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International Journal of Current Research
Vol. 7, Issue, 12, pp.23932-23943, December, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

REVIEW ARTICLE

CONSEQUENCES OF THYROID DYSFUNCTION ON MENSTRUAL CYCLICITY AND WOMEN REPRODUCTION

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ARTICLE INFO

Article History:
Received 15th September, 2015
Received in revised form
29th October, 2015
Accepted 15th November, 2015
Published online 30th December, 2015

Key words:

Hyperthyroidism,
Hypothyroidism,
Hypomenorrhea,
Oligomenorrhea,
Thyrotropin

ABSTRACT

Thyroid dysfunction is extremely common in women, as women are five to eight times more likely to have thyroid dysfunction than men, and has unique consequences related to menstrual cyclicity and reproduction. Both hyperthyroidism and hypothyroidism may result in menstrual disturbances. The most common manifestations are hypomenorrhea and oligomenorrhea. The thyroid dysfunction is also frequently associated with other menstrual disturbances including amenorrhea and anovulation. Hyperthyroidism occurs in about 0.2-0.4% of all pregnancies and Hypothyroidism is also common in pregnancy with an estimated prevalence of 2-3% and 0.3-0.5% for subclinical and overt hypothyroidism respectively. In pregnant women, even minimal hypothyroidism can increase rates of miscarriage and fetal death and may also have adverse effects on later cognitive development of the offspring. Hyperthyroidism during pregnancy may also have adverse consequences. Women often overlook their symptoms or mistake them for symptoms of other conditions. For example, women are at particularly high risk for developing thyroid disorders following childbirth. Symptoms such as fatigue and depression are common during this period, but these are also symptoms of thyroid disease. The American Thyroid Association (ATA) estimates that more than half of thyroid conditions remain undiagnosed. Accordingly, Thyroid-stimulating hormone or thyrotropin (TSH) determination is warranted for all women planning pregnancy or those already pregnant.

Citation: Swaroopa Maralla and Bharathi, 2015. "Consequences of thyroid dysfunction on menstrual cyclicity and Women Reproduction", *International Journal of Current Research*, 7, (12), 23932-23943.

INTRODUCTION

The thyroid gland is a small gland in the neck that secretes thyroid hormone. It is a butterfly-shaped gland in the middle of the neck, located below the larynx (voice box) and above the clavicles (collarbones). The thyroid produce two hormones, triiodothyronine (T3) and thyroxine (T4), which regulate how the body uses and stores energy (also known as the body's metabolism). Thyroid hormone plays an important role in the metabolism of the body and is involved in nearly every body function. The thyroid hormone is present in two forms, T3 and T4. A part of the hormones is attached to protein, whereas some part is present as free hormone. The hormone that controls the secretion of thyroid hormone is Thyroid-stimulating Hormone (TSH), which is secreted by a gland in the brain called the pituitary. Thus, if the level of thyroid hormone is low, the pituitary secretes more TSH to stimulate the thyroid. The reverse is the case if the thyroid hormone levels are high.

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The condition where thyroid hormone levels are low is referred to as hypothyroidism while the condition where thyroid hormone levels are high is referred to as hyperthyroidism. Hypothyroidism is more common in pregnancy as compared to hyperthyroidism. About 25% female infertility and 15% menstrual cycle disorders result from thyroid dysfunction. Particularly, the subclinical hypothyroidism has a high prevalence in the population; therefore, thyroid function must be examined in female with unclear infertility or menstrual disturbances. The next overlap of thyroid disorders and gynaecology represents iodine-131 use for differentiated thyroid carcinoma in fertile age with aspects to ovarian failure and gestational risk.

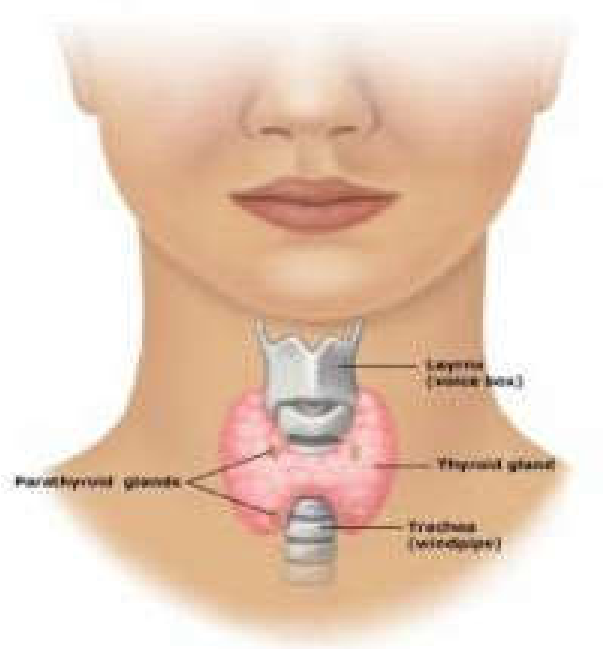
Hypothyroidism Overview

Hypothyroidism is a condition in which the thyroid gland does not produce enough thyroid hormone. It is the most common thyroid disorder.

Hypothyroidism causes

In about 95 percent of cases, hypothyroidism is due to a problem in the thyroid gland itself and is called primary hypothyroidism.

However, certain medications and diseases can also decrease thyroid function. As an example, hypothyroidism can also develop after medical treatments for hyperthyroidism, such as thyroidectomy (surgical removal of the thyroid) or radioactive iodine treatment (to destroy thyroid tissue). In some cases, hypothyroidism is a result of decreased production of thyroid-stimulating hormone (TSH) by the pituitary gland (called secondary hypothyroidism). Thyroid problems are more common in women, increase with age, and are more common in whites and Mexican Americans than in blacks.



Hypothyroidism Symptoms

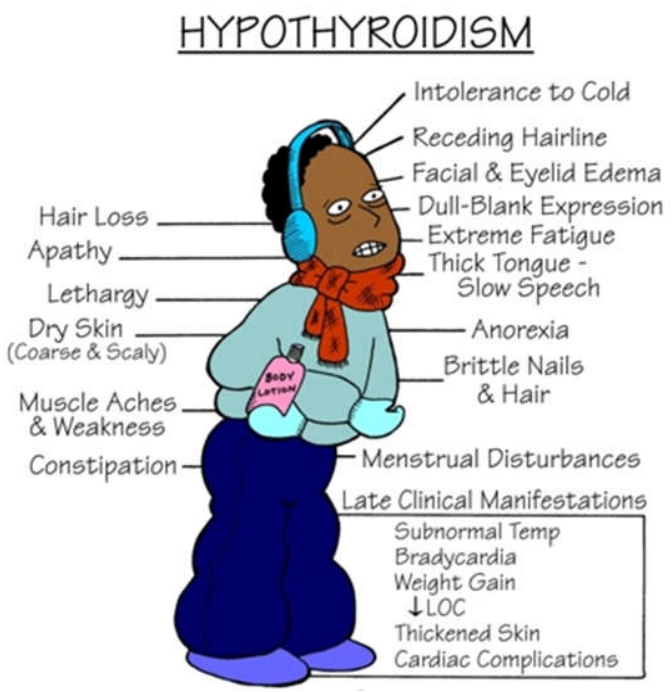
The symptoms of hypothyroidism vary widely; some people have no symptoms while others have dramatic symptoms or, rarely, life-threatening symptoms. The symptoms of hypothyroidism are notorious for being nonspecific and for mimicking many of the normal changes of aging. Usually, symptoms are milder when hypothyroidism develops gradually. Symptoms, when caused by hypothyroidism, generally are related to the degree of hypothyroidism. Many patients with mild hypothyroidism are identified on screening tests for potential hypothyroid symptoms, but have few or no symptoms that ultimately are attributed to hypothyroidism or respond to treatment of hypothyroidism. In contrast, patients with moderate to severe hypothyroidism are usually symptomatic and improve significantly with thyroid hormone replacement.

