Review Article

Nausea and Vomiting Due to Transient Hyperthyroidism in the First Trimester of Pregnancy: A Review

Ali Reza Ahmadi [1], Ezatolah Ghaemi [2], Akhtar Saifi [2], Hady Reza Mansourian [3], *Azad Reza Mansourian[1]

[1]Metabolic disorder Research Center, Golestan University of Medical Sciences, Gorgan, Iran, [2] School of Medicine, Golestan University of Medical Sciences, Gorgan, Iran, [3] Hakim Jorjani Hospital, Gorgan, Iran

ABSTRACT

Human chorionic gonadotropin (hCG) is a glycoprotein hormone produced by the placenta, which has a similar structure to thyroid-stimulating hormone (TSH).Due to this similarity, hCG could exhibit TSH-like activity and stimulate thyroid gland to produce thyroid hormones, particularly thyroxine (T4).This condition is often seen at end of the first trimester of pregnancy (weeks 10-12). In these cases, maternal serum TSH concentration is reduced and T4 level is elevated, causing overt hyperthyroidism that could lead to thyrotoxicosis if remain untreated. Pregnant women with hyperemesisgravidarum experience nausea and vomiting. These subjects seem to have elevated levels of serum hCG, particularly at the end of the first trimester when it reaches its peak, eventually leading to hyperthyroidism. There are some reports suggesting that hyperemesis gravidarum might be due to hyperthyroidism associated with elevated hCG in pregnant women at weeks10-12 of pregnancy.

KEYWORDS: Pregnancy, Human chorionic gonadotropin (hCG), hyperthyroidism, nausea and vomiting

***Correspondence:** Azad Reza Mansourian, Metabolic disorder Research Center. Golestan University of medical Sciences, Gorgan, Iran, email: azad_r_mansourian@yahoo.com

INTRODUCTION

Human chorionic gonadotropin (hCG) is an important hormone produced as the sperm meet the ova, in early human embryogenesis. Maternal serum hCG measurement is the key laboratory test for detecting pregnancy. In addition, hCG plays an important role in maintaining a healthy pregnancy [1-9]. Several studies have reported that hCG demonstrates some form of thyroid-stimulating hormone (TSH)-like activity. In other words, the increased hCG level during pregnancy could mimic TSH's biological functions and bind to the TSH receptor on the thyroid gland. Experimental studies demonstrated that hCG can bind to the TSH receptor and increase the amount of cyclic adenosinemonophosphate. Because of this elevation, thyroid begins to produce thyroid hormones, mainly thyroxin (T4). Concentration of hCG increases noticeably and reaches its peak at the end of the first trimester (end of weeks10-12).Elevated amount of hCG can stimulate TSH receptor, leading to secretion of thyroid hormones. This reduces TSH release from pituitary gland due to the impact of T4 on the hypothalamus-pituitary axis. Clinical manifestations of hyperthyroidism during the first trimester of pregnancy and particularly at the end of weeks 10-12 are due to the elevated T4 and thyroid-stimulating activity of hCG. Nausea and vomiting in the first trimester of pregnancy are often common in pregnant women, which could be accompanied with weight loss. This condition is defined as hyperemesis gravidarum that could be accompanied with hyperthyroidism. However, true thyrotoxicosis occurs only in a small population of pregnant women with hyperemesis gravidarum. Cases of abnormal pregnancy with excessive hCG level may manifest symptoms of overt hyperthyroidism, which are directly

associated with the elevated hCG concentration [10-17].

