

# Gestational Transient Thyrotoxicosis

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## ABSTRACT

*Gestational transient thyrotoxicosis refers to non-autoimmune hyperthyroidism in pregnant women and it is associated with hyperemesis gravidarum. During pregnancy, there are some alterations in thyroid gland, such as elevation of thyroxine binding globulin, increased iodine clearance in kidneys, and stimulation of thyroid gland by human chorionic gonadotropin. Hitherto, the pathophysiology underlying the development of gestational transient thyrotoxicosis has not been fully recognized. Studies showed that human chorionic gonadotropin, an agonist of thyroid stimulating hormone, may stimulate thyroid stimulating hormone receptor, leading to increased thyroid hormone. Diagnosis of gestational transient thyrotoxicosis is established based on inexistence history of previous hyperthyroidism, elevation of thyroid hormone, absence of hyperthyroid abnormalities signs on physical examination (such as: enlargement of thyroid gland, exophthalmia), and the absent of positive thyroid autoantibody. Generally, gestational transient thyrotoxicosis does not require medication, unless if hyperemesis gravidarum is present, thus the patient has to be hospitalized to receive intravenous rehydration, electrolyte correction and antiemetic medication. On cases with worsened or prolonged symptoms, anti-thyroid agents such as short term propylthiourasil is needed.*

**Key words:** *gestational transient thyrotoxicosis, thyroid stimulating hormone, pregnancy.*

## INTRODUCTION

Gestational transient thyrotoxicosis (GTT) is a type of gestational hyperthyroid disease, with non-autoimmune characteristic. Gestational transient thyrotoxicosis is marked by increased level of thyroid hormone and suppression of thyroid stimulating hormone (TSH) in women with normal pregnancy condition. The gestational hyperthyroid occurs on early pregnancy and is reported to have strong association with hyperemesis gravidarum. The symptoms of gestational transient thyrotoxicosis are transient and similar to symptoms of first trimester pregnancy, thus it is difficult to be diagnosed.<sup>1-4</sup>

The incidence rate of gestational transient thyrotoxicosis varies from 2.4 – 11% of all pregnancies. Glinoes et al<sup>5</sup> (a study in Europe in 1990) reported that the incidence rate of gestational transient thyrotoxicosis is 2-3% of all pregnancies. These reported numbers are 10 times more likely to occur than Graves' disease. Yeo et al<sup>6</sup> in 2001 by a study in Hongkong reported a higher incidence rate of gestational transient thyrotoxicosis, i.e. 11%; while Tanaka<sup>7</sup> by their study in Japan, 1998 reported a smaller number, which is 0.3% of all pregnancies. The incidence rate of gestational transient thyrotoxicosis in Indonesia is still unknown, because there have not been many reports on incidence of gestational transient thyrotoxicosis.

Gestational transient thyrotoxicosis is generally under-diagnosed due to its similarity to symptoms of normal pregnancy. A comprehend knowledge on gestational transient thyrotoxicosis is important to provide an ability to differentiate such condition with normal pregnancy and other gestational hyperthyroidism, since the condition is associated with management and impact on the pregnant women and their unborn babies.<sup>2</sup> This article will discuss about pathophysiology, diagnoses and treatment of gestational transient thyrotoxicosis.

## THYROID FUNCTION AND ITS STATUS IN PREGNANCY

During pregnancy, there are some physiological alterations on thyroid function, through several mechanisms, i.e. elevation of thyroxine binding globulin (TBG), increased iodine clearance in kidneys, and stimulation of thyroid gland by human chorionic gonadotropin.<sup>1, 8-10</sup>

### Elevation of Thyroxine Binding Globulin (TBG)

Thyroxine binding globulin will increase 2-3 times fold during pregnancy. Such increment occurs not only limited to increased blood level, but also including to its affinity to the thyroid hormone. The level of thyroxine binding globulin in blood increases in several weeks after conception and then it becomes stable during mid-pregnancy. In women without pregnancy, thyroxine binding globulin level varies from 12-30 ug/l. On the contrary, during pregnancy it may reach 30-50 ug/l. The mechanism of such increased thyroxine binding globulin involves synthesis of thyroxine binding globulin in the liver. It is assumed that the mechanism is influenced by estrogen hormone. Estrogen also induces increased *sialylation*, thus prolonging the half-life of thyroxine binding globulin from 15 minutes to 3 days.<sup>1, 8-10</sup>