General symptoms

Thyroid hormone normally stimulates the metabolism, and most of the symptoms of hypothyroidism reflect slowing of metabolic processes. General symptoms may include fatigue, sluggishness, weight gain, and intolerance of cold temperatures.

Skin

Hypothyroidism can decrease sweating. The skin may become dry and thick.



(Nursing Education Consultants, 2007)

The hair may become coarse or thin, eyebrows may disappear, and nails may become brittle.

Eyes

Hypothyroidism can lead to mild swelling around the eyes. People who develop hypothyroidism after treatment for Graves' disease may retain some of the eye symptoms of Graves' disease, including protrusion of the eyes, the appearance of staring, and impaired movement of the eyes.

Cardiovascular system

Hypothyroidism slows the heart rate and weakens the heart's contractions, decreasing its overall function. Related symptoms may include fatigue and shortness of breath with exercise. These symptoms may be more severe in people who also have heart disease. In addition, hypothyroidism can cause mild high blood pressure and raise blood levels of cholesterol.

Respiratory system

Hypothyroidism weakens the respiratory muscles and decreases lung function. Symptoms can include fatigue, shortness of breath with exercise, and decreased ability to exercise.

Hypothyroidism can also lead to swelling of the tongue, hoarse voice, and sleep apnea. Sleep apnea is a condition in which there is intermittent blockage of the airway while sleeping, causing fitful sleep and daytime sleepiness.

Gastrointestinal system

Hypothyroidism slows the actions of the digestive tract, causing constipation. Rarely, the digestive tract may stop moving entirely.

Reproductive system

Women with hypothyroidism often have menstrual cycle irregularities, ranging from absent or infrequent periods to very frequent and heavy periods. The menstrual irregularities can make it difficult to become pregnant, and pregnant women with hypothyroidism have an increased risk for miscarriage during early pregnancy. Treatment of hypothyroidism can decrease these risks.

Myxedema coma

In people with severe hypothyroidism, trauma, infection, exposure to the cold, and certain medications can rarely trigger a life-threatening condition called myxedema coma, which causes a loss of consciousness and hypothermia (low body temperature).

Hypothyroidism Diagnosis

In the past, hypothyroidism was not diagnosed until symptoms had been present for a long time. However, simple blood tests can now detect hypothyroidism at an early stage. A person may be tested for hypothyroidism if there are signs and symptoms, such as those discussed above, or as a screening test.

Blood tests

Blood tests can confirm the diagnosis and pinpoint the underlying cause of the thyroid hormone deficiency. The most common blood test for hypothyroidism is TSH (thyroid stimulating hormone). TSH is the most sensitive test because it can be elevated even with small decreases in thyroid function. Thyroxine (T4), the main product of the thyroid gland, may also be measured to confirm and assess the degree of hypothyroidism.

Routine screening

All newborn babies in the United States are routinely screened for thyroid hormone deficiency. It is not clear if all adults should be tested for thyroid disease.

Hypothyroidism Treatment

The goal of treatment for hypothyroidism is to return blood levels of TSH and T4 to the normal range and to alleviate symptoms.

Medication

The treatment for hypothyroidism is thyroid hormone replacement therapy. This is usually given as an oral form of T4. T4 should be taken once per day on an empty stomach (one hour before eating or two hours after). Generic (levothyroxine) and brand-name (Synthroid, Levoxyl, Levothroid, Unithyroid, Tirosint) formulations are equally effective. However, it is preferable to stay on the same type of T4 rather than switching between brand name and/or generic formulations. If a switch is necessary, a blood test is usually done six weeks later to determine if the dose needs to be adjusted. Color-coded tablets can help with dose adjustments. Some clinicians prescribe another form of thyroid hormone, triiodothyronine (T3) in combination with T4. However, since T4 is converted into T3 in other organs, the majority of studies have not shown an advantage of combination T3 and T4 therapy over T4 alone. In most cases, symptoms of hypothyroidism begin to improve within two weeks of starting thyroid replacement therapy. However, people with more severe symptoms may require several months of treatment before they fully recover.

Duration and dose

A healthcare provider will prescribe an initial dose of T4 and then retest the blood level of TSH after six weeks. The T4 dose can be adjusted at that time, depending upon these results. This process may be repeated several times before hormone levels become normal. After the optimal dose is identified, a provider may recommend monitoring blood tests once yearly, or more often as needed.

Most people with hypothyroidism require lifelong treatment, although the dose of T4 may need to be adjusted over time. Never increase or decrease the T4 dose without first consulting a healthcare provider. Over replacement of T4 can cause mild hyperthyroidism, with the associated dangers of atrial fibrillation (irregular heart beat) and, possibly, accelerated bone loss (osteoporosis).

Dose changes

Changes in the T4 dose are based upon the person's TSH and T4 level. The dose may need to be increased if thyroid disease worsens, during pregnancy, if gastrointestinal conditions impair T4 absorption, or if the person gains weight. A high fiber diet, calcium- or aluminum-containing antacids, and iron tablets can interfere with the absorption of T4 and should be taken at a different time of day. The dose may need to be decreased as the person gets older, after childbirth, or if the person loses weight.

Monitoring

Individual T4 doses can vary widely and depend upon a variety of factors, including the underlying cause of hypothyroidism. People with certain conditions require more frequent monitoring.

Advanced age and heart disease

Thyroid hormone makes the heart work a bit harder. Therefore, a clinician may opt for more conservative T4 treatment in older adults and in people with coronary artery disease.

Pregnancy

Women often need higher doses of T4 during pregnancy. Testing is usually recommended every four weeks, beginning after conception. Once the optimal T4 dose is established, testing is usually repeated at least once per trimester. After delivery, the woman's dose of T4 will need to be adjusted again.