Thyrotoxicosis

Triiodothyronine (T3) and T4 are vital hormones that are biosynthesized within the thyroid gland. Over-secretion of T3 and T4 leads to a condition known as thyrotoxicosis. Thyrotoxicosis is also defined as a clinical disorder triggered by elevation of thyroid hormones, leading to hyperthyroidism. Clinical symptoms of thyrotoxicosis include weight loss, fatigue, weakness, and cardiovascular, neuromuscular, reproductive and gastrointestinal disorders. Thyrotoxicosis is diagnosed by measuring the level of thyroid hormones T3 and T4 as well as TSH. Thyroid function test often indicates decreased serum TSH level and increased T4 and/or T3 level. The most important causes of hyperthyroidism and thyrotoxicosis are autoimmune disorders, toxic adenoma, and toxic multinodular goiter [18-22].

hCG-induced hyperthyroidism

hCG has a similar molecular structure to the TSH. Maternal serum hCG concentration rises at week 12 of pregnancy [23,24]. Maternal hyperthyroidism has been reported particularly during the first trimester of pregnancy. As it was mentioned earlier, the biochemical similarity of hCG and TSH enables hCG to bind to the TSH receptor on the thyroid gland. Maternal serum concentration of hCG increases during pregnancy and reaches its peak at weeks 10-12, which stimulates production of thyroid hormones and T4 in particular, and suppresses TSH [25].

Gestational hyperthyroidism

High concentration of hCG in early pregnancy may lead to hyperthyroidism ranging from subclinical to mild and overt hyperthyroidism. In such cases, laboratory findings often indicate elevated T4 concentrations [26].

Hyperemesis gravidarum

Hyperemesis gravidarum during pregnancy is characterized by symptoms such as nausea and vomiting accompanied with weight loss, which are mostly seen in the first trimester. Although weight loss of up to 5% is usually seen in some pregnancies, it only affects 0.1-0.2% of all pregnancies.

Compared to non-affected pregnant women, cases with the above disorder commonly exhibit elevated serum levels of hCG and estradiol, the main estrogen. The hCG of pregnant women with hyperemesis gravidarum seems to mimic TSH biochemical mediation, leading to higher activity of thyroid gland and eventual hyperthyroidism. As a result, the thyroid gland increases T4 secretion that causes TSH suppression, leading to hyperthyroidism in some cases [27].

Nausea, vomiting, absence of ophthalmopathy, thyroid enlargement, tachycardia, muscle abnormality, and tremor are among the common symptoms of hyperthyroidism associated with hyperemesis gravidarum in early pregnancy, which can be used to distinguish this condition from other forms of hyperthyroidism such as Graves' disease. Laboratory findings indicate that only T4 levels are elevated in hyperemesis gravidarum, while both T3 and T4 could be elevated in overt hyperthyroidism caused by other thyroid disorders such as Graves' disease.

It has to be mentioned that hyperemesis gravidarum-associated hyperthyroidism can be recovered later in pregnancy as serum hCG level begins to fall. In other words, symptoms such as nausea and vomiting that are common in the first trimester can be reduced due to decreased serum concentration of hCG and other important female hormones such as estradiol [28].

If symptoms of hyperthyroidism during pregnancy persist until the second trimester,

one should doubt the role of hCG, and other possible thyroid disorders should be considered. This is of great importance for reducing the risk of damage to the growing fetus. There have been reports on the recurrence of gestational T4 elevation resulting from hyperthyroidism in a single family due to a mutation in the TSH receptor [58]. In addition to elevated serum hCG level, abnormality in molecular structure of hCG in conditions such as molar pregnancy (a gestational trophoblastic disorder) can also lead to hyperthyroidism, which is mediated through activation of TSH receptor on the thyroid gland. Nausea and vomiting in such patients are among clinical features of hyperemesis gravidarum [29-36].

CONCLUSION

- hCG is an important hormone produced at early stages of embryogenesis.
- Measurement of maternal serum hCG is the key laboratory test for detection of pregnancy.
- hCG demonstrates some form of TSH-like activity.
- The similarity in biochemical structure of hCG and TSH could induce TSH-like action i.e. binding to the TSH receptor on the thyroid gland and stimulating thyroid gland to secrete thyroid hormones.
- At the end of the first trimester (weeks 10-12) whenmaternal hCG level is highest, over-secretion of T4 leads to TSH suppression and eventually hyperthyroidism.
- Hyperemesis gravidarum in pregnancy is characterized by nausea and vomiting accompanied with weight loss, which are commonly seen in the first trimester of pregnancy.
- In hyperemesis gravidarum, T4 level is elevated which could leadto hyperthyroidism and eventually thyrotoxicosis due to excessive maternal hCG levels in early pregnancy.
- Nausea and vomiting in pregnant women, particularly in early pregnancy, could be due to hyperthyroidism and elevated maternal hCG level.

