



Original Research Article

## Thyrotoxicosis during Pregnancy: Etiologies and Outcome

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### ABSTRACT

**Clinical Objective:** Thyrotoxicosis during pregnancy: etiologies and outcome: 1) Examine etiologies of thyrotoxicosis in pregnancy. 2) Examine the relation between maternal anti-TPO antibody and fetal heart rate.

**Materials and Methods:** It is a prospective study of 82 patients screened at the departments of endocrinology and obstetrics, in the Calicut Medical College, India. Cases were matched with a control of 100 normal pregnant subjects. Inclusion criteria: Pregnant women during any gestational age with signs, symptoms, and biochemical evidence of thyrotoxicosis. Exclusion criteria: Biochemical evidence of thyrotoxicosis without clinical signs and symptoms. All patients were followed for the gestational period and two months postpartum. History, physical examination, basic investigations with emphasis on thyroid function test, antithyroid peroxidase antibody, ultrasound thyroid, and antenatal ultrasonogram for assessing fetal heart rate were carried out. All patients with Graves' disease and multinodular goiter were treated with propylthiouracil throughout pregnancy. Thirty-five out of 42 patients with gestational thyrotoxicosis required treatment due to significant symptoms, which was restricted to first trimester. Natural course of the disease, fetal response, and intra-/postpartum maternal, and fetal complications were assessed.

**Results:** Out of 82 patients included in the study, 42(51%) patients had gestational transient thyrotoxicosis, 18(22%) had Graves' disease, 10 (12%) had toxic multinodular goiter. Five (6%) were diagnosed to have lymphocytic thyroiditis, 3 (4%) each had vesicular mole and toxic adenoma, and one patient had papillary thyroid carcinoma. Fetal heart rate was detected with antenatal ultrasound during 16th to 18th week of gestation. Out of 18 patients with Graves' disease, 15 (83%) were antibody positive and the rest negative. In all anti-TPO-positive patients, fetal heart rate was more than 164 compared to 130–145 in antibody-negative patients. Fetal goiter was detected by ultrasonogram in two patients with Graves' disease.

**Conclusion:** The most common etiology of thyrotoxicosis in pregnancy is gestational-transient thyrotoxicosis followed by Graves' disease. There is a positive correlation between fetal heart rate and maternal circulating anti-TPO antibodies.

**Key Words:** Thyrotoxicosis, Pregnancy, Anti-TPO antibody, fetal heart rate.

## INTRODUCTION

Thyrotoxicosis is a common endocrine disorder. It has been estimated indirectly that approximately one or two of 1,000 pregnancies will be complicated by hyperthyroidism. The evaluation and treatment of pregnant women with hyperthyroidism parallels that of non-pregnant women and men, but presents some unique problems. There are several important issues that must be considered when hyperthyroidism occurs during pregnancy. These include understanding normal thyroid physiology during pregnancy, establishing the diagnosis, treatment, and neonatal complications. A detailed study contemplated to understand the clinical profile and etiologies of thyrotoxicosis complicating pregnancy would help the treating doctor to institute appropriate therapy, follow up and monitor the patients during the course of treatment, guide him when and where to start as well as stop the treatment, to foresee the complications and manage them accordingly.

Thyroid disorders may not only be the cause of infertility but also increase 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. 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.<sup>[1]</sup> Thyroid disorders are common in pregnancy and affect maternal and fetal outcome.<sup>[2]</sup> There is a known association between untreated maternal hypothyroidism and increased risk of several adverse outcomes for both mother and foetus at all stages of pregnancy.<sup>[3]</sup> Moreover, children born to mothers who experience even mild thyroid insufficiency at early gestational stages may be at risk for neuro-motor and cognitive deficits.<sup>[4]</sup> In view of the severity of these consequences, and the awareness that they may be successfully prevented by prompt therapeutic intervention, many have recommended that thyroid function screening be routinely performed in pregnant women.<sup>[5]</sup> The present study gives certain interesting disclosures supporting and contradicting various previously conducted studies for better understanding of the disease entity suited for our part of the world.

## MATERIALS & METHODS

### *Objectives:*

Thyrotoxicosis during pregnancy: etiologies and outcome: 1) Examine etiologies of thyrotoxicosis in pregnancy. 2) Examine the relation between maternal anti-TPO antibody and fetal heart rate.

***Study Design and Period of Study:*** This study of 'thyrotoxicosis in pregnancy' is basically an observational study with two components. First is a descriptive component throwing light in to manifestations of the disease under study; second being analytical study of case control type for analysing different variables and for determining the significance and the strength of associations. The study duration was 1 year and 10 months including 2 months follow up for each case. Approval from Institutional Ethics Committee was

obtained for the study. 82 patients who were eligible for inclusion in the study as per the inclusion criteria were taken up.