Surgery

Hypothyroidism can increase the risk of certain surgery-related complications; bowel function may be slow to recover and infection may be overlooked if there is no fever. If pre-operative blood tests reveal low thyroid hormone levels, non-emergency surgery is usually postponed until treatment has returned T4 levels to normal.

Hypothyroidism without symptoms

In some cases, hypothyroidism is extremely mild or causes no obvious symptoms (called subclinical hypothyroidism). The decision to treat subclinical hypothyroidism with T4 is controversial. Many experts treat patients with subclinical hypothyroidism if their TSH is >10 mU/L to prevent the development of hypothyroidism and associated symptoms. Treatment is also recommended for people who have a goiter or nonspecific symptoms of hypothyroidism, such as fatigue, constipation, or depression.

Hyperthyroidism Overview

Hyperthyroidism is a disease in which the thyroid is hyperactive and makes too much thyroid hormone. Like most conditions of the thyroid gland, it is more common in women. Hyperthyroidism can be caused by either overproduction of thyroid hormone or excessive release of thyroid hormone from the thyroid gland due to inflammation and/or destruction. It is important to distinguish between these two causes, in order to choose the appropriate treatment.

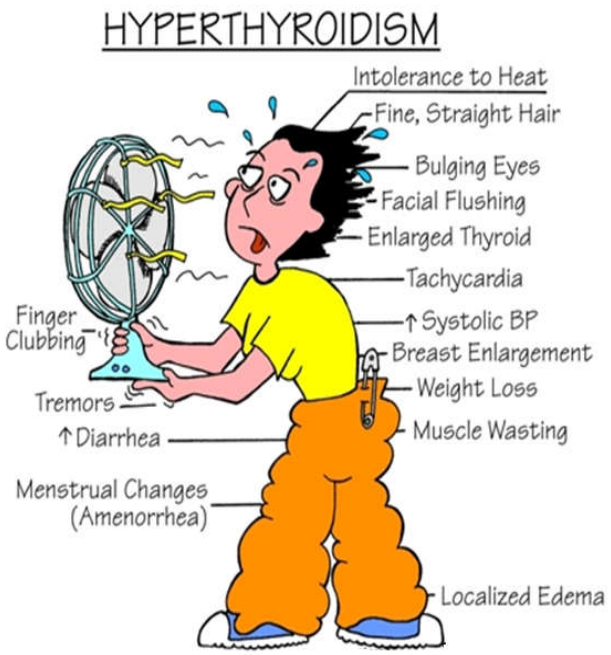
A thyroid uptake scan (also known as a radioactive iodine scan) can help tell the difference between these two causes. Problems causing thyroid hormone overproduction have increased uptake on thyroid scanning (i.e. a "hot" scan), while thyroid gland inflammation and/or destruction have low uptake on thyroid scanning. Overproduction of thyroid hormone is the most common cause of hyperthyroidism and can be caused by Graves' disease, toxic multinodular goiter, and toxic adenoma.

Symptoms

Symptoms that may be associated with hyperthyroidism include anxiety, insomnia (inability to sleep through the night), tremors, palpitations, weight loss, muscle weakness, heat intolerance, excessive sweating, and menstrual changes. The number, degree, and severity of these symptoms can provide some clue as to the severity of hyperthyroidism.

Diagnosis

Diagnosing hyperthyroidism is based on history and physical exam findings along with appropriate laboratory testing. On physical exam, the physician may find that the patient has a rapid heart rate (tachycardia), irregular heartbeats (arrhythmias, including atrial fibrillation), eye symptoms (such as dryness, burning, bulging, double vision), or hand tremors. In addition, the thyroid gland may be larger than normal.



(Nursing Education Consultants,2007)

Laboratory testing to confirm the diagnosis of hyperthyroidism will include thyroid function tests. Usually, the TSH level will be lower than normal and the T3 and/orT4 levels will be higher than normal. Subclinical hyperthyroidism is defined as cases where there are no clear symptoms or physical signs of hyperthyroidism on history and physical examination, but the blood level of TSH is low, and T3/T4 levels are normal. Thyroid uptake scanning is used to determine if the thyroid is making too much thyroid hormone, leading to a high, or "hot" uptake scan versus if the thyroid is being destroyed (as in thyroiditis), in which case the scan will be a low, or "cold" uptake scan.

Common causes

Graves' disease

Graves' disease is an autoimmune problem where the body's immune system overstimulates the thyroid. It is the most common cause of hyperthyroidism. TSH-R Ab, an antibody to the TSH receptor, causes the overproduction of thyroid hormone. Laboratory findings show a low TSH and high T4 and T3. The thyroid uptake scan will be high, or "hot". On physical exam, patients with Graves' disease may have bulging eyes and violet plaque-like lesions, on the front of their lower legs, which are possibly associated with itchiness.

Toxic multinodulargoiter

Hyperthyroidism due to *toxic* multinodulargoiteroccurs when one or more nodules (growths) in the thyroid begin to make too much thyroid hormone. In general, the hyperthyroidism tends to be less severe than that seen in Graves' disease. Laboratory diagnosis is the same as in other cases of hyperthyroidism with low TSH and high T4 and T3 levels. Thyroid uptake scans may note several separate "hot" spots corresponding to the hyperactive nodules, while the rest of the gland has decreased activity.

Toxic adenoma

If a single nodule, or a solitary toxic adenoma, in an otherwise normal thyroid gland makes too much thyroid hormone, it can lead to hyperthyroidism. This is a less common cause of hyperthyroidism than either Graves' disease or toxic multinodulargoiter. The diagnosis can be made in the same fashion as above.

Treatment

The three main treatments for hyperthyroidism are: 1) medical therapy, 2) surgery, and 3) RAI ablation. The best treatment depends on a number of factors and the treatment plan should be made with the help of experts in thyroid disease including endocrinologists and surgeons. In general, the first treatment that is usually tried once a diagnosis is made is usually antithyroid medications. If medical therapy does not work, then a more definitive therapy such as surgery or RAI ablation is considered. The choice between surgery and RAI ablation will depend on the expertise and experience of the patient's doctors. Both have equal success rates and low risks of complications.

Medical Therapy

The two goals for medical therapy are to control symptoms and to prevent excess thyroid hormone production. Beta blockers are medications that are used to control symptoms such as palpitations, anxiety, and tremors. These medications are usually given until thyroid function has returned to normal. Antithyroid medications are used to block excess thyroid hormone production. The two drugs used most commonly are Methimazole and propylthiouracil (PTU). Methimazole is the preferred medication because it acts faster and has fewer side effects. Usually, patients are put on antithyroid medications for one to two years. At that point the medication is stopped. If hyperthyroidism returns, as happens in over 50% of patients, a more definitive treatment to cure the disease is considered. The options for definitive treatment of hyperthyroidism are RAI ablation or surgical removal of all or part of the thyroid. Both are effective in the long-term control of hyperthyroidism.

