

International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622
© Gynaecology Journal
www.gynaecologyjournal.com
2019; 3(1): 131-135
Received: 04-11-2018
Accepted: 08-12-2018

Dr. Mangal Puri

M.D D.G.O Professor Obstetrics and Gynaecology, Dr. D.Y. Patil Medical College, Hospital and Research Centre. DPU Sant Tukaram Nagar, Pimpri, Pune, Maharashtra, India

Dr. Divya Punetha

M.B.B.S (M.S Obgyn), Chief Resident Obstetrics and Gynaecology, Dr. D.Y. Patil Medical College, Hospital and Research Centre. DPU Sant Tukaram Nagar, Pimpri, Pune, Maharashtra, India

Dr. Monica Maan

M.S Obgyn, Senior Resident Obstetrics and Gynaecology, Dr. D.Y. Patil Medical College, Hospital and Research Centre. DPU Sant Tukaram Nagar, Pimpri, Pune, Maharashtra, India

Dr. Shankar Burute

M.D Obgyn Professor Obstetrics and Gynaecology, Dr. D.Y. Patil Medical College, Hospital and Research Centre. DPU, Sant Tukaram Nagar, Pimpri, Pune, Maharashtra, India

Correspondence

Dr. Divya Punetha

M.B.B.S (M.S Obgyn), Chief Resident Obstetrics and Gynaecology, Dr. D.Y. Patil Medical College, Hospital and Research Centre. DPU Sant Tukaram Nagar, Pimpri, Pune, Maharashtra, India

Transient hyperthyroidism in hyperemesis gravidarum

Dr. Mangal Puri, Dr. Divya Punetha, Dr. Monica Maan and Dr. Shankar Burute

DOI: <https://doi.org/10.33545/gynae.2019.v3.i1c.22>

Abstract

Physiologically there is increased thyroid activity due to increase in circulating levels of thyroid binding globulin (TBG) in response to estrogen, with increase in the bound portion of thyroid hormone and due to thyrotropic substances secreted by the placenta. Contributors are placental chorionic thyrotropin and HCG. These patients have higher levels of HCG and transient hyperthyroidism which decides the severity of hyperemesis.

Data collected from patients with hyperemesis gravidarum and antenatal patients with morning sickness from our hospital. Total sample size is 200, 100 cases and 100 controls. It is a prospective study and the period of study is July 2016 to sept 2018. The patients are investigated for serum T3, T4, TSH and beta HCG level correlation.

Hyperthyroidism associated with hyperemesis gravidarum is of a transient nature where serum T3 and serum T4 levels are elevated between 8-14 weeks of gestation and normalize by 18-20 weeks of gestation without anti-thyroid treatment. We need to treat these patients diagnostically in a supportive manner.

Keywords: hyperemesis gravidarum, hyperthyroidism, beta HCG

Introduction

There is an increase in the metabolic demands in pregnancy, as a result of which there is an increase in the basal metabolic rate (which is mainly due to fetal metabolism), iodine uptake increases, and so increase in the size of the thyroid gland caused by hyperplasia and increased vascularity. Despite of increase in the thyroid activity, the thyroid levels in a pregnant woman remain in the normal range, with normal TSH, free T3, free T4. In case of any thyroid nodules and goiter clinical evaluation is required.

Iodine clearance increases in pregnancy due to increased renal clearance, due to which the prevalence of goiter is more in areas of iodine deficiency.

Increased thyroid activity in pregnancy comes along with significant increase in circulating levels of thyroid binding globulin (TBG) in response to estrogen, as a result of which a new equilibrium is reached with increase in the bound portion of thyroid hormone.

Increased thyroid activity is also due to thyrotropic substances secreted by the placenta. Placental chorionic thyrotropin and human chorionic gonadotropin also contributes to thyrotropic activity. Majority of patients with hyperemesis gravidarum have laboratory values consistent with hyperthyroidism, however the severity of hyperemesis corresponds with the degree of hyperthyroidism. These patients have higher levels of HCG and transient hyperthyroidism and severity of hyperemesis may be mediated by thyrotropic and steroidogenic activity of the HCG.