**Inclusion Criteria:** Pregnant females during any gestational age presenting with

- At least one clinical feature described in thyrotoxic patient or clinical feature peculiar to thyrotoxicosis in pregnancy.
- Biochemical evidence of thyrotoxicosis in the form of elevated T3, T4, FreeT3 or Free T4 with reduced TSH.

**Exclusion Criteria:** Those with no clinical features of thyrotoxicosis and only biochemical evidence of thyrotoxicosis being low TSH with elevated thyroid hormones as it may be a normal physiological response during pregnancy.

**Controls:** Two sets of control populations were studied for comparison of different variables.

1. 100 pregnant subjects with no evidence of thyrotoxicosis.
2. 30 non-pregnant female patients with thyrotoxicosis.

**Matching:** The controls were age matched. Other confounding factors including gestational age, parity and socio-economic status were matched to maximum possible extend.

**Follow Up:** Follow up of the enrolled patients were done throughout the gestational period and for 2 months postpartum for analysis of natural course of the disease, fetal response and intra/post partum maternal and fetal complications.

**Evaluation:** A detailed history including gestational age, gravidity, out come and complications of previous pregnancies, symptoms of the disease and dietetic history were taken from the enrolled subjects. A review of previous records, thorough physical examination, basic investigations with emphasis on thyroid profile, anti-thyroid peroxidase antibody and antenatal

ultra sonogram for assessing fetal status and heart rate were carried out. A detailed Performa was prepared to guide through the interview and examination of the subjects.

**Statistical Analysis:** Data were analysed by standard statistical techniques with Epi-info 3.3.2 and SPSS 13.0. P value was calculated using Fischer's test and Chi square test and values <0.05 were taken as significant (in 95% confidence limits). Odds ratios were calculated for analysing the strength of association between variables in the case-control study design. Data were represented using Bar charts and Pie charts; scatter diagrams were used for depicting correlation between certain variables and line diagrams were used to show the trend of certain variables with passage of time. The etiology of hyper function of the thyroid gland was determined using clinical and biochemical data. Presence of clinical features and anti TPO antibody positivity helped in making the diagnosis of Graves' disease. Evidence of lymphocytic infiltration of the gland in FNAC and TPO antibodies along with clinical findings was set as the diagnostic criteria of lymphocytic thyroiditis. Gestational transient thyrotoxicosis was diagnosed based on antibody negative transient thyrotoxicosis with or without diffuse goitre. Toxic MNG was diagnosed based on palpable multinodular goitre with clinical and biochemical evidence of toxicity. FNAC helped in the diagnosis of toxic adenoma and papillary carcinoma. Vesicular mole was diagnosed with help of ultra sonogram.

## RESULTS

82 patients were included in the study, out of which 42(51%)patients had gestational transient thyrotoxicosis,18(22%) patients had Graves' disease ,10 (12%) patients had toxic multinodular goiter. 5 (6%) patients were diagnosed to have lymphocytic thyroiditis, 3 ( 4%) patients

each had vesicular mole and toxic adenoma and one patient had papillary carcinoma thyroid (Figure1). Among 42 patients with gestational transient thyrotoxicosis, 12(29%) patients were primigravida and 30(71%) patients were multigravida. Among 18 patients with Graves' disease, 6 (33%) patients were primigravida and 12 (67%) patients were multigravida. Out of 10 patients with multinodular toxic goiter 6(60%) patients were primigravida and 4 (40%) patients were multigravida. Control population was pregnant ladies with no evidence of thyrotoxicosis (Figure 2).

Among 18 patients with Graves' disease studied, 8 patients had past history of 1 abortion (44%), 2 patients had 2 abortions

each (11%) and 1 patient (6%) had multiple abortions. Of the 42 patients with Gestational transient thyrotoxicosis, 6 patients had history of 1 abortion (14%) and 2 patients had 2 abortions (5%). Of the 10 patients with toxic MNG, 1 patient had single abortion (10%) and no patients had history of multiple abortions. The control population (pregnant non-thyrotoxic) showed 4 patients with single abortion, 1 patient with 2 abortions and 1 patient with multiple abortions among 100 subjects taken. Frequency of occurrence of abortions were significantly higher in those with Graves' disease (p value<0.0001) and GTT (p<0.028) and not significant in toxic MNG (p=0.497) (Figure 3).