Surgery

Surgery for hyperthyroidism usually means removing the entire thyroid gland (total thyroidectomy) with the goal of making the patient hypothyroid and then starting thyroid hormone replacement pills. Trying to leave remove enough thyroid to cure the hyperthyroidism while leaving enough thyroid to have normal thyroid function (subtotal thyroidectomy) without medication is very difficult. Even if everything is ok at first, over time, the thyroid can grow back and cause recurrent hyperthyroidism (i.e. return of hyperthyroidism). For this reason, most experienced surgeons now perform a total thyroidectomy for the surgical treatment of hyperthyroidism, in order to lower the risk of recurrence that can otherwise occur with leaving part of the thyroid behind. Surgery does have the small risk of postoperative complications, but it has the advantages of rapidly fixing the hyperthyroidism with only a 3% recurrence rate. When performed by an experienced surgeon, thyroid surgery is safe. After a total thyroidectomy, patients absolutely must take thyroid hormone replacement pills because removing the whole thyroid makes them hypothyroid. Patients with a large goiter, with significant compressive symptoms, suspicion for thyroid cancer, moderate or severe eye disease in Graves' disease, and pregnant patients who cannot tolerate antithyroid medications should have an operation.

RAI ablation

In RAI ablation, the patient is given a pill that contains radioactive iodine that is absorbed by thyroid cells and destroys them. RAI ablation has the advantage of avoiding thyroid surgery. Currently, most patients are given doses of RAI that are high enough to destroy the entire thyroid and then are started on thyroid hormone replacement pills. This controls the hyperthyroidism sooner and more definitively. With proper treatment, hypothyroidism following RAI ablation should occur within three to six months.

In general, the chance of the hyperthyroidism returning (i.e. recurrence) is less than 3%. A disadvantage of RAI ablation is the potential to worsen thyroid eye disease (ophthalmopathy) associated with severe cases of Graves' disease. Patients who are pregnant, have large thyroids, suspicious thyroid nodules, risk factors for thyroid cancer, or who have symptoms from a large goiter should not have RAI ablation. There is debate as to whether young children should have RAI ablation because they may then be at increased risk for other cancers and heart damage later on in life. In general, most practitioners do not recommend RAI ablation for patients younger than 15 years old.

Thyroid and women reproductive health

Thyroid disorders are often ubiquitous and insidious in their presentation. They have been implicated in a broad spectrum of reproductive disorders ranging from abnormal sexual development to menstrual irregularities and infertility. If pregnancy occurs in a patient with thyroid disease, the physician must ensure that therapeutic measures instituted to restore the health of the mother do not adversely affect the developing fetus.

Thyroid diseases and Menstrual disturbances

The prevalence of menstrual disturbances, including secondary amenorrhea, hypomenorrhea, oligomenorrhea, hypermenorrhea, polymenorrhea and irregular menstrual cycle were prospectively examined in 586 patients with hyperthyroidism due to Graves' disease, 111 with hypothyroidism, 558 with euthyroid chronic thyroiditis, 202 with painless thyroiditis and 595 with thyroid tumor. In the overall patient group, the prevalence did not different from that in 105 healthy controls. However, patients with severe hyperthyroidism showed a higher prevalence of secondary amenorrhea (2.5%) and hypomenorrhea (3.7%) than those (0.2% and 0.9%, respectively) with mild or moderate hyperthyroidism. Moreover, patients with severe hypothyroidism had a higher prevalence (34.8%) of menstrual disturbances than mild-moderate cases (10.2%). Menstrual

disturbances in thyroid dysfunction were less frequent than previously thought.

The role of the thyroid in menstrual problems

Many women suffer from problems with their periods. These problems range from PMS to painful periods, irregular cycles or heavy bleeding. When this is further investigated, they are often diagnosed with ovarian cysts, Polycystic Ovarian Syndrome (PCOS) or Polycystic Ovarian Disorder (PCOD), endometriosis or fibroids. The focus with these disorders is often on the female hormones, and while it is true that oestrogen dominance or low progesterone levels do play an important role, we do need to look further to find out why these hormones are out of balance in the first place.

Thyroid hormones affect menstrual periods

Women with irregular periods, heavy periods, difficulty conceiving or sustaining a healthy pregnancy often have an underlying thyroid dysfunction (Poppe *et al*., 2007 and Abalovich and Mitelberg, 2007). The menstrual cycle is influenced by thyroid hormones, hypothyroidism leads to ovulatory dysfunction. It is quite complicated how this works, but what it comes down to is that immature egg cells have thyroid receptors and that these receptors need to be activated for proper maturation and ovulation. If this stimulation doesn't happen, ovulation doesn't follow either. This lack of ovulation is characteristic of PCOS or PCOD. Furthermore, low thyroid hormones decrease levels of SHBG but increase prolactin secretion, once again impairing ovulation. With no ovulation, less progesterone is produced, opening the door for heavy bleeding (Poppe *et al*., 2007, 2008). Low progesterone levels then create an oestrogen dominant environment, which in itself can lower thyroid function (Poppe *et al*., 2007), creating a vicious cycle that is hard to break without proper support.

Heavy bleeding with periods is not only the result of low progesterone levels, but can also be caused by hypothyroidism. Low levels of active thyroid hormones negatively influence the production of coagulation factors. Less coagulation means longer, heavier bleeding, as is often the case in women with endometriosis and fibroids. (Poppe *et al*., 2008).Research has shown that thyroid function is often low in women who fail to ovulate and have heavy periods (Poppe *et al*., 2007).

The Thyroid Impact

No one knows exactly how the thyroid hormones influence a woman's monthly cycle, but in women with thyroid disease, the monthly menstrual cycle can be significantly altered or disrupted. A thyroid problem can also affect teenage girls. Girls who get their period very early — before the age of 10 — may be suffering from an overactive thyroid. Those who are 15 or older when they get their first period may have hypothyroidism. In women who have hypothyroidism, it's not uncommon for their periods to become much heavier than before.

The duration of their periods may also increase, or they may notice that their cycle has gotten shorter, and they're getting their periods more frequently. According to one study, approximately 23 percent of women with hypothyroidism experience menstrual irregularities. Other estimates have found that the impact is significantly higher.