Increased thyroxine binding globulin level will lead to elevation of total  $T_4$  ( $TT_4$ ) and total  $T_3$  ( $TT_3$ ) level during early pregnancy and such level will last persistently until the second trimester. The level of  $TT_4$  and  $TT_3$  will be increased up to 30-100% compared to the level prior to pregnancy. The altered condition of free triiodotironin ( $FT_3$ ) and free thyroxin's ( $FT_4$ ) level during pregnancy is still controversial. Some researchers reported that  $FT_3$  and  $FT_4$  decrease during pregnancy and others reported normal value or even increased level; however, in general, most of pregnant women (>78%) showed normal  $FT_3$  and  $FT_4$ .<sup>1, 9</sup>

### Increased Iodine Clearance in Kidneys

During pregnancy, iodine clearance increases due to elevation of thyroxine binding globulin (TBG) rate/glomerular filtration rate (GFR). Such iodine loss causes low iodine level in circulation and leads to thyroid compensation through increased activity of thyroid glands.<sup>8, 9</sup> The increased thyroid activity causes enlargement of thyroid volume and elevation of thyroglobulin production. The increased thyroglobulin production is apparent in the first trimester of pregnancy.<sup>9</sup>

### Thyroid Stimulation of Human Chorionic Gonadotropin

Human chorionic gonadotropin is a member of hormone family of luteinizing hormone (LH), follicle stimulating hormone (FSH) and thyroid stimulating hormone which has alpha subunit and hormone-specific beta subunit. Human chorionic gonadotropin and thyroid stimulating hormone have 85% similarity on the first 114 amino acids and 12 residual cysteine on beta subunit.<sup>1, 5, 9, 11</sup>

Such similar structure of human chorionic gonadotropin and thyroid stimulating hormone causes human chorionic gonadotropin to be able to stimulate thyroid stimulating hormone receptor (TSHR) to produce thyroid hormone, just like the thyroid stimulating hormone. This is proven by a study using thyroid cell of rats, which demonstrated increased iodine uptake and cyclic adeninemonophosphate (cAMP) production after administering human chorionic gonadotropin.<sup>12</sup> On the culture of human thyroid follicle, there is an increased of iodine uptake stimulation, organification and secretion of  $T_3$ .<sup>13</sup>

On the first trimester of pregnancy, human chorionic gonadotropin has the highest level, thus it will stimulate the thyroid gland to produce thyroid hormone and suppresses thyroid stimulating hormone level. On the second and third trimester of pregnancy, the concentra-

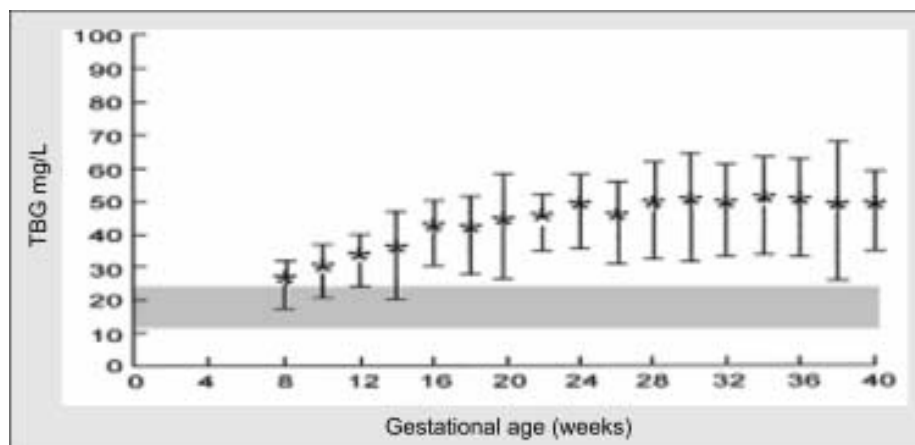


Figure 1. The Thyroxine binding globulin level during normal pregnancy, with 2 weeks interval<sup>8</sup>

tion of thyroid stimulating hormone will increase gradually, due to reduced human chorionic gonadotropin level. Such mechanism generates mirror curve image.<sup>1,6,9</sup>

Some studies reported that every 10,000 mIU/L elevation of human chorionic gonadotropin level will be followed by 0.6 pmol/L (0.1 ng/dL) elevation of FT<sub>4</sub> level and reduced thyroid stimulating hormone level of 0.1mIU/L. The elevation of FT<sub>4</sub> during the first trimester is presumed can only be detected if the human chorionic gonadotropin level of 50,000-75,000 mIU/L last for more than a week.<sup>1,5,9</sup>