REFERENCES

1. Messinis IE, Messini CI, Dafopoulos K. The role of gonadotropins in the follicular phase. Annals of the New York Academy of Sciences. 2010; 1205: 5–11.

2. Cole LA. Biological functions of hCG and hCG-related molecules. Reproductive Biology and Endocrinology. 2010;8: 102–115.

3. Filicori M, Fazleabas AT, Huhtaniemi I, Light P,Rao CV,Tesarik J, Zygmunt M. Novel concepts of human chorionic gonadotropin: Reproductive system interactions and potential in the management of infertility. Fertility and Sterility. 2005; 84: 275–284.

4.Weissman A, Lurie S, Zalel Y, Goldchmit R, Shoham Z. Human chorionic gonadotropin: Pharmacokinetics of subcutaneous administration. Gynecological Endocrinology. 1996;10: 273–276.

5. Cole LA. New discoveries on the bioogy and detection of human chorionic gonadotropin. Reproductive Biology and Endocrinology. 2009;7- 8

6. Filicori, M,Cognini G.E, Gambertini E,Parmegiani L,Troilo E, Roset B. Efficacy of low-dose human chorionic gonadotropin alone to complete controlled ovarian stimulation. Fertility and Sterility. 2005;84: 394–401.

7. Filicori M, Cognini GE, Taraborrelli S,Spettoli D, Ciampaglia W, de Fatis CT. Low-dose human chorionic gonadotropin therapy can improve sensitivity to exogenous follicle-stimulating hormone in patients with secondary amenorrhea. Fertility and Sterility. 1999; 72: 1118–1120.

8. Lopata A, Hay DL. The potential of early human embryos to form blastocys hatch from their zona and secrete hcg in culture. Human Reproduction. 1989; 4: 87–94.
9. Tsampalas M, Gridelet V, Berndt S,Foidart J.M,Geenen V, Perrier d'Hauterive S. Human chorionic gonadotropin: A hormone with immunological and angiogenic properties. Journal of Reproductive Immunology. 2010; 85:93–98.
10. Krysiak R, Okopień B, Herman ZS. [Hyperthyroidism in pregnancy]. Polski Merkuriusz Lekarski. 2006; 21(126):579-84.
11. Rodien P, Jordan N, Lefèvre A, Royer J, Vasseur C, Savagner F, Bourdelot A, Rohmer V. HumAbnormal stimulation of the thyrotrophin receptor during gestation. Reproduction Update. 2004; 10(2):95-105.
12. Ardawi MS, Nasrat HA, Rouzi AA, Mustafa BE Are women at an increased risk of gestational thyrotoxicosis?. Saudi Medical Journal. 2002;23(6):651-7.
13. Nelson-Piercy C. Nelson-Piercy C .Treatment of nausea and vomiting in pregnancy. When should it be treated and what can be safely taken?. Drug Safety. 1998;19(2): 155-64.
14. Leylek OA, Cetin A, Toyaksi M, Erselcan THyperthyroidism in hyperemesis gravidarum. International Journal of Gynecology & Obstetrics. 1996; 55(1):33-7.
15. Appierto U, Subrizi DA, Minozzi M, Unfer V Nausea, vomiting and thyroid function before and after induced abortion in normal pregnancy. Clinical and Experimental Obstetrics and Gynecology. 1996;23(1):18-20.
16. Becks GP, Burrow GN Thyroid disease and pregnancy. Medical Clinics of North America. 1991;75(1): 121-50.
17. Mori M, Amino N, Tamaki H, Miyai K, Tanizawa O.Morning sickness and thyroid function in normal pregnancy. Obstetrics & Gynecology. 1988;72(3 Pt 1):355-9
18. Mansourian AR. A review on hyperthyroidism: Thyrotoxicosis under surveillance. Pakistan Journal of Biological Sciences. 2010; 13: 1066-1076.
19. Mansourian AR.Thyroid function tests during first-trimester of pregnancy: A review of literature. Pakistan Journal of Biological Sciences. 2010; 10: 2166-2177.
20. Mansourian AR. A review on post-puberty Hypothyroidism: A glance at myxedema. Pakistan Journal of Biological Sciences. 2010,13:866-876.
21. Mansourian AR. A review on the metabolic disorders of iodine deficiency. Pakistan Journal of Biological Sciences. 2011; 14: 412-424.
22. Mansourian AR. Female reproduction physiology adversely manipulated by thyroid disorders: A review of literature. Pakistan Journal of Biological Sciences. 2013;16: 112-120.
23. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocrine Reviews. 2010; 31:702-55.
24. Davis LE, Lucas MJ, Hankins GD, Roark ML, Cunningham FG. Thyrotoxicosis complicating pregnancy. American Journal of Obstetrics & Gynecology. 1989; 160:63-70.
25. Haddow JE, Craig WY, Neveux LM, Haddow HR, Palomaki GE, Lambert-Messerlian G, et al. Implications of High Free Thyroxine (FT4) concentrations in euthyroid pregnancies: the FaSTER trial. The Journal of Clinical Endocrinology & Metabolism. 2014; 99:20-38.
26. Lambert-Messerlian G, McClain M, Haddow JE, Palomaki GE, Canick JA, Cleary-Goldman J, et al. First- and second-trimester thyroid hormone reference data in pregnant women: a FaSTER (First- and Second-Trimester Evaluation of Risk for aneuploidy) Research Consortium study. American journal of obstetrics and