Clinical manifestations in normal pregnancies can be lined to a specific population of HCG molecules having greater thyrotropic bioactivity. The highly purified, standard HCG has only trivial TSH-like activity. HCG with reduced sialic acid content is increased in pregnant women with hyperemesis and hyperthyroidism.

Pregnant women with hyperemesis gravidarum do not require antithyroid drug treatment unless they show symptoms of hyperthyroidism which is supported by significant laboratory results.(1)

Aims and Objectives

The aims and objectives of the study is to study the incidence of hyperemesis gravidarum in our institute. Also to study the incidence of transient hyperthyroidism of hyperemesis gravidarum

(THHG).we also correlated beta HCG levels with thyroid function tests in THHG to signify whether evaluation of only HCG levels can help us to diagnose THHG and evaluated thyroid antibody profile (TPO) in patients of THHG.

Review of Literature

In 1983, Kimura M1, Amino N, Tamaki H, Ito E, Mitsuda N, Miyai K, Tanizawa O studied Gestational thyrotoxicosis and hyperemesis gravidarum and the possible role of HCG with higher stimulating activity.

The thyroid gland is physiologically stimulated during normal early pregnancy. However, clinical thyrotoxicosis in normal pregnancy has not been well explained. In order to clarify this they examined thyroid function and thyrotoxic symptoms in relation to hyperemesis in normal pregnancy. They also investigated the possible mechanism of gestational thyrotoxicosis.

Thyroid function was evaluated in view of the clinical thyrotoxic symptoms and the severity of gestational emesis in early pregnancy of 51 normal women. Two pregnant women who showed clinical thyrotoxicosis were followed serially during and after pregnancy.

They measured Serum free T4, free T3 and TSH and hCG. In their study, Fifty-one pregnant women were divided into three groups: those without emesis (n = 24), with emesis (n = 19) and with hyperemesis (n = 8). They found that Serum free T4 and free T3 were higher in the hyperemesis group (P < 0.01) and the emesis group higher in the hyperemesis group (P < 0.05) and the emesis group (P < 0.05) compared with that in the group without emesis(P < 0.01), and serum TSH was suppressed to less than 0.1 mU/l in both groups [2].

In 1994, AJ Krentz, H Redman and KG Taylor found that hyperemesis gravidarum is an uncommon presentation of hyperthyroidism in pregnancy which is usually attributable to autoimmune (Graves') disease. While this condition requires treatment with antithyroid drugs, a syndrome of transient hyperthyroidism associated with hyperemesis gravidarum that resolves spontaneously is also recognised. They reported two cases of hyperthyroidism associated with severe hyperemesis gravidarum. Intractable hyperemesis continued in one of their patient despite normalisation of circulating free thyroid hormone levels with carbimazole. Neither of their patient exhibited clinical or immunological features of autoimmune thyroid disease, suggesting in retrospect that they had the syndrome of transient hyperthyroidism associated with hyperemesis gravidarum rather than Graves' disease, which resolved spontaneously. Hence, they concluded that the role of antithyroid drugs in the treatment of self-limiting transient hyperthyroidism associated with hyperemesis gravidarum requires significant evaluation [3].

JY Tan, KC Loh, GS Yeo, YC Chee, published an article in the British journal of obstetrics and gynaecology in 2002

Their aim of the study was to characterise the clinical presentation, biochemical and thyroid antibody profile in women with transient hyperthyroidism of hyperemesis gravidarum. It was a prospective observational study in which 53 women were admitted with hyperemesis gravid arum and were found to have hyperthyroidism. All women were examined for clinical signs of thyroid disease and underwent routine investigations and thyroid antibody profile and serial thyroid function tests until reports were normal. Gestation at which thyroid functions normalised, pregnancy outcome (APGAR) and clinical signs and symptoms normalised were observed.