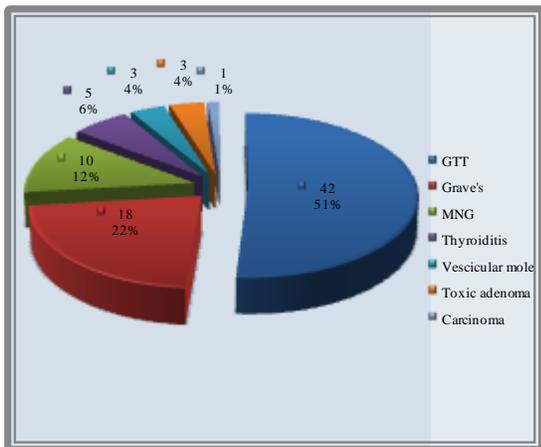


Figure1: Clinical types of thyrotoxicosis in pregnancy.

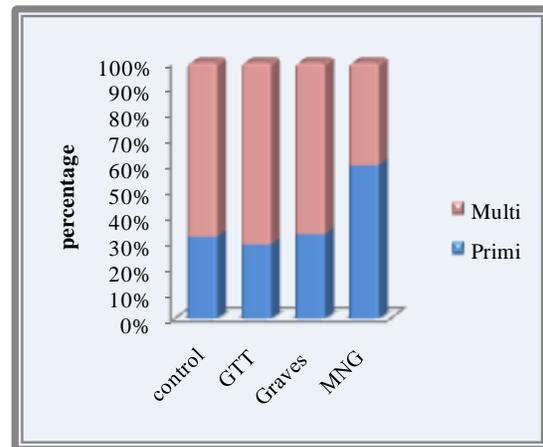


Figure 2: Relation of thyrotoxicosis in pregnancy to gravidity.

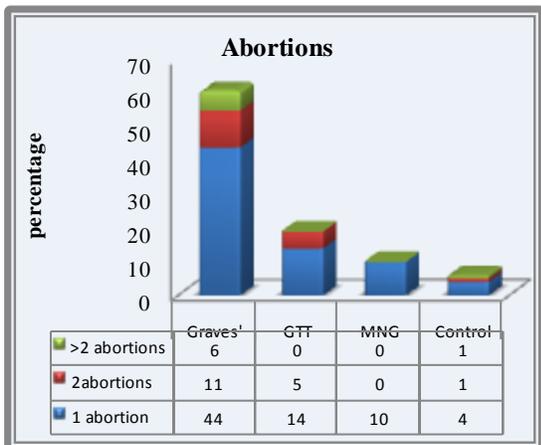


Figure 3: Frequency of previous abortions.

Heat intolerance was a prominent clinical feature in 72% patients with Graves' disease, 29% patients with GTT and 30% patients with toxic MNG compared with 2% of control population. There was statistically significant association (p value<0.0001) of this symptom, with thyrotoxicosis in pregnancy with Odds ratio of 38.5. Palpitation was present in 78% patients with Graves', 43% patients with GTT and 60% with toxic MNG compared with 20% control. (Odds ratio-17.25, p<0.0001). Fatigue was present in 89% patients with Graves' disease, 22% patients with GTT

and 60% patients with toxic MNG compared to 8% of control ( odds ratio-14.8,  $p<0.0001$ ). Weight loss was present in 55% patient with Graves' disease, 12% patients with GTT and 20% patients with toxic MNG. Weight loss, when taken as an

independent feature had highly significant positive predictive value with thyrotoxicosis in pregnancy; though of low sensitivity when compared to other symptoms (Table 1).

**Table 1 : Symptomatology of thyrotoxicosis in pregnancy.**

| Symptoms                    | GTT           | Graves'       | MNG        | Control |
|-----------------------------|---------------|---------------|------------|---------|
| Fatigue                     | 22<br>(52.4)  | 16<br>(88.8%) | 6<br>(60%) | 8%      |
| Palpitations                | 18<br>(42.9%) | 14<br>(77.8%) | 6<br>(60%) | 20%     |
| Hyperactivity, irritability | 14<br>(33.3%) | 12<br>(66.7%) | 5<br>(50%) | 3%      |
| Heat intolerance, sweating  | 12<br>(28.5%) | 13<br>(72.2%) | 3<br>(30%) | 2%      |
| Weight loss                 | 12<br>(28.5%) | 10<br>(55.5%) | 2<br>(20%) | 0%      |
| Increased appetite          | 10<br>(23.8%) | 6<br>(33.3%)  | 4<br>(40%) | 36%     |
| Diarrhoea                   | 3<br>(7.1%)   | 2<br>(11.1%)  | 1<br>(10%) | 0%      |
| Polyuria                    | 1<br>(2.4)    | 0             | 0          | 1%      |