The problems are different in women who have hyperthyroidism. Women whose thyroids are overactive tend to experience lighter periods, less frequent periods, or even complete absence of their monthly cycles. Approximately 22 percent of hyperthyroid women have menstrual problems, though again, some estimates suggest the rate is much higher. The most common disturbances are defined as:

- **Amenorrhea**
  Amenorrhea is the medical term for the lack of menstrual periods. In women who have been menstruating, it is called secondary amenorrhea and defined by the absence of periods for more than three to six months. It is also diagnosed in girls who have not had their first periods by the age of 16 and is called primary amenorrhea.
- **Oligomenorrhea**
  When a woman has fewer than six to eight menstrual periods in a year, she may be diagnosed with oligomenorrhea, or infrequent periods. While some women may celebrate the fact that their periods have become less frequent, diminished frequency is usually a sign of a potential medical problem such as thyroid disease.
- **Dysmenorrhea**
  In some women, hypothyroidism can cause painful menstrual periods, known as dysmenorrhea. Dysmenorrhea can also involve lower back pain, nausea, bowel problems, achiness in the lower extremities, and excessive bloating.
- **Menorrhagia**
  Extremely heavy or prolonged menstrual bleeding is called menorrhagia. Women with menorrhagia may need to change their sanitary pad every hour over the period of several hours.
- **Shortened Cycles**
  Some women with hypothyroidism will notice that their menstrual cycle shortens by a few days. They may also have bleeding that lasts longer.

Mechanism by which thyroid dysfunction affects the menstrual cycle

Thyroid dysfunction is associated with a range of menstrual abnormalities, including oligomenorrhea, amenorrhea, and menorrhagia. Women with hypothyroidism may also be at increased risk of pregnancy loss. The connection between thyroid hormone levels and the menstrual cycle is mainly mediated by thyrotropin-releasing hormone (TRH), which has a direct effect on the ovary. Additionally, abnormal thyroid function can alter levels of sex hormone-binding globulin, prolactin, and gonadotropin-releasing hormone, contributing to menstrual dysfunction. For example, increased levels of TRH may raise prolactin levels, contributing to the amenorrhea associated with hypothyroidism.

Thyroid and infertility

Thyroid disorders may not only be the cause of infertility but also increases the incidence of miscarriages and the morbidity

of the pregnancies. During pregnancy the demand of thyroid hormones increases to about 30−50% and the thyroid has to cope with this increase. In Germany the iodine intake has improved significantly during the last 20 years, but still is borderline low with a mean intake of about 120 µg iodide per day. Therefore it is still recommended that pregnant women are supplemented with about 100−150 µg of iodide during pregnancy and the time of breast-feeding, to avoid hypothyroidism of the foetus with concomitant delay of the brain development. Not only women with subclinical hypothyroidism, but only elevated TPO antibodies have a significant increase in early miscarriage and preterm delivery. An early supplementation with Levothyroxin despite euthyroidism might reduce these risks. Those women also more frequently develop postpartum thyroiditis.

This risk can be reduced by a supplementation with selenium during and after pregnancy. Graves' disease is a rare disorder and only about 0.1−0.4 pregnancies are affected. The course of the disease is biphasic, with an exacerbation within the first trimester and an improvement thereafter, but a recurrence after delivery. Overt thyrotoxicosis has to be treated with propylthiouracil, to maintain euthyroidism during pregnancy. The TSH receptor antibodies are transferred to the foetus with the risk of thyrotoxicosis.

Special care of the foetus is therefore necessary. Transient mild hyperthyroidism may occur in women with very high HCG levels during the first three months of pregnancy. This often is associated with hyperemesis gravidarum. Subclinical hypothyroidism of the mother will disturb the normal development of the foetus and therefore has to be treated even when TSH is within the upper normal level. Special care is necessary in women with elevated TPO antibodies, because these more often develop postpartum thyroiditis.

Thyroid disease and reproduction dysfunction

Thyroid disorders have been implicated in a broad spectrum of reproductive disorders ranging from abnormal sexual development to menstrual irregularities and infertility. Hyperthyroidism in the male is thought to cause gynecomastia. In the female hypo and hyperthyroidism results in changes in cycles length and amount of bleeding. The hypothyroidism in the male has less clear-cut effect on the reproductive system. Long-standing, untreated hypothyroidism is associated with galactorrhea. These abnormalities are reversible with adequate thyroid supplementation or collection of hyperthyroidism. Thus during the investigation of hirsurism, menstrual irregularity, infertility, galactorrhea, and gynecomastia, the possibility of thyroid dysfunction must always be considered.

Thyroid and miscarriages/pregnancy loss

Thyroid hormone is well known to be essential for development of many tissues, including the brain and heart. The potential role of thyroid hormone in the development of reproductive tissues that might impact fertility is not clear (Kennedy *et al*., 2010). Thyroid dysfunction is quite prevalent and affects many organs, including the male and female gonads. It interferes with human reproductive physiology, reduces the likelihood of pregnancy and adversely affects pregnancy outcome, thus becoming relevant in the algorithm of reproductive dysfunction. (Kennedy *et al*., 2010) Thyroid dysfunction and thyroid autoimmunity are prevalent among women at reproductive age and are associated with adverse pregnancy outcomes. Subclinical hypothyroidism may be associated with ovulatory dysfunction and adverse pregnancy outcome (Kennedy *et al*., 2010).

Even minimal hypothyroidism can increase rates of miscarriage and fetal death and may also have adverse effects on later cognitive development of the offspring. Pregnancy affects thyroid economy with significant changes in iodine metabolism, serum thyroid binding proteins, and the development of maternal goiter, especially in iodine-deficient areas. 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 (Kennedy *et al*., 2010).

Pregnancy is also accompanied by immunologic changes, mainly characterized by a shift from a T helper-1 lymphocyte to a T helper-2 lymphocyte state. Thyroid autoimmunity increases the miscarriage rate, and thyroxine treatment does not seem to protect. Thyroid peroxidase antibodies are present in 10% of women at 14 weeks' gestation, and are associated with (i) an increased pregnancy failure (i.e., abortion), (ii) an increased incidence of gestational thyroid dysfunction, and (iii) a predisposition to postpartum thyroiditis (Abbassi-Ghanavati, 2011).

During the first trimester, however, pregnant women with autoimmune thyroiditis (AITD) carry a significantly increased risk for miscarriage compared to women without AITD, even if euthyroidism (Kaprara and Krassas, 2008). Presence of thyroid autoimmunity does not interfere with normal embryo implantation, but the risk of early miscarriage is substantially raised. Autoimmune thyroid disease is present in around 4% of young females, and up to 15% are at risk because they are thyroid antibody-positive(Kaprara and Krassas, 2008). There is a strong relationship between thyroid immunity and infertility, miscarriage, and thyroid disturbances in pregnancy and postpartum. In the current review, we elaborate on the pathogenesis that underlies infertility and increased pregnancy loss among women with autoimmune thyroid disease. Such mechanisms include thyroid auto antibodies that exert their effect in a thyrotropin (TSH)-dependent but also in a TSH-independent manner. Lack of vitamin D was suggested as a predisposing factor to autoimmune diseases, and was shown to be reduced in patients with thyroid autoimmunity (Kennedy *et al*., 2011). In turn, its deficiency is also linked to infertility and pregnancy loss, suggesting a potential interplay with thyroid autoimmunity in the context of infertility. In addition, thyroid autoantibodies were also suggested to alter fertility by targeting zona pellucida, human chorionic gonadotropin receptors and other placental antigens.