According to their study, the full data obtained for 44 women,

free t4 levels normalised in 39 women at 15 weeks of gestation with transient hyperthyroidism, but TSH remained suppressed until 19 weeks of gestation.

None of these women showed clinical signs of hyperthyroidism and thyroid antibodies were also not found in most of them. Five of their patients were diagnosed with Graves disease.

Their study concluded that in transient hyperthyroidism of hyperemesis gravidarum thyroid function normalises by the middle of the second trimester on its own. There was no need of any anti thyroid treatment [4].

Materials and Methods

Materials: Data collected from patients with hyperemesis gravidarum and antenatal patients with morning sickness from our hospital, where the sample size is 200, which includes 100 cases and 100 controls. it is a prospective study and the period of study is July 2016 to sept 2018.

Inclusion Criteria

Study Group: All antenatal cases with hyperemesis gravidarum willing to get enrolled for the study **Control group:** All antenatal patients with complaints of morning sickness, willing to get enrolled in the study.

Exclusion Criteria

- All patients not willing to get enrolled for the study.
- Patients with overt hyperthyroidism and/or Grave's Disease. Institutional Ethics Committee (IEC) clearance has been taken. Population of women diagnosed as hyperemesis gravidarum were admitted in the hospital and and examined for clinical signs of hyperthyroidism and underwent following investigations
- Thyroid function tests (serum T3, serum T4, Serum TSH)
- Thyroid peroxidase antibody (TPO) [will be done only in those women of hyperemesis gravidarum who have biochemical hyperthyroidism.]
- beta HCG levels

In the population of women in the control group, having morning sickness, serum T3, serum T4, serum TSH and beta HCG levels was b investigated.

Samples were taken in the first half of pregnancy at the time of admission and repeat samples were taken for women having hyperemesis gravidarum with hyperthyroidism at around 18- 20 weeks. We correlated elevated beta HCG levels with thyroid function tests. We also analyzed the presence of anti-thyroid antibodies particularly TPO in patients with Transient hyperthyroidism of Hyperemesis Gravidarm.

Data was be analyzed by CHI -SQUARE TEST and P value and significance will be inferred in our study. Data representation will be done in the form of tables and bar graphs.

This study will help in identifying new cases of THHG, and will also help in differentiating THHG from Grave's Disease, and proving the significance of thyroid function tests in all cases of hyperemesis gravidarum.

Observations and Results

According to our study there were 6000 antenatal cases in our Unit OPD in two years, out of which 100 cases were of hyperemesis gravidarum, hence the incidence of hyperemesis gravidarum in our institute was 1.66%.

In our study, we have included 200 first trimester antenatal women, out of which 100 were cases with hyperemesis gravidarum and 100 were having complaint of morning sickness included in control group.

Women Included were of different age group and with diverse socio-economic status in both study and control group. Patients with overt hyperthyroidism and/or Grave's disease were

excluded. All data collected was gathered in the master chart and then analysed. Significance of the findings is shown by applying P value and CHI- Square Test.

Table 1: Indicates distribution of women according to their obstetrical history

Parity	Study group		Control group		Statistical comparison	
	Number	Percentage	Number	Percentage	Chi square value	P
Primigravida	48	48.0	44	44.0	0.325	0.84
Nullipara with previous abortions	17	17.0	18	18.0		
Parous	35	35.0	38	38.0		
Total	100	100.0	100	100.0		

Table 1 indicates distribution of women according to their obstetrical history, in both study and control group. In the study group 48% women were primigravida, 17% were nulliparous

with previous abortions and 35% were parous women as compared to 44%, 18% and 38% respectively in the control group. P value was 0.84, which is not significant.