**Table 2: Signs of Thyrotoxicosis.**

| Signs               | GTT         | Graves'     | MNG      | Control |
|---------------------|-------------|-------------|----------|---------|
| Tachycardia         | 20<br>47.6% | 18<br>100%  | 4<br>40% | 12%     |
| Wide pulse pressure | 12<br>28.5% | 16<br>88.8% | 0        | 0       |
| Warm & moist skin   | 12<br>28.5% | 10<br>55.5% | 3<br>30% | 4%      |
| Tremor              | 10<br>28.3% | 16<br>88.8% | 3<br>30% | 4%      |
| Lid retraction      | 4<br>9.5%   | 8<br>44.4%  | 1<br>10% | 0       |
| Palmar erythema     | 7<br>16.6%  | 6<br>33.3%  | 0        | 2%      |
| Proximal myopathy   | 3<br>7.1%   | 4<br>22.2%  | 1<br>10% | 0       |
| Lid lag             | 0           | 2<br>11.2%  | 0        | 0       |
| Spider nevi         | 2<br>4.7%   | 1<br>5.5%   | 0        | 1%      |
| Atrial fibrillation | 1<br>2.4%   | 2<br>11.1%  | 0        | 0       |

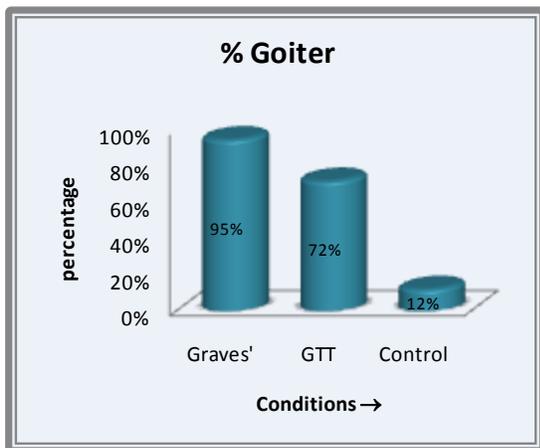


Figure 04: Comparison of occurrence of goiter in Graves' disease and GTT.

Hyperemesis was a prominent clinical feature in 48% patients with GTT, 33% patients with Graves' and 30% patients with toxic MNG when compared to 6% control population. Thyrotoxicosis was a significant risk factor for the development of hyperemesis (odds ratio- 9.2,  $p<0.0001$ ) and was more prominent with GTT (odds ratio-

14.5,  $p<0.0001$ ). Out of 29 patients with hyperemesis 26(90%) patients had elevated free T4 levels. There was significant relation between hyperemesis and elevated free T4 levels (odds ratio-32,  $p<0.0001$ ); but there was no significant correlation between raising free T4 levels and incidence of hyperemesis as observed ( 28% of patients had free T4 in range of 1.7-2.3 ng/dl, 38% in 2.3-2.9ng/dl and lower number of patients i.e. 24% with freeT4>2.9ng/dl). Tachycardia was observed in 20(48%) patients with GTT, 18(100%) patients with Graves' disease and 4(40%) patients with toxic MNG compared to 2% of control population. Presence of tachycardia in thyrotoxicosis complicating pregnancy was statistically significant when compared to non-thyrotoxic control ( $p<0.0001$ , odds ratio-83.4). Wide pulse pressure was observed in 12(29%) patients with GTT, 16(89%) patients with Graves' disease ( $p<0.0001$ ). Warm and moist skin was

observed in 12(29%) patients with GTT, 10(56%) patients with Graves' and 3(30%) patients with toxic MNG compared 4% in control population( $p < 0.001$ , odds ratio-18.1). Tremor was observed in 10(28%) patients with GTT, 16(89%) patients with Graves' disease, 3(30%) patients with toxic MNG compared to 4% in control population. ( $p < 0.0001$ , odds ratio 24.5) (Table 2). Lid retraction was the most common eye sign which was present in 44% patient with Graves' disease and 10% patients with GTT. Exophthalmos was present only in Graves' disease patients (11% patients). In the first trimester there was an average weight loss of 5.8 kg in symptomatic patients. Control population had an average weight gain of 4.9 kg. There was a significant correlation of weight loss

with thyrotoxicosis in first trimester of pregnancy. ( $p < 0.0001$ ). At least one symptom was present in 100% cases with thyrotoxicosis. 40% of normal pregnant subjects had one symptom. Simultaneous presence of 2 symptoms was observed in 96% of thyrotoxic patients and only 36% patient with normal pregnancy. 88% patients with thyrotoxicosis had simultaneous presence of 3 or more symptoms while only 9% of normal controls had the same. This shows significant positive predictive value for presence of 3 or more symptoms as a predictor of thyrotoxicosis in pregnancy.(P value 0.0001, odds ratio-74.15).

95% patients with Graves' disease had goiter when compared to 72% with GTT and 12% of the control population (pregnant non-thyrotoxic controls) (Figure 4).

