinical-and overt hyperthyroidism).[141]

AITD can be present without thyroid dysfunction and is thus undiagnosed. There are numerous studies that examine the prevalence of AITD in patients with infertility. A difficulty arising from the interpretation of the available data is that studies are often of heterogeneous groups with infertility problems, of retrospective design and often no control data are available. Some variability between studies can further be explained by differences in sample size (small series), by differences of the assays used to detect AITD and different geographical locations of the studies. Overall the studies favour an increased prevalence of AITD in infertility clinical.[142]

Pooling of the data shows that for all female patients of couples with infertility the RR of AITD is slightly but significantly increased: RR 1.95 (CI 1.50 – 2.53; P, 0: 0001).

Some studies have examined the association between AITD and a particular cause of infertility. In a survey by Singh et al in 1985, the

frequency of AITD in different causes of infertility was comparable to women without AITD.[143]

Muller et al also found that AITD was not associated with a particular infertile condition. We prospectively evaluated in a case-control design the occurrence of thyroid autoimmunity among women of infertile couples n ¼ 438 presenting for the first time at the Department of reproductive Medicine. The control population consisted of 100 fertile women, matched for age. In the case of female origin of infertility, women had an increased risk of associated AITD 2.25 (1.02-1.52) compared with the control population. This risk further increases in the presence of endometriosis to 3.57 (1.09-11.8) compared with controls. Gehard et al reported similar results in endometriosis. In women with AITD 44% had endometriosis, compared with only9% in women without AITD.[144]

The association between AITD and endometriosis strengthens the hypothesis of an altered immunity in this disease. Numerous types of non-organ-specific antibodies were indeed found in association with endometriosis as well as a deficient cellular immunity. Natural killer cell activity is reduced, and the concentrations of activated leukocytes and macrophages increased in the peritoneum of patients with this disease. The immune system may thus determine who will develop endometriosis.[145]

In order to delineate prospectively the impact on pregnancy rate of autoimmunity during ART, a cohort of 234 women undergoing a first IVF procedure was evaluated. Of the 234 women included, 32 (32/234) or 14% of the cohort had AITD (TPOab levels. 100kU/l). Pregnancy (including clinical and biochemical) occurred in 53% (17/32) of the AITD women and in 43% (87 out of 202) of women without.[146]

These results do not support a correlation between pregnancy rate after ART and AITD. In a similar prospective design, Grassi et al investigated the influence of AITD on the couple's chances of pregnancy. The authors report a high prevalence of thyroid antibodies in infertile patients, but the presence of these auto-antibodies per se did not reduce the change of pregnancy after medical treatment for super ovulation induction. However, in most studies, the presence of thyroid antibodies carried a significant increased risk of subsequent miscarriage in the first trimester of pregnancy.

Purpose of review: This review highlights the 'gap' in knowledge regarding the contribution of thyroid dysfunction in reproduction. Thyroid dysfunction, which is quite prevalent in the population affects many organs including the male and female gonads, interferes with human reproductive physiology, reduces the likelihood of pregnancy and adversely affects pregnancy outcome, thus becoming relevant in the algorithm of reproductive dysfunction.

Recent findings: Although menstrual irregularities are common, ovulation and conception can still occur in hypothyroidism, where thyroxin treatment restores a normal menstrual pattern and reverses hormonal changes. Subclinical hypothyroidism may be associated with ovulatory dysfunction and adverse pregnancy outcome. Thyroid autoimmunity increases the miscarriage rate, and thyroxin treatment does not seem to protect. Menstrual disturbances, frequent in thyrotoxicosis are restored following treatment. In males, thyrotoxicosis has a significant but reversible effect on sperm motility. Although radioactive Iodine (I^{131}) in ablation doses may transiently affect the gonads, it does not decrease fertility or increase genetic malformation rate in the offspring.

MATERIAL AND METHODS

The study conducted as screening for hypothyroidism among (40) infertile women attending out patient clinic department of obstetrics and gynecology, Banha university hospital during the period form September 2009 to June 2010.

Every women submitted to:

- **Full history taking including:**

A. **Personal history:** Name, age, address, occupation; marital state and special habits of medical importance.

B. **Compliant and present history:**

- Type and duration of infertility.
- Symptoms of hypothyroidism (Fatigue, sense of coldness, increase in weight, headache and depression, constipation and increase size of thyroid gland).
- Investigation for hypothyroidism.
- Infertility investigation as semen analysis, serial foliculometry, post coital test, hysterosalpingogram, diagnostic laparoscopy and hysteroscopy.
- Analysis of treatment.