Table 2: Distribution of women according to period of gestation

Period of weeks of gestation	Study group		Control group		Statistical comparison	
	No.	%	No.	%	Chi square value	P
less than 8 weeks	12	12.0	9	9.0	0.914	0.82
8-12 weeks	59	59.0	58	58.0		
12-16 weeks	25	25.0	33	33.0		
16-20 weeks	4	4.0	0	0.0		
Total	100	100	100	100		

In Table 2, 71% of the women of the study group were less than 12 weeks gestation. In the study group 4% of the women had prolonged vomiting beyond 16 weeks of gestation, however all

the controls were at less than 16 weeks of gestation. p value is 0.82 which is not significant. On clinical examination there was no enlargement of thyroid gland in both groups.

Table 3: Distribution of women according to serum T3 level

Serum T3 level ng/ml	Study group		Control group		Statistical comparison	
	NO.	%	No.	%	Chi square value	P
0.5 -1.65	79	79.0	98	98.0	17.87	0.001
1.66- 2.00	11	11.0	1	1.0		
2.01- 2.9	7	7.0	1	1.0		
More than 3.00	3	3.0	0	0		
	Mean ± SD		Mean ± SD		T statistics value	P Value
Mean T3 + - SD	1.84± 0.744		1.088 ± 0.428		9.374	0.001

In Table no 3, both study and control group are evaluated for serum T3 values and it is found that 79% of patients in the study group have normal serum T3 as compared to 98% in the control group. 11% have raised serum T3 values between 1.6 - 2 as compared to only 1% in the control group 7% have increased

serum T3 between 2- 2.9 as compared to only 1% in the control group and 3% have increased serum T3 more than 3 as compared to none in the control group. P value is 0.001, which is highly significant.

Table 4: Distribution of women according to serum T4 level

serum T4 level ug/dl	study group		Control group		Statistical comparison	
	No.	%	No.	%	Chi square value	P
4.5 -12	76	76.0	96	96.0	16.89	0.001
12.01-15.00	14	14.0	3	3.0		
15.01- 20.00	8	8.0	1	1.0		
20.01- 25.00	2	2.0	0	0		
	Mean ± SD		Mean ± SD		T statistics value	P Value
Mean T4 level + - SD	13.42 ± 6.054		7.416 ± 1.984		9.424	0.001

In Table no 4 we observed that 76% of the women in study group had normal serum T4 levels as compared to 96% in the control group, whereas 14% of patients in the study group had elevated T4 levels between 12-15 ug/dl as compared to 3% in the control group. Only 8% patients in the study group had T4

levels between 15- 20 ug/dl as compared to 1% in control group. Elevated serum T4 levels more than 20ug/dl was found in 2% of the patients in the study group as compared to none in the control group. P value is 0.001, which is highly significant.

Table 5: Distribution of Women According To Serum TSH Level

Serum TSH level μ IU/ml	Study group		Control group		Statistical comparison	
	No.	%	No.	%	Z value	P
<0.47	32	32.0	3	3.0	33.81	0.001
0.47- 2.50	61	61.0	74	74.0		
2.51- 5.01	7	7.0	23	23.0		
>5.01	0	0	0	0		
	Mean \pm SD		Mean \pm SD		T statistics value	P Value
Mean TSH level + - SD	1.679 \pm 1.059		2.560 \pm 0.939		6.224	0.001

We analysed the serum TSH levels in both study and control group in Table 5. According to the data analysis serum TSH levels are found low in 32% of patients in the study group (<0.47) as compared to 3% patients in the control group. 68% of

patients had serum TSH levels Within the normal range in the study group as compared to 97% of patients in the control group. None of them had elevated TSH levels. P value was 0.001 which is highly significant.