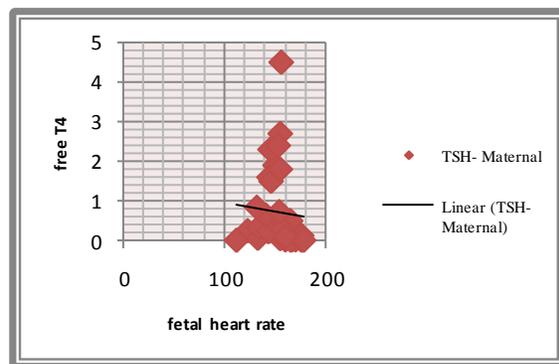
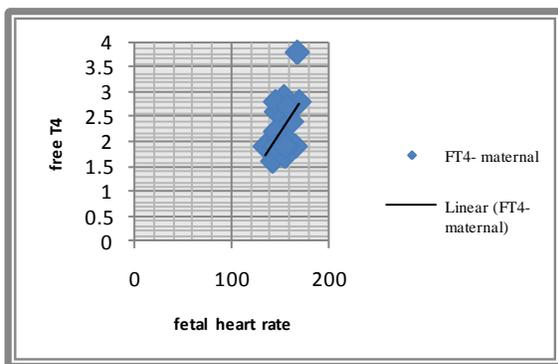


Figure 5 & Figure 6: Correlation of fetal heart rate with maternal t4 levels.

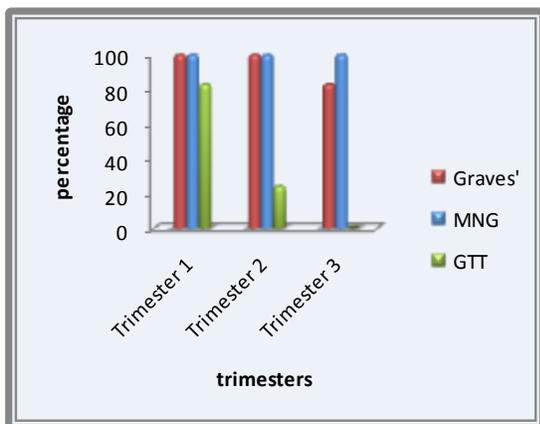


Figure 7: Duration of treatment.

Out of 42 patients with GTT 4 (9.5%) patients carried twin pregnancies when compared to 1% control subjects and no patients with MNG or Graves' disease. There was a significantly higher association of twin pregnancies with GTT ( $p = 0.027$ , odds ratio-114.6) This scatter diagram depicted below shows significant positive correlation of rising fetal heart rate with rising maternal Free T4 levels. There was a linear correlation and values were clustered around the line. (Fig-5). There was a minimal negative correlation of maternal TSH with fetal heart rate which was

statistically not significant. ( $p < 0.2$ ) (Fig-6). Out Of 42 patients with GTT disease 35(83%) required treatment with PTU in the first trimester, 10 (24%) required treatment in the second trimester and no patients required treatment in the third trimester. All patients with Graves' disease and MNG required treatment in first and second trimester. Among Graves' disease patients

15 patients (83%) required treatment in the third trimester compared to all patients with MNG who required treatment (Figure 7). The average duration of treatment for Graves' disease and MNG was 38 weeks when compared to 24.5 weeks in GTT (in symptomatic cases). There was a steady decline in values of free T4 in Graves' and MNG with treatment.

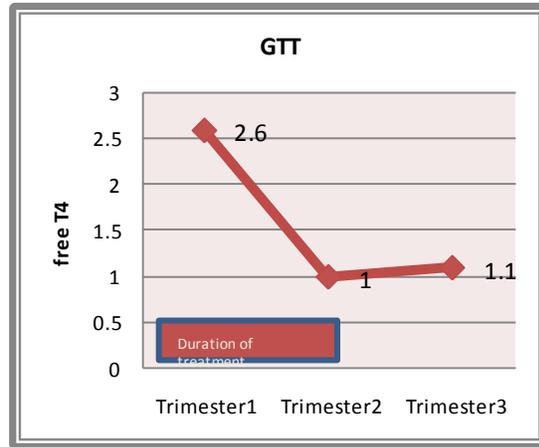
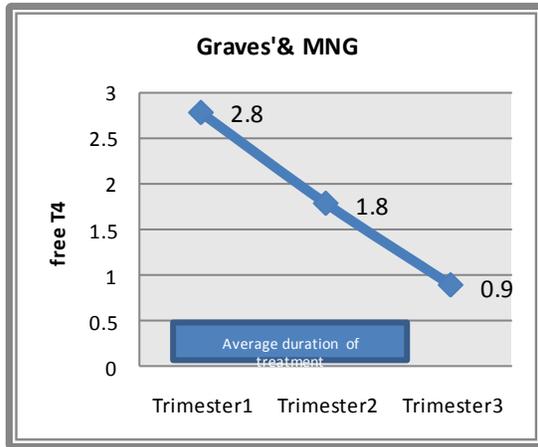


Figure 8 & Figure 9: Relation of free t4 to gestational age and average duration of treatment.