**THE PATHOPHYSIOLOGY OF GESTATIONAL TRANSIENT THYROTOXICOSIS**

The pathophysiology aspect underlying gestational transient thyrotoxicosis has not been fully understood yet

until recently; however, some studies showed that the etiology of gestational transient thyrotoxicosis is directly correlated to stimulation of thyroid hormone by human chorionic gonadotropin due to increased human chorionic gonadotropin level during the first trimester of pregnancy.<sup>1,2,4,11</sup> In addition to gestational transient thyrotoxicosis, the effect of human chorionic gonadotropin can also be observed in twin pregnancy and mola pregnancy. In both of these events, we can find an increase of human chorionic gonadotropin level followed by elevation of FT<sub>4</sub> and suppression of thyroid stimulating hormone.<sup>2,14</sup>

Human chorionic gonadotropin, an agonist of thyroid stimulating hormone, may stimulate thyroid stimulating hormone receptor that causes increased thyroid hormone production. Such phenomenon may lead

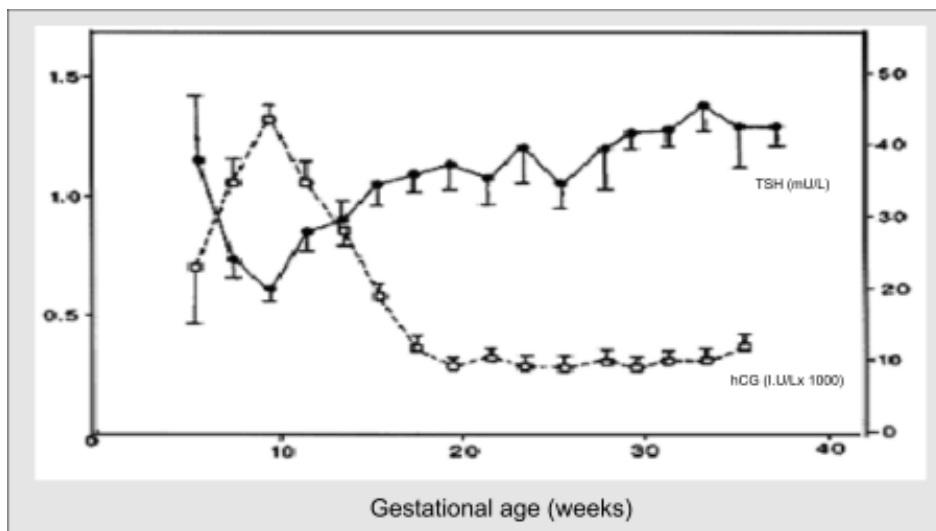


Figure 2. Mirror curve of thyroid stimulating hormone and human chorionic gonadotropin level during pregnancy.