Table 6: Comparison of thyroid function tests in the study group at 12-14 weeks and 18-20 weeks gestation

Thyroid function tests	12-14 weeks		18-20 weeks	
	Study	Control	Study	Control
Thyroid-stimulating hormone	Decreased	Normal	Normal	Normal
Free triiodothyronine	Elevated	Normal	Normal	Normal
Free thyroxine	Elevated	Normal	Normal	Normal

According to our analysis among women of different age groups in both study and control groups, 49% of women were in the age group 18-22 years in the study group whereas 38% in the control group. 46% were in the study group 23-27 years as compared to 48% in the control group. 5% were in 27-31 years in the study group, as compared to 12% in the control group. None of the women in the study group were found in the age group between 32-36 years as compared to only 2% in the control group P value is 0.09.

On Follow up visit at 18-20 weeks we found that the serum T3, T4 and TSH values returned back to normal in patients with elevated thyroid levels in the study group, hence proving transient hyperthyroidism.

Discussion

According to our study there were 6000 antenatal cases in our Unit OPD in two years, out of which 100 cases were of hyperemesis gravidarum, hence the incidence of hyperemesis gravidarum in our research centre was 1.66% as compared to the studies by Fergus *et al.* [5], Philip [6], which stated the incidence of hyperemesis gravidarum is 0.3% - 2% of all pregnancies. Hyperemesis Gravidarum is the commonest indication for admission to hospital in the first half of pregnancy and is second only to preterm labor as a cause of hospitalization during pregnancy [7, 8]

According to our study, incidence of THHG in patients with hyperemesis is 24%, whereas incidence among all antenatal cases in the hospital was 0.4%. This is comparable with the studies done by TJ Caffrey [9], who stated in his study that Hyperemesis gravidarum occurred in about 1 in 2000 pregnancies. He also mentioned that THHG might occur in up to 0.7 of 2000 pregnancies. Also, N K Kuscu, F Koyuncu in their study evaluated that transient hyperthyroidism was seen in about 60% of patients with hyperemesis gravidarum. [10, 11] Alexander *et al.* [12] observed in their study that in a high percent of women affected by hyperemesis gravidarum, 30 to 73% of the women had abnormal thyroid tests consistent with hyperthyroidism. Hyperemesis Gravidarum is the most common cause of THHG. Tan *et al.* [14] conducted a study and observed that over a period of 18 months, 87 women were hospitalised for hyperemesis gravidarum, out of which 53 women i.e 60.9% were identified to have hyperthyroidism. 83% of the women having

hyperthyroidism had THHG. The difference in values may be due institutional variations and different population groups.

According to our study BHCG levels were found on the higher side in patients with elevated serum T3 and serum T4 and decreased serum TSH. 3 patients with twin pregnancy with hyperemesis had high Bhcg with elevated serum T3 and T4 levels and low serum TSH. This is comparable to Tan *et al.* study in 2002 who stated that 18% of women in the first trimester had transiently subnormal TSH levels (as well as higher mean hCG levels) with almost half being undetectable (<0.05 mU/L). Eleven percent of the women with undetectable TSH levels also had elevated free T4 levels. Similarly, Glinoe *et al.* [13] showed that hCG remained abnormally elevated for several weeks during the second trimester and that normalisation of free T4 levels paralleled the decline in hCG, supporting its role in the pathogenesis of transient hyperthyroidism of hyperemesis gravidarum, however in our study we did not follow β HCG levels serially for several weeks till the second trimester. In our study 3% of the patients in the study group had hyperemesis with twin gestation, out of which 2 cases had hyperthyroidism, compared to study by Grün *et al.* [14], they described hyperthyroidism in women with twin pregnancy, due to a much higher and more sustained peak of hCG.

According to our study we tested thyroid peroxidase antibodies for patients with THHG, and the results were found to be negative, hence there is no correlation between THHG and thyroid antibodies. Thyroid antibodies are differentiating feature between THHG and Grave's disease.

As per our Research patients of Hyperemesis Gravidarum should be investigated for THHG, though it is a self-limiting condition.

Conclusion

To conclude, hyperthyroidism associated with hyperemesis gravidarum is of a transient nature where serum T3 and serum T4 levels are elevated between 8-14 weeks of gestation and normalize by 18-20 weeks of gestation without anti-thyroid treatment. We need to treat these patients diagnostically in a supportive manner.