Spontaneous pregnancy loss is a common clinical problem. With the use of sensitive human chorionic gonadotropin (hCG) assays, it has been shown that 31% of pregnancies end in a

miscarriage, with two-third of the losses occurring before clinical detection (Kaprara and Krassas,2008). It is postulated that the presence of thyroid auto antibodies reflects a generalized activation of the immune system and a generally heightened autoimmune reactivity against the feto-placental unit. Most but not all studies have shown a significant association between the presence of thyroid antibodies and a higher miscarriage rate. However, patients with high titers of thyroid autoantibodies do not show a higher rate of miscarriages compared with patients with low titers. The mechanisms involved still remains unclear (Abbassi-Ghanavati, 2011).

Thyroid disorders associated with pregnancy: etiology, diagnosis, and management

Thyroid disorders may not only be the cause infertility but also increases the incidence of miscarriages and the morbidity of the pregnancies. During pregnancy the demand of thyroid hormones increases to about 30 - 50 % and the thyroid has to cope with this increase.

Pregnancy has an effect on thyroid economy with significant changes in iodine metabolism, serum thyroid binding proteins, and the development of maternal goiter especially in iodine-deficient areas. Pregnancy is also accompanied by immunologic changes, mainly characterized by a shift from a T helper-1 (Th1) lymphocyte to a Th2 lymphocyte state. Thyroid peroxidase antibodies are present in 10% of women at 14 weeks' gestation, and are associated with (i) an increased pregnancy failure (i.e. abortion), (ii) an increased incidence of gestational thyroid dysfunction, and (iii) a predisposition to postpartum thyroiditis. Thyroid function should be measured in women with severe hyperemesis gravidarum but not in every patient with nausea and vomiting during pregnancy. Graves hyperthyroidism during pregnancy is best managed with propylthiouracil administered throughout gestation.

Thyroid-stimulating hormone-receptor antibody measurements at 36 weeks' gestation are predictive of transient neonatal hyperthyroidism, and should be checked even in previously treated patients receiving thyroxine. Postpartum exacerbation of hyperthyroidism is common, and should be evaluated in women with Graves disease not on treatment. Radioiodine therapy in pregnancy is absolutely contraindicated. Hypothyroidism (including subclinical hypothyroidism) occurs in about 2.5% of pregnancies, and may lead to obstetric and neonatal complications as well as being a cause of infertility. During the last few decades, evidence has been presented to underpin the critical importance of adequate fetal thyroid hormone levels in order to ensure normal central and peripheral nervous system maturation. In iodine-deficient and iodine-sufficient areas, low maternal circulating thyroxine levels have been associated with a significant decrement in child IQ and development. These data suggest the advisability of further evaluation for a screening program early in pregnancy to identify women with hypothyroxinemia, and the initiation of prompt treatment for its correction.

Hypothyroidism in pregnancy is treated with a larger dose of thyroxine than in the nonpregnant state. Postpartum thyroid dysfunction (PPTD) occurs in 50% of women found to have thyroid peroxidase antibodies in early pregnancy. The hypothyroid phase of PPTD is symptomatic and requires thyroxine therapy. A high incidence (25-30%) of permanent hypothyroidism has been noted in these women. Women having transient PPTD with hypothyroidism should be monitored frequently, as there is a 50% chance of these patients developing hypothyroidism during the next 7 year.

Hypothyroidism & pregnancy

When a woman is pregnant, her body needs enough thyroid hormone to support a developing fetus and her own expanded metabolic needs. Healthy thyroid glands naturally meet increased thyroid hormone requirements. If someone has Hashimoto's thyroiditis or an already overtaxed thyroid gland, thyroid hormone levels may decline further. So, women with an undetected mild thyroid problem may suddenly find themselves with pronounced symptoms of hypothyroidism after becoming pregnant.

Most women who develop hypothyroidism during pregnancy have mild disease and may experience only mild symptoms or sometimes no symptoms. However, having a mild, undiagnosed condition before becoming pregnant may worsen a woman's condition. A range of signs and symptoms may be experienced, but it is important to be aware that these can be easily written off as normal features of pregnancy. Untreated hypothyroidism, even a mild version, may contribute to pregnancy complications. Treatment with sufficient amounts of thyroid hormone replacement significantly reduces the risk for developing pregnancy complications associated with hypothyroidism, such as premature birth, preeclampsia, miscarriage, postpartum hemorrhage, anemia and abruptio placentae.

For a woman being treated for hypothyroidism, it's imperative to have her thyroid checked as soon as the pregnancy is detected so that medication levels may be adjusted. TSH levels may be checked one to two weeks after the initial dose adjustment to be sure it's normalizing. Once the TSH levels drop, less frequent check-ups are necessary during the pregnancy. Although thyroid hormone requirements are likely to increase throughout the pregnancy, they tend to eventually stabilize by the middle of pregnancy. The goal is to keep TSH levels within normal ranges, which are somewhat different than proper levels in a non-pregnant woman. Pre-pregnancy doses are usually resumed after giving birth.

There is no difference between treating hypothyroidism when a woman is pregnant than when she isn't. Levothyroxine sodium pills are completely safe for use during pregnancy. They will be prescribed in dosages that are aimed at replacing the thyroid hormone the thyroid isn't making so that the TSH level is kept within normal ranges. Once it is consistently in the normal range, the doctor will check TSH levels every six weeks or so. The physician may also counsel patients to take their thyroid hormone pills at least one-half hour to one hour before or at least four hours after eating or taking iron-containing prenatal vitamins and calcium supplements, which can interfere with the absorption of thyroid hormone.

Hyperthyroidism & pregnancy

Diagnosing hyperthyroidism based on symptoms can be tricky because pregnancy and hyperthyroidism share a host of features. Still, one should be aware of the symptoms and bring them to the attention of a doctor if they are experiencing them. For instance, feeling a heart flutter or suddenly becoming short of breath, both symptoms of hyperthyroidism, can be normal in pregnancy, but a doctor still may want to investigate these symptoms. An individual with any risk factors for thyroid disease should make certain they are tested.

Very mild hyperthyroidism usually does not require treatment, only routine monitoring with blood tests to make sure the disease does not progress. More serious conditions require treatment. However, treatment options are limited for pregnant women. Radioactive iodine, which is typically used to treat Graves' disease, cannot be used during pregnancy because it easily crosses the placenta, potentially damaging the baby's thyroid gland and causing hypothyroidism in the baby. Due to its potential risks, the goal of treatment is to use the minimal amount of antithyroid drugs possible to maintain a patient's T4 and T3 levels at or just above the upper level of normal, while keeping TSH levels low. When hormones reach the desired levels, drug doses can be reduced. This approach controls hyperthyroidism while minimizing the changes of a baby developing hypothyroidism.