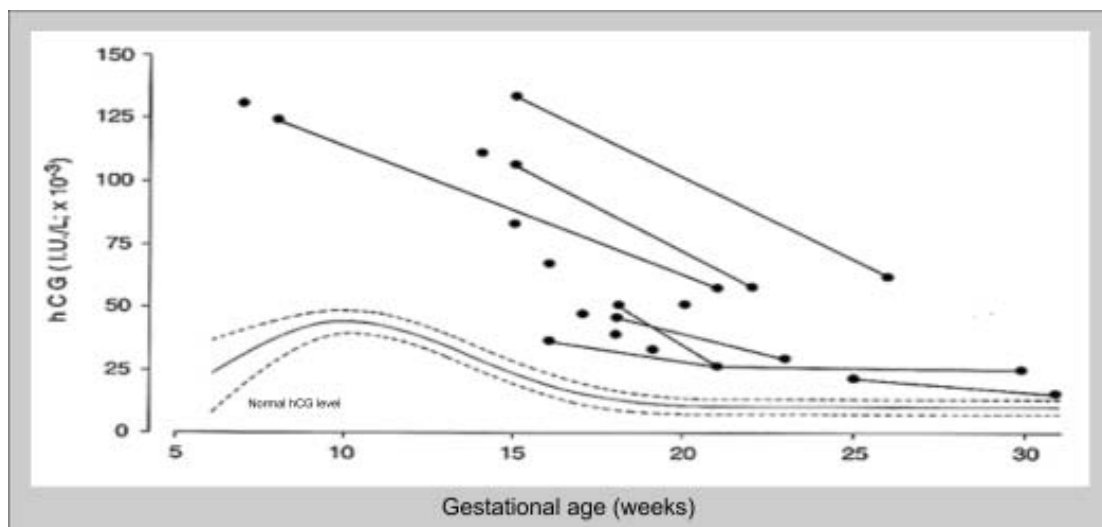


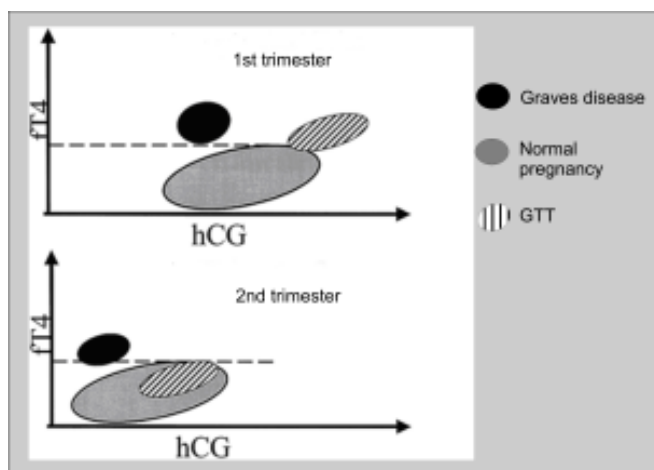
Figure 3. Evaluation of human chorionic gonadotropin level based on gestational age in women with gestational transient thyrotoxicosis.<sup>1</sup>

to thyrotoxicosis. Thyrotoxicosis occurs only for temporary time, i.e. on the 10<sup>th</sup> – 15<sup>th</sup> weeks of pregnancy which has the highest peak of human chorionic gonadotropin level. Thyroid function will further decrease on the 20<sup>th</sup> weeks of pregnancy in keeping with the reduced human chorionic gonadotropin level.<sup>1, 2, 14</sup>

During the first trimester of normal pregnancy, human chorionic gonadotropin level ranges from 50,000-100,000 mIU/ml. A study of Glinoe<sup>1</sup> in 1997 that performed screening tests in 1900 pregnant women showed that in gestational transient thyrotoxicosis, there was increased human chorionic gonadotropin level greater than 100,000 mIU/ml and the FT<sub>4</sub> level ranged on 33 pmol/L; while the normal FT<sub>4</sub> value is 26 pmol/L.

The human chorionic gonadotropin and FT<sub>4</sub> level in GTT and Graves disease will increase exceeding the normal level during the first trimester; while in normal pregnancy human chorionic gonadotropin level increases but the FT<sub>4</sub> level is still normal. Entering the second trimester period, FT<sub>4</sub> level decreases in gestational transient thyrotoxicosis but it persists on high level in Graves disease.<sup>4</sup> (Figure 4)

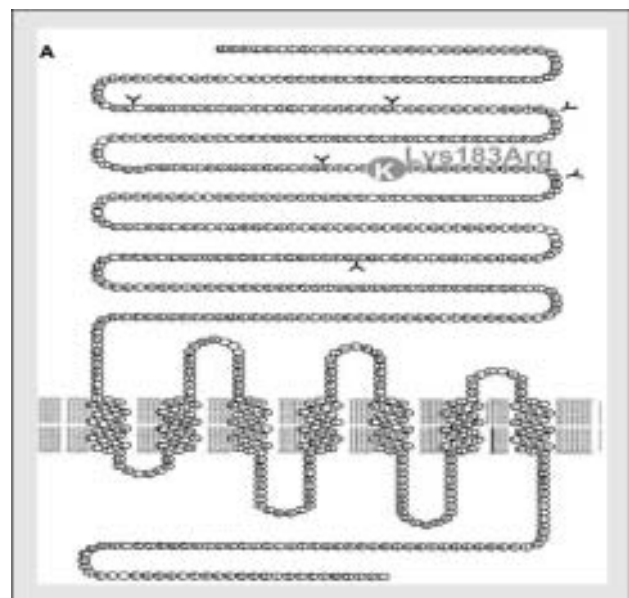
Most of gestational transient thyrotoxicosis cases demonstrate human chorionic gonadotropin level greater than 100,000 mIU/ml; however, it is reported that there are several cases which demonstrate the same human chorionic gonadotropin level as in the normal pregnancy. Such condition is caused by other factor which also plays a role on the gestational transient thyrotoxicosis pathophysiology. Rodien et al<sup>15</sup> reported some cases of gestational transient thyrotoxicosis which have similar human chorionic gonadotropin level to the normal pregnancy condition and they found that there is a mutation of thyroid stimulating hormone receptor. In such