C. Past history diseases or operations.

D. Family history of D.M. or hypertension or hypothyroidism.

E. Menstrual history: Including age of menarche,

- Frequency of menstruation.
- Duration of bleeding.
- Presence of blood clots.
- Dysmenorrhea.
- Premenstrual tension syndrome.

F. **Obstetric history: If present:**

- Number of pregnancies.
- Number of abortion.
- Number of labour.
- Mode of delivery either vaginal delivery or C.S.
- Any complications during pregnancy, labour or puerperuim.

G. Sexual history.

- **General examination:**
  - General appearance, cachectic, well nourished, anxious or calm.
  - Vital signs, pulse, blood pressure, temperature and respiratory rate. Height and weight head and neck examination.
  - Breast examination; Inspection for symmetry, nipple direction and discharge, palpation systematically and examination of axilla.
  - Cardiac and pulmonary examination.
  - Abdominal examination: The abdomen should be inspected for scars, distention, masses and discoloration. Palpation away from the site of pain if present for masses and tenderness. Auscultation of intestinal movement.
  - Back and spine examination, for symmetry, masses and tenderness.

- **Pelvic examination:**

External genital examination:

Inspection: Inspection labia, clitoris and perineum for masses, ulcers, discharge scars and cracks.

Palpation:

A- Examination of urethral opening by milking for discharge. Examination of Skenes tubules for tenderness and discharge.

B- Examination of Bartholin glands for discharge tenderness and masses.

C- Examination of vagina for discharge, masses, ulcers and fistula.

Speculum examination:

For inspection of the vaginal walls and cervix for discharge and fistula.

Bimanual examination:

The uterus is palpated for site, size, direction, mobility, consistency and tenderness.

Adnexiae are palpated for masses mobility and tenderness.

- **Rectovaginal examination,** to palpate the surface of the uterus and check for tenderness or masses between the uterus and rectum.

- **Investigation;**
  - Serum free T4.
  - Serum TSH.

The results were tabulated and statistically analyzed.

RESULTS

Table: (1) Demographic criteria of the study group.

Variable	Range	Mean	± S.D
Age	**21 – 36**	**28.21**	**± 6.2**
BMI	**20 – 28**	**26.2**	**± 1.4**
Duration of infertility	**3 – 8**	**5.2**	**± 1.2**

Table: (2) Menstrual history among the study group.

Variable	Range	Mean	± S.D
Age of menarche (years old)	**9.5 – 13**	**11.3**	**± 0.6**
Cycle frequency (days)	**26 – 45**	**39.8**	**± 3.6**
Duration of Menses (days)	**1-5**	**3.1**	**± 1.2**

Table: (3) Clinical picture of hypothyroidism among study group (N=40) Infertile women.

Symptom and signs	Distribution	Percentage
Easy fatigue	**25**	**62.5%**
Sense of coldness	**21**	**52.5%**
Increase in weight	**18**	**45%**
Headache	**19**	**47.5%**
Psychic disturbance	**11**	**27.5%**
Constipation	**18**	**45%**
Puffiness of eyelid	**11**	**27.5%**
Hoarseness of voice	**4**	**10%**
Bradycardia	**13**	**32.5%**
Hypertension	**9**	**22.5%**
No C/P	**12**	**30%**

Table: (4) Cause of infertility among study group (N=40) Infertile women.

Symptom and signs	Distribution	Percentage
Ovulatory disorders	**20**	**50%**
Combined (ovulatory disorders and others)	**12**	**30%**
Unexplained	**8**	**20%**

Table: (5) Serum T4 and serum TSH before beginning of treatment of hypothyroidism (N=40) Infertile women.

Variable	Range	Mean	± S.D
Serum T4	**10 – 11.9**	**11.22**	**± 2.12**
Serum TSH	**4.9 – 6.3**	**5.1**	**± 2.31**

Table: (6) Serum T4 and TSH after treatment for hypothyroidism.

Variable	Range	Mean	± S.D
Serum T4	**12.1 – 18.99**	**16.21**	**± 1.1**
Serum TSH	**0.2 – 3.5**	**1.98**	**± 3.1**

Table: (7) Duration and dose of treatment by Eltroxin.

Variable	Range	Mean	± S.D
Dose (mg)	**25 – 100**	**63**	**± 5.5**
Duration (month)	**3 – 12 m**	**6.6**	**± 3.1**

Table: (8) Outcomes of treatment of cases.