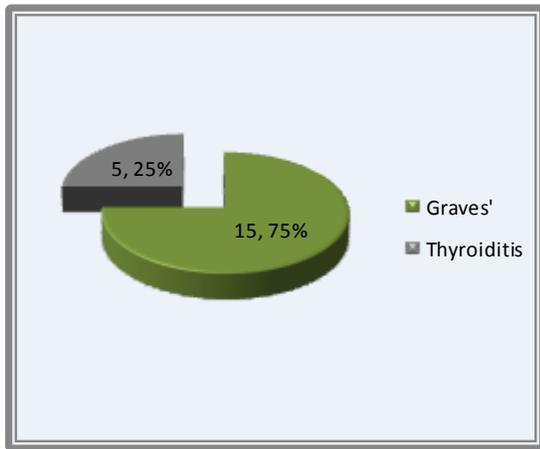


Figure 10: Distribution of anti-TPO positive thyrotoxicosis.

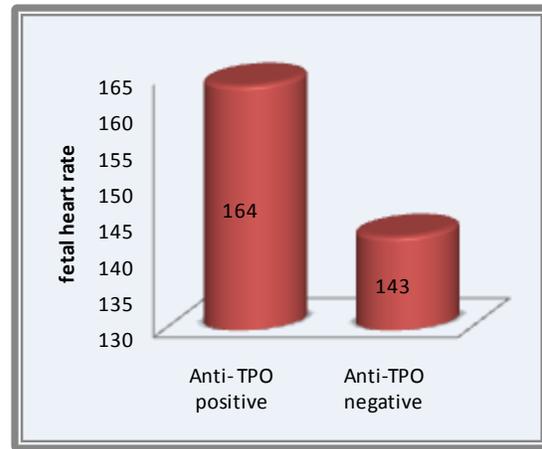


Figure 11: Average fetal heart rate and anti-TPO antibodies.

There was normalisation of free T4 values in GTT with early treatment of symptomatic cases and maintenance of steady state in subsequent period of gestation. (Fig 8 and 9) Out of 20 patients with antibody positive thyrotoxicosis 15 (75%) belonged to Graves' disease and 5 (25%) were

lymphocytic thyroiditis (Figure 10). Out of 18 patients with Graves disease 15 (83%) were antibody positive and the rest were antibody negative. Average fetal heart rate in anti-TPO positive Graves' disease was 164 and in antibody negative patients was 143 (Figure 11). 3(17%) patients with

Graves' disease had preeclampsia when compared to 3(7%) patients with GTT and 4% patients in control population. There was no statistically significant association of preeclampsia with either Graves' ( $p < 0.07$ ) or with GTT ( $p < 0.42$ ) Fetal goitre was detected by antenatal ultra sonogram in one patient with Graves' disease. Goitre was present in 2 neonates of thyrotoxic mothers with Graves' disease. Fetal hyperthyroidism was present in one of those patients and antibody was positive amounting to neonatal Graves' disease. Other neonate was clinically and biochemically euthyroid.

**Other Observations:** 3 cases of vesicular mole had associated biochemical evidence of thyrotoxicosis which normalised with the surgical removal of the mole. There was recurrence of thyrotoxicosis in one patient with Graves' disease and one patient with GTT in subsequent pregnancies during the period of study. There was one case of papillary carcinoma that was treated surgically in the first trimester of pregnancy after medical termination. Comparison of treated and untreated GTT showed no evidence of statistically significant complication rate among untreated patients. ESR was more than 60mm but less than 100 in 4 patients with graves and 6 patients with GTT. ANA was positive in one patient with Graves with elevated ESR.

## DISCUSSION

The most common clinical type of thyrotoxicosis associated with pregnancy according to the present study was Gestational transient thyrotoxicosis accounting for 51% cases followed by Graves' disease (22%). The prevalence of GTT is 7.86% in the first trimester and it is the main cause of thyrotoxicosis found in the first trimester, accounting for 80.77% of all the causes. [6]

Study by Liberman CS et al, showed prevalence of Gestational transient

thyrotoxicosis in 2-3% of pregnant ladies but owing to its transient nature it is not detected routinely. [7] Our study which included only symptomatic patients showed 2.3 times frequent occurrence of Gestational transient thyrotoxicosis compared to Graves' disease.