Transient hyperthyroidism can be correlated with elevated levels of β HCG. TSH levels remain suppressed for a longer period. Clinically overt hyperthyroidism and thyroid antibodies are

usually not seen in women with THHG. The presence of certain clinical signs of hyperthyroidism, significantly elevated thyroid antibodies and persistently abnormal thyroid function tests beyond the gestation that is not present in transient hyperthyroidism of hyperemesis gravidarum helps to distinguish THHG with Grave's disease.

According to our study we recommend that thyroid functions should be assessed in all cases of hyperemesis gravidarum although the condition resolves spontaneously.

Acknowledgement

I forward my heartiest appreciation to Dr. J. S. Bhawalkar, Dean, Dr. D.Y. Patil Medical College, Hospital and Research centre, Pimpri, Pune for allowing me to access and utilize the clinical material and facilities.

I would also like to take the opportunity to thank Dr. Hemant Deshpande, HOD and Professor Dr. S.K. Kathpalia, Obstetrics and Gynaecology for offering valuable advice and support during the whole period of the study.

Funding: no funding sources

Conflict of interest: none declared

Ethical approval: The study was approved by institutional ethical committee.

References

1. Fritz MA, Speroff L. Clinical gynecologic endocrinology and infertility (8th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2011.
2. Kimura M, Amino N, Tanaki H *et al.*, Gestational thyrotoxicosis and hyperemesis gravidarum: possible role of hCG with higher stimulating activity. *Clin Endocrinol.* 1993; 38:345-50.
3. Krentz AJ, Redman H, Taylor KG. Hyperthyroidism associated with hyperemesis gravidarum. *Br J Clin Pract.* 1994; 48(2):75-6.
4. Tan JYL, Loh KC, Yeo GSH, Chee YC. Transient hyperthyroidism of hyperemesis gravidarum. *Br J Obstet Gynecol* 2002; 109:683-8.
5. Fergus P McCarthy, Jennifer E Lutomski and Richard A Greene. *Hyperemesis gravidarum: current perspectives*, 2011.
6. Philips BO. hyperemesis gravidarum literature review *Wisconsin medical journal.* 2003.
7. Hod M, Orvieto R, Kaplan B, Friedman S, Ovadia J. Hyperemesis gravidarum. A review. *J Reprod Med.* 1994; 39(8):605-12.
8. Bashiri A, Neumann L, Maymon E, Katz M. Hyperemesis gravidarum: epidemiologic features, complications and outcome. *Eur J Obstet Gynecol Reprod Biol.* 1995; 63(2):135-8.
9. Caffrey TJ. Transient hyperthyroidism of hyperemesis gravidarum: a sheep in wolf's clothing. *Journal of the American Board of Family Practice.* 2000; 13(1):35-38.
10. Kuscu NK, Koyuncu F. Hyperemesis Gravidarum: Current Concepts and Management. *Postgraduate Medical Journal.* 2002; 78:76-79. <http://dx.doi.org/10.1136/pmj.78.916.76>
11. Leylek OA, Cetin A, Toyaksi M *et al.* Hyperthyroidism in hyperemesis gravidarum. *Int J Gynaecol Obstet.* 1996; 55:33-7.
12. Transient Non-Autoimmune Hyperthyroidism of Early Pregnancy Alexander M. Goldman and Jorge H. Mestman Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA

13. Glinoe G, Spencer CA. Serum TSH determinations in pregnancy: how, when and why?" *Nature Reviews Endocrinology.* 2010; 6:526-529.
14. Grün JP, Meuris S, De Nayer P, Glinoe D. The thyrotrophic role of human chorionic gonadotrophin (hCG) in the early stages of twin (versus single) pregnancies. *Clinical Endocrinology.* 1997; 46(6):719-725.