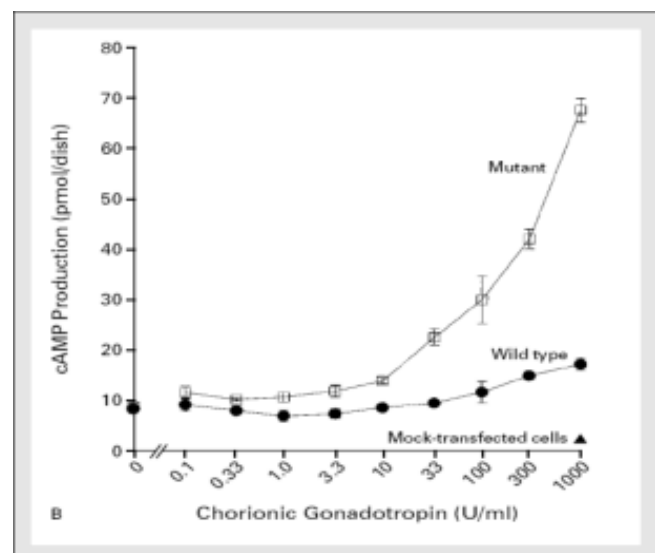
**Figure 4.** Evaluation of thyroid function during pregnancy by comparing the FT<sub>4</sub> and human chorionic gonadotropin level

mutation, lysine is replaced by arginine chain 183 (TSH receptor mutation [K183R]). Thus, the sensitivity of thyroid stimulating hormone receptor to the human chorionic gonadotropin increases and induces the stimulation of cAMP production leading to increased thyroid hormone level. (Figure 5 and 6)

Other factor, which is still controversial, is the role of morphologically abnormal human chorionic gonadotropin (asialo — human chorionic gonadotropin). Tsurata et al<sup>16</sup> reported that asialo — human chorionic gonadotropin stimulates thyroid better than other normal human chorionic gonadotropin, hence thyroid hormone level increases.



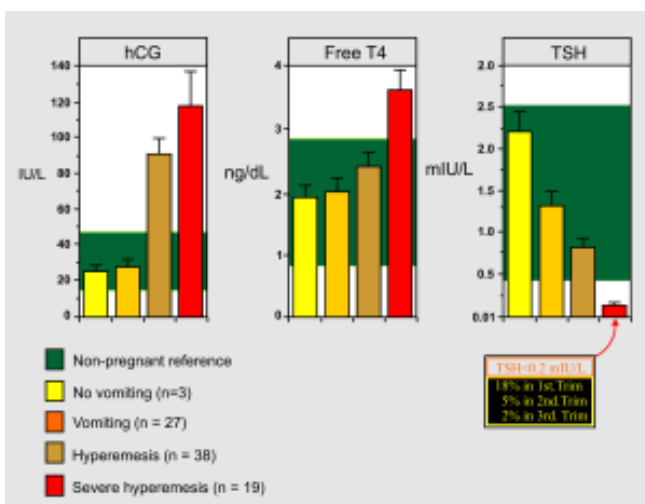
**Figure 5.** Mutation of thyroid stimulating hormone receptor<sup>15</sup>



**Figure 6.** Stimulation of cAMP production correlated to the mutation of thyroid stimulating hormone receptor<sup>15</sup>

It is known that gestational transient thyrotoxicosis is strongly associated with hyperemesis gravidarum and in such condition the human chorionic gonadotropin level is greater than its level during normal pregnancy. This condition is proven by 15 prospective comparative studies comparing FT<sub>4</sub> level in patients with hyperemesis gravidarum. It is reported that there were increased FT<sub>4</sub> level and reduced thyroid stimulating hormone in patients with hyperemesis gravidarum.<sup>1</sup>

Figure 7 demonstrates that patients with high human chorionic gonadotropin level causes more severe hyperemetic symptom and on the laboratory test, it is found that the FT<sub>4</sub> level is above normal limit and there is low thyroid stimulating hormone level.<sup>1</sup>



**Figure 7.** The correlation between severity of hyperemetic symptoms and the concentration of human chorionic gonadotropin, FT<sub>4</sub> and thyroid stimulating hormone<sup>1</sup>