History of previous abortions was significantly higher in Graves' disease and Gestational transient thyrotoxicosis with reasonable strength of association. Studies by Mestman JH, [8] Mendel et al 1994, [9] Davis LE et al [10] and Mitsuda N et al [11] identified important fetal complications of Graves' disease as premature deliveries, fetal loss, LBW infants and fetal malformations. Since pregnant ladies included in the study were adequately treated, the occurrence of these complications was not observed. Past history of abortions could be attributed to presence of the disease in previous pregnancies that were undiagnosed or to presence of underlying autoimmune disease.

Wilson et al studied pregnancy outcomes in 24,883 women for pregnancy hypertension and found that women with subclinical hypothyroidism identified during pregnancy have an increased risk for severe preeclampsia when compared with euthyroid women. [12]

Reports of Glinoe D, Larsen PR 1999 [13] & Bahn Chair RS et al [14] had stated that historical clues and physical findings in thyrotoxic patients are same as those of pregnant non-thyrotoxic subjects. The present study showed a definite significant association of fatigue, palpitations, heat intolerance, weight loss, tachycardia, wide pulse pressure, warm skin and tremor with thyrotoxicosis in pregnancy. Simultaneous occurrence of 3 or more above mentioned features had a significant predictive value of thyrotoxicosis which holds true even in pregnancy associated thyrotoxicosis despite similarity of symptoms.

Presence of weight loss or failure to weight gain was the most significant single clinical finding which when taken in isolation stood as predictor of thyrotoxicosis in pregnancy. This is well proven and reported in various studies.

This study showed a significant association of hyperemesis with thyrotoxicosis in pregnancy especially so with Gestational transient thyrotoxicosis which showed 48% association with hyperemesis. Presence of hyperemesis leading to weight loss should raise the possibility of thyrotoxicosis complicating pregnancy. [15-17]

7 cases of threatened abortions, 2 cases of periodic paralysis and 1 case of pregnancy psychosis were observed in the study group though statistically significant association could not be elicited due to limited study group. There was no significant linear positive correlation of occurrence of hyperemesis with free T4 levels.

Lid retraction was the most common eye sign observed in the study group which was seen both in Graves' disease and Gestational transient thyrotoxicosis. Exophthalmos was observed only in patients with Graves' disease. In general the incidence of eye signs and ocular complications were low among this study group probably attributable to prompt treatment and strict follow up.

5% patients with Graves' disease and 72% patient with Gestational transient thyrotoxicosis had goitre according to the present study. The presence of goitre alone cannot indicate the thyroid disease complicating pregnancy (12% normal control had physiological goitre) unless considered in the appropriate clinical setting.

Gestational transient thyrotoxicosis showed significant association with twin pregnancies indicating and further supporting the relation of thyrotoxicosis to

raising hCG levels. This fact is supported by studies by Vassart G, Dumont JE [18] which proved the relation of hCG to levels of free T4 in multiple pregnancies and vesicular mole. Present study also showed 3 cases of vesicular mole with biochemical evidence of thyrotoxicosis which normalised after removal of the molar pregnancy.

As far as fetal response to maternal thyrotoxicosis was concerned, there was a significant positive linear correlation of the fetal heart rate with maternal T4 levels. Mestman JH [19] described the prediction of fetal hyperthyroidism based on fetal heart rate. Our study supports the view and hence fetal heart rate can be used a good clinical and sonographic data to assess the response to therapy with anti thyroid drugs. There was no significant fetal growth retardation, fetal hypermotility or accelerated bone maturation observed by ultrasonogram, which could be attributed to appropriate treatment of the study group. Average neonatal weight of the patients with symptomatic thyrotoxicosis was lower than that of normal pregnant ladies; but there was no statistical significance for this observation.

As per the present study the sensitivity and specificity of total hormone levels and free hormone levels were comparable and there was no demonstrable advantage of one over the other. This observation was not supported by a larger study by Osathanondh R, Tulchinsky D, Chopra IJ. [19] Larger studies are required to prove or disprove this important observation.

Anti- TPO antibody positivity was observed in Graves' disease as well as lymphocytic thyroiditis according to the present study. It was positive in 83% patients with Graves' disease which is close to the value (80%) mentioned in Werner and Ingbar's The Thyroid - A Fundamental and Clinical Text - 8th ed. Average fetal heart

rate was higher in TPO antibody antibody positive Graves disease indicating the increased risk of fetal hyperthyroidism with antibody positivity.

83% patients with Gestational transient thyrotoxicosis required treatment with ATD during the first trimester in our study which included only symptomatic patients. Only 24% of them required treatment in the second trimester and none required treatment in the third trimester. Graves' disease and toxic MNG in comparison required treatment nearly throughout the gestational period. Amino N et al described progressive improvement of hyperthyroidism due to Graves' during the course of Gestation and post partum exacerbations of the same. Both these phenomena were not observed in our population due to unknown reasons.