gynecology. 2008; 199:62.e1.

27. Salvi M, How J. Pregnancy and autoimmune thyroid disease. Endocrinology and metabolism clinics of North America.1987; 16:431-444.
28. Kung AW, Lau KS, Kohn LD. Epitope mapping of tsh receptor-blocking antibodies in Graves' disease that appear during pregnancy. Journal of clinical endocrinology and metabolism. 2001; 86:36-47.
29. Rodien P, Brémont C, Sanson ML, Parma J, Van Sande J, Costagliola S, et al. Familial gestational hyperthyroidism caused by a mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin. New England Journal of Medicine. 1998; 339:1823-6.
30. Boelig RC, Barton SJ, Saccone G, Kelly AJ, Edwards SJ, Berghella V. Interventions for treating hyperemesis gravidarum: A Cochrane systematic review and meta-analysis. Journal of Maternal-Fetal & Neonatal Medicine. 2017; 14:1-21.
31. Adlan AS, Chooi KY, Mat Adenan NA. Acupressure as adjuvant treatment for the inpatient management of nausea and vomiting in early pregnancy: A double-blind randomized controlled trial. Journal of Obstetrics and Gynaecology Research. 2017;43(4):662-668.
32.Morgan SR, Long L, Johns J, Angwin C, Maitra S, Ross JA. Are early pregnancy complications more common in women with hyperemesis gravidarum?. Journal of Obstetrics and Gynaecology. 2017;37(3): 355-357.
33. Campbell K, Rowe H, Azzam H, Lane CA. The Management of Nausea and Vomiting of Pregnancy. Journal of Obstetrics and Gynaecology Canada. 2016; 38 (12):1127-1137.
34. Lima LL, Parente RC, Maestá I, Amim Junior J, de Rezende Filho JF, Montenegro CA, Clinical and radiological correlations in patients with gestational trophoblastic disease. Braga A. Radiol Bras. 2016; 49(4):241-250.
35. Kinomoto-Kondo S, Umehara N, Sato S, Ogawa K, Fujiwara T, Arata N, Sago H. The effects of gestational transient thyrotoxicosis on the perinatal outcomes: a case-control study.Archives of Gynecology and Obstetrics. 2017; 295(1):87-93.
36. Sharp BR, Sharp KM, Patterson B, Dooley-Hash S. Treatment of Nausea and Vomiting in Pregnancy: Factors Associated with ED Revisits. Western Journal of Emergency Medicine. 2016; 17(5):585-90.