Variable	Distribution	Percentage
Correction of symptoms	**28**	**100%**
Correction of ovulatory dysfunction	**28**	**87.5%**
Get pregnancy	**14**	**35%**

DISCUSSION

Thyroid disorders are quite prevalent in the population of reproductive age, four to five times more frequent in women than men. Both hyper and hypothyroidism may result in menstrual disturbances, an increased risk of miscarriage, possible long – term health effects in the off-spring ***(Wang and Crapo 1997)***. Although menstrual irregularities are common, ovulation and conception can still occur in hypothyroidism, where thyroxin treatment restores a normal menstrual pattern and reverses hormonal changes. Subclinical hypothyroidism may be associated with ovulatory dysfunction and adverse pregnancy outcome ***(Krinos et al.,2 006)***.

The prevalence of hypothyroidism in the population of reproductive age ranges from 2 to 4% ***(Bjoro et al., 2000).***

The demographic criteria of the study group, regarding age of the patients, body mass index and the duration of infertility are concordant with other related studies.

The menstrual abnormalities are well documented in hypothyroidism which may even precede clinical symptoms and signs of hypothyroidism. In our study the frequency of menstrual irregularities was 60% (Table 2), which in accordance with ***Goldsmith et al., (1992)***. But the frequency was higher than results pointed out by ***Krassas et al., (1999)*** which was 23.4%. The difference with Krassas' study may be due to the difference in the demographic criteria of the patients between the studies.

Moreover, the most common pattern of menstrual irregularities was oligomenorrhea, this point was in accordance with study of ***Krassas et al., (1999)*** The cause of this menstrual irregularity is due to accumulation of estrogen hormone, as hypothyroidism may lead to decrease in hepatic excretion of estrogen hormone. The state of hyperestrogenism which associated with hypothyroidism may lead to many effects on female genital tract such as endometriosis, endometrial hyperplasia, myohyperplasia and may be uterine neoplasia. (Dommy, 2001).

The clinical picture of hypothyroidism in our study group was similar to the percentages documented by other authors in the review of the literature, as percentages of easy fatigue, sense of coldness, increase in weight, headache, psychic disturbances, constipation, hoarseness of voice, bradycardia and hypertension.

Regarding the causes of infertility in hypothyroidism group, the most prevalence disorder occurred in ovulation (50%). This concept in accord with data collected by ***Arojoki et al., (2000)*** who investigated retrospectively the prevalence of hypothyroidism in 299 women with different causes of infertility. The highest percentage of women with increased TSH was found in the group with ovulatory disorders.

Eltroxin (glaxo-wellcome) (microgm) with a mean dose 63 ug and a mean duration 6.6 months corrected 100% of symptoms in symptomatic patients. Regarding reproductive function, treatment corrected 87.5% of ovulatory dysfunction and 35% of these corrected patient got pregnancy (Table 8).

The dose and duration of the treatment were in accordance with other studies, Dommy, 2001, mentioned the dose of eltroxin (60-70) mg, with the duration of treatment ranged from 6-12 months with mean duration of 7.7 months. Regarding the outcome, the correction of symptoms was 100%, the correction of ovulatory dysfunction was 87.5% and the female which got pregnancy were 35%. This results are in accordance with other results like, **Daphson** et al (2000), which mentioned 80% correction of ovulation and 33% occurrence of pregnancy.

In study from Finland the prevalence of abnormal TSH levels was highest in the ovulatory dysfunction (6.3%) and unknown infertility (4.8%) groups and lowest in the tubal infertility (2.6%) and male infertility (1.5%) groups, although no statistically significant differences between the groups were observed. Oligo/amenorrhea was present in (34%) women in the whole study population and in eight (67%, $p < 0.5$) women with elevated serum TSH at screening. The relatively high occurrence of abnormal TSH levels in infertile women with ovulatory dysfunctions or unknown infertility, as well as oligo/amenorrhea, emphasizes the importance of TSH screening in these patient groups. These results of this study are in agreement with our study.

SUMMARY AND CONCLUSION

The menstrual pattern is influenced by thyroid hormones directly through impact on the ovaries and indirectly through impact on SHBG, PRL and GnRH secretion and coagulation factors. Treating thyroid dysfunction can reverse menstrual abnormalities and thus improve fertility. In infertile women, the prevalence of autoimmune thyroid disease (AITD) is significantly higher compared to parous age-matched women. This is especially the case in women with endometriosis and polycystic ovarian syndrome (PCOS). AITD does not interfere with normal fetal implantation and comparable pregnancy rates have been observed after assisted reproductive technology (ART) in women with and without AITD.