Maternal complications other than preeclampsia were not observed among the study group. Incidence of preeclampsia was greater among patients with Graves' disease when compared to Gestational transient thyrotoxicosis and toxic MNG. There was recurrence of thyrotoxicosis in one patient with Graves' disease and one patient with Gestational transient thyrotoxicosis in subsequent pregnancies during the period of the study.

Comparison of treated and untreated Gestational transient thyrotoxicosis showed no evidence of statistically significant complication rate among untreated patients. Only symptomatic Gestational transient thyrotoxicosis patients received treatment which relieved their symptoms and reduced the complication rate.

## **CONCLUSIONS & RECOMMENDATIONS**

1. The most common type of thyrotoxicosis in pregnancy is Gestational transient thyrotoxicosis

followed by Graves' disease and toxic multinodular goiter.

2. Undetected and untreated thyrotoxicosis in pregnancy is associated with significant fetal loss.
3. Fatigue, palpitations, heat intolerance, weight loss, tachycardia, wide pulse pressure, warm skin and tremor are the most significant clinical features associated with thyrotoxicosis in pregnancy. Simultaneous presence of 3 or more of these features has excellent predictive value for thyrotoxicosis in pregnancy.
4. Presence of weight loss or failure to weight gain is the most significant single clinical finding which when taken in isolation stands as predictor of thyrotoxicosis in pregnancy
5. Gestational transient thyrotoxicosis is associated with hyperemesis and has to be detected early by routine screening in all cases of life threatening hyperemesis and treated promptly to prevent maternal and fetal complications. Presence of hyperemesis with weight loss should prompt investigation in line of thyrotoxicosis.
6. Exophthalmos when present points towards Graves' disease rather than any other cause of thyrotoxicosis. Lid retraction is the earliest but nonspecific sign of thyrotoxicosis in pregnancy.
7. The presence of goitre alone cannot indicate the presence of thyroid disease complicating pregnancy unless considered in the appropriate clinical setting.
8. Gestational transient thyrotoxicosis has significant association with twin pregnancies indicating and further supporting the relation of thyrotoxicosis to raising hCG levels.

9. There is association of vesicular mole with thyrotoxicosis which normalises with the removal of the molar pregnancy.
10. There is a significant positive correlation of the fetal heart rate with maternal T4 level.
11. Fetal heart rate can be used a good clinical and sonographic data to assess the response to therapy with anti thyroid drugs. So it is advisable to make a routine to auscultate for fetal heart rate in patients on treatment and those on follow up.
12. Sensitivity and specificity of total hormone levels and free hormone levels are comparable in pregnancy and there is no demonstrable advantage of one over the other.
13. Anti-TPO antibody is positive in 83% patients with Graves' disease. Average fetal heart rate is higher in TPO antibody positive Graves' disease indicating the increased risk of fetal hyperthyroidism with antibody positivity. So antibody positive thyrotoxicosis requires prompt treatment and strict follow up to prevent fetal complications.
14. Gestational transient thyrotoxicosis requires treatment only in first trimester and early second trimester if symptomatic. Treatment decision of uncomplicated Gestational transient thyrotoxicosis in first trimester would be made on the basis of constellation of at least 3 symptom and/or weight loss in the presence of biochemical evidences. Closely monitor while on treatment and never produce an iatrogenic hypothyroid state which is more detrimental to the fetus than an asymptomatic hyperthyroid state.
15. Graves' disease more often requires treatment throughout the gestational period – partial response in later half gestation possible in less than 10% patients in whom antithyroid drugs has to be stepped down or stopped.
16. Gestational transient thyrotoxicosis - complicated cases are to be kept under follow up for evolution into other forms of the disease and for recurrence in subsequent pregnancies. The entity should not be neglected as untreated severe Gestational transient thyrotoxicosis is associated with maternal and fetal complications.
17. Graves' disease is more severe and complicated when compared to other etiologies of thyrotoxicosis in pregnancy. Hence early recognition and treatment mandatory.

#### ***Limitations***

1. Bias due to confounding-confounding factors other than age and gestational age could not be strictly compared in the control.
2. Interviewer bias- there was only one interviewer for this study who knew the manifestations of the disease, the literature and studies regarding the topic under study.
3. Diagnosis of Graves' disease could not be confirmed as the TSH-R antibodies could not be done due to its prohibitive cost.
4. Differentiation between direct and indirect association between various variables could not be studied because of limited sample size.
5. Incidence of diseases could not be estimated from this study as it is not a population based study.
6. True relative risk of the factors involved in various diseases could not be calculated because there was no true denominator.

7. Repeat antibodies could not be done in antibody positive cases for comparison, and estimation of risk of fetal Graves' disease, due to cost factor.
8. Attrition- Follow up of 20% patients was lost during the gestational period and 47% during post partum period.

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