Hyperthyroidism, if untreated, can lead to stillbirth, premature birth, or low birth weight for the baby. Sometimes it leads to fetal tachycardia, which is an abnormally fast pulse in the fetus. Women with Graves' disease have antibodies that stimulate their thyroid gland. These antibodies can cross the placenta and stimulate a baby's thyroid gland. If antibody levels are high enough, the baby could develop fetal hyperthyroidism, or neonatal hyperthyroidism. A woman with hyperthyroidism while pregnant is at an increased risk for experiencing any of the signs and symptoms of hyperthyroidism. And unless the condition is mild, if it is not treated promptly a woman could miscarry during the first trimester; develop congestive heart failure, preeclampsia, or anemia; and, rarely, develop a severe form of hyperthyroidism called thyroid storm, which can be life threatening.

Graves' disease tends to strike women during their reproductive years, so it should come as no surprise that it occasionally occurs in pregnant women. Pregnancy may worsen a preexisting case of Graves' disease. Graves' disease can also emerge for the first time, typically during the first trimester of pregnancy. The disease is usually at its worst during the first trimester. It tends to then improve in the second and third trimesters and flare up again after delivery.

Causes of Thyroid Disease in Pregnancy

The most common cause of maternal hyperthyroidism during pregnancy is the autoimmune disorder Grave's disease. In this disorder, the body makes an antibody (a protein produced by the body when it thinks a virus or bacteria has invaded) called thyroid-stimulating immunoglobulin (TSI) that causes the thyroid to make too much thyroid hormone. The most common cause of hypothyroidism is the autoimmune disorder known as Hashimoto's thyroiditis. In this condition, the body mistakenly attacks the thyroid gland cells, leaving the thyroid without enough cells and enzymes to make enough thyroid hormone.

Diagnosis of Thyroid Disease in Pregnancy

Hyperthyroidism and hypothyroidism in pregnancy are diagnosed based on symptoms, physical exam, and blood tests to measure levels of thyroid-stimulating hormone (TSH) and thyroid hormones T4, and for hyperthyroidism also T3.

Screening of Thyroid disorders

Universal screening for thyroid hormone abnormalities is not routinely recommended at present. Preconception or early pregnancy screening for thyroid dysfunction has been proposed but is not widely accepted. However, measurement of thyroid function and auto antibodies should certainly be considered in those who are at high risk of thyroid disease and in those whose pregnancy is otherwise high risk. In women at reproductive age, hypothyroidism can be reversed by thyroxine therapy to improve fertility and avoid the need for use of assisted reproduction technologies.

Accordingly, TSH determination is warranted for all women planning pregnancy or those already pregnant. Women with thyroid dysfunction at early gestation stages should be treated with l-thyroxine to avoid pregnancy complications. Whether thyroid hormones should be given prior to or during pregnancy in euthyroid women with AITD remains controversial. To date, there is a lack of well-designed randomized clinical trials to elucidate this controversy. Subclinical and overt forms of hypothyroidism are associated with increased risk of pregnancy-related morbidity, for which thyroxine therapy can be beneficial. Suboptimal iodine status affects a large proportion of the world's population, and pregnancy further depletes iodine stores. There is controversy surrounding the degree to which iodine should be supplemented and the duration of supplementation. The practicing clinician needs to be aware of the thyroid changes which accompany pregnancy.

Treatment of Thyroid Disease in Pregnancy

For women who require treatment for hyperthyroidism, an antithyroid medication that interferes with the production of thyroid hormones is used. This medication is usually propylthiouracil or PTU for the first trimester, and — if necessary, methimazole can be used also, after the first trimester. In rare cases in which women do not respond to these medications or have side effects from the therapies, surgery to remove part of the thyroid may be necessary. Hyperthyroidism may get worse in the first 3 months after you give birth, and your doctor may need to increase the dose of medication. Hypothyroidism is treated with a synthetic (manmade) hormone called levothyroxine, which is similar to the hormone T4 made by the thyroid. Your doctor will adjust the dose of your levothyroxine at diagnosis of pregnancy and will continue to monitor your thyroid function tests every 4-6 weeks during pregnancy. If you have hypothyroidism and are taking

levothyroxine, it is important to notify your doctor as soon as you know you are pregnant, so that the dose of levothyroxine can be increased accordingly to accommodate the increase in thyroid hormone replacement required during pregnancy. Because the iron and calcium in prenatal vitamins may block the absorption of thyroid hormone in your body, you should not take your prenatal vitamin within 3-4 hours of taking levothyroxine.

Prescribing in pregnancy for Thyroid disease

When treating thyroid disease, as with other conditions in pregnancy, one is concerned with the welfare of both mother and developing child. Thyroid disease causes few maternal problems; thyrotoxicosis in fact tends to improve in pregnancy, allowing medical management with lower drug doses than usual. Relapse of thyroid disease may occur postpartum, when transient hypo- and hyperthyroidism are relatively common. In contrast, the fetus and neonate are threatened in a number of ways by drugs given to the mother and by transplacental passage of maternal antibodies capable of inducing thyroid disease. Antithyroid drugs may cause fetal goitre with airway obstruction, and are associated with mild neonatal hypothyroidism.

Thyroid antibodies in primary myxoedema and Hashimoto's thyroiditis are occasionally implicated in neonatal hypothyroidism and may even cause thyroid dysgenesis. Neonatal hyperthyroidism has a high morbidity and mortality and may have long-term skeletal effects such as craniosynostosis. Fetal problems may not be apparent at birth but may emerge in the next eight to ten days, especially in hyperthyroidism when the mother has been on treatment. Close monitoring throughout pregnancy and for the first ten days postpartum is required to minimize risks to the fetus and neonate. Most pregnancies associated with thyroid disease will have a successful outcome. If the occasional at-risk fetus is to be identified and treated successfully there should ideally be close cooperation between obstetrician, endocrinologist and paediatrician.

Foetal and neonatal thyroid disorders

Thyroid hormones have been shown to be absolutely necessary for early brain development. During pregnancy, both maternal and foetal thyroid hormones contribute to foetal brain development and maternal supply explains why most of the athyreoticnewborns usually do not show any signs of hypothyroidism at birth. Foetal and/or neonatal hypothyroidism is a rare disorder. Its incidence, as indicated by neonatal screening, is about 1:4000. Abnormal thyroid development (i.e.agenesia, ectopic gland, hypoplasia) or inborn errors in thyroid hormone biosynthesis are the most common causes of permanent congenital hypothyroidism. Recent studies reported that mutations involving Thyroid Transcriptor Factors (TTF) such as TTF-1, TTF-2, PAX-8 play an important role in altered foetal thyroid development. Deficiency of transcriptor factor (Pit-1, Prop-1, LHX-3) both in mother and in the foetus represents another rare cause of foetal hypothyroidism. At birth clinical picture may be not always so obvious and typical signs appear only after several weeks but a delayed diagnosis could have severe consequences consisting of delayed physical and mental development. Even if substitutive therapy is promptly started some learning difficulties might still arise suggesting that intrauterine adequate levels of thyroid hormones are absolutely necessary for a normal neurological development. Placental transfer of maternal antithyroid antibodies inhibiting fetal thyroid function can cause transient hypothyroidism at birth.