During the first trimester, however, pregnant women with AITD carry a significantly increased risk for miscarriage compared to women without AITD, even when euthyroidism was present before pregnancy. It has also been demonstrated that controlled ovarian hyper stimulation (COH) in preparation for ART has a significant impact on thyroid function, particularly in women with AITD. It is therefore advisable to measure thyroid function and detect AITD in infertile women before ART, and to follow-up these parameters after COH and during pregnancy when AITD was initially present. Women with thyroid dysfunction at early gestation stages should be treated with L-thyroxin to avoid pregnancy complications. Whether thyroid hormones should be given prior to or during pregnancy in euthyroid women with AITD remains controversial. To data, there is a lack of well-designed randomized clinical trials to elucidate this controversy.

The thyroid gland and gonadal axes interact continuously before and during pregnancy. Hypothyroidism influences ovarian function by decreasing levels of sex hormone binding globulin and increasing the secretion of prolactin. In women of reproductive age, hypothyroidism can be reversed by thyroxin therapy to improve fertility and avoid the need for use of assisted reproductive technologies. For infertile women, preparation for medically assisted pregnancy comprises controlled ovarian hyper stimulation that substantially increase circulating estrogen concentrations, which in turn can severely impair thyroid function.

In women without thyroid autoimmunity these changes are transient, but in those with thyroid autoimmunity estrogen stimulation might lead to abnormal thyroid function throughout the remaining pregnancy period.

Prevalence of thyroid autoimmunity is significantly higher among infertile women than among fertile women, especially among those whose infertility is caused by endometriosis or ovarian dysfunction. Presence of thyroid autoimmunity does not interfere with normal embryo implantation, but the risk of early miscarriage is substantially raised.

Subclinical and overt forms of hypothyroidism are associated with increased risk of infertility, for which thyroxin therapy can be beneficial. Systematic screening for thyroid disorders in pregnant women remains controversial but might be advantageous in women at high risk, particularly infertile women.

ELTROXIN:

Glaxo wellcome:

50 ug: each white tablet contains: levothyroxine sodium USP 50 ug.

Eltroxin (levothyroxine) should not be used to treat infertility unless it is caused by low thyroid hormone levels. The usual full replacement dose of levothyroxine sodium for younger, healthy adults is approximately 1.7 mcg/kg/day administered once daily. In the elderly, the full replacement dose may be altered by decreases in T4 metabolism and levothyroxine sodium absorption. Older patients may require less than 1 mcg/kg/day.

Women who are maintained on levothyroxine sodium during pregnancy may require increased doses. Therapy is usually initiated in younger, healthy adults at the anticipated full replacement dose. Clinical and laboratory evaluations should be performed at 6 to 8 week intervals (2 to 3 weeks in severely hypothyroid patients), and the dosage adjusted until the serum TSH concentration is normalized and signs and symptoms resolve. Treatment of subclinical hypothyroidism may require lower than usual replacement doses, e.g. 1.0 mcg/kg/day. Patients for whom treatment is not initiated should be monitored yearly for changes in clinical status, TSH thyroid disease.

Women struggling with fertility still don't get routine thyroid tests. People who can't lose weight are still not having thyroid evaluations. Doctors frequently hand out prescriptions for antidepressants and cholesterol medications without ever testing for hypothyroidism first, which is the recommended procedure.

Adds shomon, "It's gotten to the point where patients must be educated about thyroid disease, because we often need to take the lead with doctors when it comes to our own thyroid diagnosis and treatment". Some patients need autoimmune thyroid antibodies tests not just a TSH test to diagnose their thyroid condition.

Endocrinologists are not necessarily the best doctors to treat all. Thyroid conditions.

- There are many effective brand-name thyroid medication…and almost all of them are expensive.
- Infertility can be thyroid symptom-but many doctors and fertility clinics do not test for thyroid problems.
- Every woman should have her thyroid evaluated before and during pregnancy. Thyroid patients who become pregnant must be knowledgeable, and seek extra attention and care, because obstetricians are generally not knowledgeable about how to treat thyroid conditions.
- When the sex drive is suffering, a lack of thyroid hormone could be to blame and should be thoroughly evaluated.
- Your thyroid can make you fat an undiagnosed or improperly treated thyroid condition can sabotage even the best diet and exercise plan.
- High cholesterol-and cholesterol levels that don't respond to medication could be due to an undiagnosed or poorly treated thyroid condition.