## DIAGNOSIS OF GESTATIONAL TRANSIENT THYROTOXICOSIS

Establishing the diagnosis of gestational transient thyrotoxicosis is difficult when it is only based on clinical symptoms due to its similarity to common symptoms of first trimester pregnancy. The diagnosis also has to be made carefully in order to differentiate gestational transient thyrotoxicosis with other gestational hyperthyroid condition, such as Graves disease since it may correlate to the treatment.<sup>1, 2, 4</sup>

### Clinical Manifestation

In the history taking for patients with gestational transient thyrotoxicosis, there are symptoms of severe nausea and vomiting, unexplainable weight loss or inability to gain weight, accompanied by other thyrotoxicosis symptoms, such as heat intolerance, tremor, palpitation, restlessness and fatigue. Lack of

previous hyperthyroid history substantially supports the GTT diagnosis.<sup>1, 2, 17</sup>

Physical findings that associated with thyrotoxicosis are important for diagnosing and determining the differential diagnosis. In gestational transient thyrotoxicosis, we can find tachycardia and slight tremor; however, there is no other significant finding for physical examination on thyroid gland.<sup>1, 2, 18, 19</sup>

### Laboratory Findings

The result of thyroid function test has to be carefully interpreted since during pregnancy, there is increased total thyroid hormone due to the pregnancy itself. Evaluation on laboratory test consists of thyroid stimulating hormone serum level and free thyroid hormone (FT<sub>3</sub> and FT<sub>4</sub>) level, but excluding the total thyroid hormone level. Evaluation of TT<sub>4</sub> or TT<sub>3</sub> is not appropriate since both levels increase during the pregnancy due to increased thyroxine binding globulin. In gestational transient thyrotoxicosis, there are increased FT<sub>3</sub> and FT<sub>4</sub> level, reduced thyroid stimulating hormone level and absent of positive autoantibody test.<sup>1, 2, 4, 11, 20</sup>

### DIFFERENTIAL DIAGNOSIS

The differential diagnoses of gestational transient thyrotoxicosis are Graves disease, thyrotoxicosis induced by mola hidatidosa, multinodular struma, toxic adenoma, sub acute tyroiditis and iatrogenic hyperthyroidism, thyroid stimulating hormone-producing pituitary tumor and ovarian struma. The majority of gestational hyperthyroidism is caused by gestational transient thyrotoxicosis and Graves disease; while the other diseases rarely occur. Occasionally, gestational Graves disease and gestational transient thyrotoxicosis have somewhat similar clinical symptoms, thus it is important to differentiate both diseases.<sup>20</sup>

Pregnant women with Graves disease has the same symptoms as gestational transient thyrotoxicosis, but usually there is prior hyperthyroid history on Graves disease. On Graves disease, we can find symmetrical thyroid gland enlargement, without tenderness and infrequently bruit may be heard, accompanied by eye abnormality in the form of exophthalmia. The laboratory findings indicate increased FT<sub>3</sub> and FT<sub>4</sub> levels with suppression of thyroid stimulating hormone, which are also found on gestational transient thyrotoxicosis. Nonetheless, the most important test results include the thyroid peroxidase antibody (TPO antibody) and thyroid hormone receptor antibody (TRABs), that are positive on ≥ 80% patients with Graves disease. There is no positive autoantibody test in gestational transient thyrotoxicosis.<sup>1, 2, 18, 19</sup>

## TREATMENT

The treatment of gestational hyperthyroid is closely related to the condition of the women and their fetus. Therefore, the efficacy of treatment should be considered thoroughly.<sup>7,14</sup> The symptoms of gestational transient thyrotoxicosis usually will ameliorate by 18<sup>th</sup> - 20<sup>th</sup> week of gestation. Thus, if it is not such a nuisance it does not require any medication, but it still needs further attention to avoid dehydration.<sup>6,14</sup>

Severe vomiting symptoms and signs of dehydration, as well as weight loss and electrolyte imbalance are indications for hospitalization. Treatments for such condition include intravenous rehydration, electrolyte correction and antiemetic medication; at the same time waiting for spontaneous recovery.<sup>21,22</sup> Beta-adrenergic blocker can be administered for intolerable tachycardia. Rarely, in several cases, the symptoms may become more severe and persistent. Therefore, the patient needs propiltiurasil (PTU) for several weeks. The recommended dose is 300 mg/day.<sup>6,14,23</sup>

Several authors suggest administering anti-thyroid agents for patients with hyperthyroid symptoms who also has increased FT<sub>4</sub> and FT<sub>3</sub> level greater than 50% of normal value during pregnancy, and the treatment is discontinued when hyperemesis ceases in mid pregnancy.<sup>6,14,23</sup>

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