If the mother with thyroid autoimmune disease is also hypothyroid during pregnancy and she doesn't receive substitutive therapy, a worse neurological outcome may be expected for her foetus. Foetal and/or neonatal hyperthyroidism is a rare condition and its incidence has been estimated around 1:4000-40000, according to various authors. The most common causes are maternal thyroid autoimmune disorders, such as Graves' disease and Hashimoto's thyroiditis. Rarer non autoimmune causes recently identified are represented by TSH receptor mutations leading to constitutively activated TSH receptor. Infants born to mothers with Graves' history may develop neonatal thyrotoxicosis. Foetal/neonatal disease is due to transplacentalthyrotrophin receptor stimulating antibodies (TRAb) passage. It's extremely important recognizing and treating Graves' disease in mothers as soon as possible, because a thyrotoxic state may have adverse effects on the outcome of pregnancy and both on the foetus and newborn.

Thyrotoxic foetuses may develop goitre, tachycardia, hydrops associated with heart failure, growth retardation, craniosynostosis, increased foetal motility and accelerated bone maturation. Neonatal Graves' disease tends to resolve spontaneously within 3-12 weeks as maternal thyroid stimulating immunoglobulin’s are cleared from the circulation but subsequent development may be impaired by perceptual motor difficulties. Hashimoto's thyroiditis is a very common autoimmune thyroid disease. In presence of maternal Hashimoto's thyroiditis, there are usually no consequences on foetal thyroid, even if anti TPO and anti Tg antibodies can be found in the newborn due to transplacental passage. However there are some literature reports describing foetal and neonatal hyperthyroidism in the affected mothers' offspring.

Postpartum Thyroid Disease - Trouble after delivery

They say that new mothers are stressed out, depressed, weak, and irritable - because of the birth and caring for the baby.

- But that's not the whole story - 5% of new mothers are producing too little or too much thyroid hormone, and that can be helped if it is identified. For most women, the hormone levels go back to normal in a year or so, but meanwhile, life is harder than it need be.
- 20% of mothers with problems never go back to normal thyroid levels and always will need supplemental thyroid hormone treatment.

So getting the basic thyroid test done - for the TSH (thyroid-stimulating hormone) in the blood will indicate the problem, other tests can indicate what to do to help you. Nowadays doctors will treat the thyroid problems in that important first year and won't just wait for it to "snap out of it", and fixing the thyroid levels may help a lot in getting feel better.

Congenital Hypothyroidism

Babies who are born with underactive thyroid function have a disorder known as congenital hypothyroidism. The usual cause of this condition is the failure of the thyroid gland to develop during pregnancy. At birth the infants look normal and then slowly over a period of weeks the clinical features of hypothyroidism appear. Because there are no conspicuous signs or symptoms, the diagnosis of congenital hypothyroidism is seldom made at birth by the examining physician.

If the condition goes unrecognized, which is usually the case, then signs and symptoms such as constipation, dry skin, hoarse cry, large tongue, swelling around the eyes, failure to suckle well, and prolonged periods of sleep will appear within a few weeks. Accompanying these overt clinical changes in the infant is the less obvious damage to the brain resulting in mental retardation. Although treatment at this juncture will reverse the clinical signs and symptoms, the damage to the baby's brain is irreversible. The longer the disorder goes unrecognized (and thus untreated) the greater the insult to the brain.

The Screening Process

Every child born in North America has blood collected on filter paper by heel stick before discharge from the hospital or birthing center. The dried blood specimens are forwarded to a central laboratory where a one-eighth inch paper blood spot is tested for the amount of T4 and/or thyroid stimulating hormone (TSH). A low T4 and elevated TSH indicate that an infant lacks normal thyroid function. Although an elevated TSH is a more sensitive and specific marker of hypothyroidism, the majority of North American screening programs use T4 as the initial test and confirm the diagnosis with the measurement of TSH.

Incidence and Types

Approximately one baby with congenital hypothyroidism is born out of 3,500 births. However, it is estimated that 15-20% of hypothyroid infants have a temporary form of the disorder and will only require treatment for a limited number of years. When there is a question of permanence of the disorder, the physician should discontinue treatment after 3 years of age and repeat the blood tests for TSH and T4 in a few weeks to be sure they are now normal.

There are three different types of thyroid abnormalities that are associated with congenital hypothyroidism. Approximately 40% of infants have under-developed or absent thyroid glands; 40% have thyroid glands that are in the wrong place, such as under the tongue or at the far side of the neck. The remaining 20% are unable to manufacture thyroid hormone because of defects within the thyroid gland. The latter condition is usually familial in nature.

Low T4 Values

Only a tiny number of infants with low T4 levels actually have congenital hypothyroidism. More than 90% of low T4 values (not accompanied by elevated TSH levels) in neonates are associated with other conditions such as prematurity, low birth weight, illness, a deficiency in the protein that carries T4 to various body tissues, or pituitary failure. The latter is a rare disorder in which the pituitary gland is unable to secrete TSH. This condition should be considered in an infant whose growth rate falls off its expected growth curve and has a low T4 and a low or normal TSH.

Treatment

The infant with suspected hypothyroidism should be seen without delay by a physician, preferably by a pediatric endocrinologist. Blood should be obtained to confirm the diagnosis, and treatment with thyroxine should begin before the confirmatory T4 and TSH values are available. Measurements of T4 and TSH should be made 2 and 4 weeks after starting the thyroxine, 2 weeks after a dosage change, and every 1 to 2 months during the first year of life. Optimal intellectual outcome depends on maintaining the circulating level of T4 in the upper half of the normal range (10-16 µ g/dl) during the first year of life. If the T4 value is not above 10µ g/dl and the TSH is below 20 mU/l within 2 to 4 weeks after starting therapy, the physician should consider the possibility that the baby has not been receiving the medication or that there is a problem with absorption of T4 (soy-based formula or iron supplement will interfere with absorption of T4).

Conclusion

Future research, within the setting of clinical trials, should focus on the potential health gain of identification, and effect of treatment, of thyroid disease on pregnancy outcome. none Furthermore, it was recently shown that thyroxine administration to pregnant women with positive thyroid auto antibodies and a history of recurrent abortions may improve the final outcome. Regarding prevention of miscarriage, there are few studies showing that thyroxine treatment may be effective in reducing the number of miscarriages when given during the early stages of pregnancy. Further studies are required with a greater number of women in order to reach definitive conclusions. At present, routine screening and treatment of autoimmune thyroid disease in euthyroid pregnant women is not warranted. There are few instances in the practice of medicine where the health and welfare of future generations can be positively affected; early treatment of congenital hypothyroidism through newborn screening is one of those instances.

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