Conclusion:

Thyroid disorders have a relevant role in male and female infertility. Thyroid dysfunction may result in menstrual disturbances, an increased risk of miscarriage, and possible long-term health effects in the offspring as well as spermatogenetic abnormalities in the male. TAI, which is more prevalent in infertile women, does not seem to affect the conception rate, but is associated with increased miscarriage rate. Thyroxin treatment does not appear to affect conception rate nor to play a protective role in live birth. Sufficient data on subclinical hypothyroidism, hypothyroidism and isolated TAI in infertility are lacking, and further research is needed to elucidate the impact of thyroid dysfunction on reproduction.

Awareness of the thyroid status in the infertile couple is crucial, because of its significant, frequent and often reversible or preventable

effect on infertility. Many aspects of the role of thyroid disorders however in infertility need further research.

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الملخص العربي

تعددت اسباب العقم عند السيدات فمنها ماهو يمكن تشخيصة وعلاجة بسهولة ومنها ما يحتاج الى حس اكلينيكى عالى مثال ذلك: هبوط مستوى هرمون الغدة الدرقية حيث انه ينقسم الى نوعين : الاول له اعراضه الاكلينيكية الواضحة اما الثانى فليثت له اعراض سريرية واضحة ولكنه قد يكون السبب للعقم وقد يكون تفسير ذلك هو ان هرمون الثيروكسين يدخل فى كل الوظائف الحيوية لمختلف اعضاء جسم الانسان ومنها المبيضين وبالتالى تأتى اهمية قياس هرمون الثيروكسين والTSH لاكتشاف حالات نقص هرمون الثيروكسين وبالتالى علاجها ومن ثم علاج حالة العقم لدى هذه السيدات واستفاضت الدراسات من مختلف المراكز فى هذه النقطة واوضحت بجلاء ان العقم قد يكون عرضا لامراض الغدة الدرقية وطالبوا بالاهتمام بتقييم وظائف الغدة الدرقية كجزء هام من فحوص العقم وعلاج نقص افراز الغدة الدرقية كما اوضحت الابحاث هو هرمون الثيروكسين لفترة مناسبة مع المتابعة بواسطة قياس مستوى هرمون TSH.

وقد يكون تأثير نقص هرمون الثيروكسين ناتج من ارتفاع TSH حيث يؤدى الى ارتفاع هرمون اللبن (البرولاكتين) وتأثيره الضار على التبويض كما ان التبروكسين له دورة الضرورى فى حدوث الاخصاب وتكوين الاجنة .

وقد تظهر علامات نقص إفراز الغدة الدرقية على هيئة الحساسية للبرد وزيادة الوزن مع إمساك مزمن أو تورم باليد والقدمين وتحت الجفون

ويعطل نقص الثيروكسين افراز الاستروجين و FSHوLH مما يقلل التبويض مما يعن العقم.

وقد يحدث نقص الثيروكسين اضطرابا فى نمط الدورة الشهرية غالبا ما تكون زيادة فى كميتها مما يؤدى الى فقر دم وهناك فجوة فى المعلومات الخاصة بدور الغدة الدرقية فى التكاثر بالرغم من اهميه هذا الدور .

ويتراوح معدل حدوث نقص افرازات الغدة الدرقية فى العقم لدى السيدات من ٥ الى ٧% اما غير المشخص فيصل الى ٢-٤% ويصاحب نقص هرمون الثيروكسين زيادة فى افراز هرمون اللبن مما يؤدى بدوره الى العقم وتكمن اهمية البحث فى نقص افرازات الغدة الدرقية الى انها قد تكون غير ملحوظة سريريا ولا تظهر الا اذا راعينا الاهتمام بقياس الثيروكسين و T 3 وفى حالات العقم الأولى او الثانوى سيبقى الاهتمام بذلك حيث وجد من مختلف الأبحاث الطبية فى هذا المجال ان نقص افراز الغدة الدرقية يتسبب فى نسبة لا بأس بها من حالات العقم وتأخر الحمل وكذا الاجهاض المتكرر ولا تعطى لها الاهمية الكافية من ناحية تشخيص والبحث مما قد يدخل المريضات فى ابحاث اخرى او يقلل فرصة حدوث الحمل من اساسه.

وفى هذه الدراسة نحاول القاء الضوء على هذا الارتباط ربما غير الواضح بين نقص افرازات الغدة الدرقية وبين العقم خاصة عندما لا تكون

هناك علامات تشخيصية واضحة لتشخيص حالات نقص وظائف الغدة الدرقية .

ومما لاشك فيه ان قياس هذه الهرمونات TSH و3 T و4 T يساعد على الوصول الى التشخيص المناسب فى الوقت المناسب وبالتالى العلاج فى وقته توفيرا للوقت والجهد.