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Original Article

Obstetrics and Gynaecology Section

Status of Thyroid Peroxidase Antibodies in Pregnant Women and Association with Obstetric and Perinatal Outcomes in Tertiary Care Center

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ABSTRACT

Introduction: Thyroid dysfunction is reported in 8.25% of pregnant women in Indian subcontinent. About two thirds of these women have subclinical hypothyroidism and the rest have overt hypothyroidism.

Aim: To study the prevalence and impact of Thyroid Peroxidase (TPO) antibodies on obstetric and perinatal outcome in a tertiary health centre.

Materials and Methods: This was a prospective cohort study conducted in antenatal clinic of Department of Obstetrics and Gynaecology in collaboration with Department of Biochemistry at King George Medical University, Lucknow, India. Total 230 antenatal women upto 20 weeks of gestational age were recruited, venous blood sample was assessed for serum TSH and TPO Ab and women were classified as subclinical or overt hypothyroid. Subsequently, serum TSH was repeated at interval of 4-6 weeks after initiation of treatment. All the enrolled women were followed for obstetric and perinatal outcome.

Results: The prevalence of TPO Ab in pregnant women was 49 (21.3%). The proportion of hypothyroid women was higher in TPO positive group as compared to TPO negative group (48.98% V/s 27.22%, p=0.01). There were 10 abortions, 4 of them had TPO Ab V/s 6 who were TPO Ab negative. Among TPO Ab positive hypothyroid women 37.5% had preterm labour Vs 5.26% in TPO Ab positive euthyroid women (p-value=0.04). GDM was observed more in TPO Ab positive group (14.2%vs 7.56% p=0.157). There was no difference in terms of caesarean section or neonatal outcome in the study.

Conclusion: The study shows the high prevalence (21.3%) of TPO antibody in antenatal women. Hypothyroidism was more prevalent in TPO Ab positive group. Preterm labour was seen more often in hypothyroid women with TPO Ab.

Keywords: Hypothyroidism, Pregnancy, Preterm birth, Thyroid autoimmunity

INTRODUCTION

Among pregnant women about 8.25% women are diagnosed to have thyroid dysfunction in Indian subcontinent [1]. Subclinical hypothyroidism outnumbers the women with overt hypothyroidism. For a long time it is known that both overt hypothyroidism and subclinical hypothyroidism lead to poor obstetric and perinatal outcomes like miscarriage, preterm labour, gestational hypertension, pre-eclampsia, gestational diabetes mellitus, placental abruption, caesarean delivery for fetal distress, postpartum hemorrhage, low birth weight and NICU admissions [2,3].

The most common etiology of hypothyroidism in pregnant women is Hashimoto's thyroiditis, an autoimmune disease with autoantibodies against TPO enzyme and thyroglobulin protein. TPO enzyme is responsible for oxidation of iodide to iodine in formation of thyroxine hormone. TPO and thyroglobulin auto antibodies can be detected in 10-20% of women of child bearing age group. TPO Ab are produced by B-lymphocytes and lead to thyroid follicular cell destruction by means of cytokines and Antibody Dependent Cell Cytotoxicity (ADCC). There is evidence that thyroid autoantibodies are important risk factors for adverse outcomes like miscarriage and preterm birth. The prevalence is 6-20% among pregnant women with it being higher in women with recurrent miscarriages [4].

Some studies have found an association of TPO Ab with adverse pregnancy outcome even in women with normal thyroid function [5-7] while others have failed to find any definite association. The exact pathogenesis is still not clear [8]. In a study conducted in our institute, prevalence of hypothyroidism was 6.4% [9] but the exact prevalence of TPO Ab is not known. Hence, this study was planned to evaluate the prevalence of TPO antibody in pregnant women in a tertiary health centre in North India and to study the

association between TPO Ab and adverse perinatal and obstetric outcome.

MATERIALS AND METHODS

This prospective cohort study was conducted in the Antenatal clinic of Department of Obstetrics and Gynaecology in collaboration with Department of Biochemistry, at King George's Medical University, Lucknow, India, for the duration of one year (August 2014-2015). Women attending antenatal clinic between 11-20 weeks of pregnancy were enrolled in the study. Those with a known autoimmune disorder, multiple pregnancy and those already on treatment for thyroid dysfunction were excluded from the study. Total 229 antenatal women were enrolled. All these women were evaluated for TPO Ab levels to assess the prevalence of TPO Ab. Serum TSH and free thyroxine (FT4) done to ascertain hypothyroid, hyperthyroid or euthyroid status of antenatal women. The study was approved by the Institute's ethics committee and a written informed consent was taken from all women before participation in the trial. Demographic details, prior obstetric history were recorded in a prestructured questionnaire.

Hormonal Assessment

Under aseptic precautions 5 ml of venous blood sample was drawn in plain vial. The samples were immediately transported to Biochemistry Department. There samples were centrifuged at 3500 to 4500 rpm for 5 min and separated serum was stored at -20 degree centigrade.

Further sample was assessed for serum TSH and TPO Ab by using Cobas e 411 kit based on the principle of electrochemical-luminescence. The kit comprised of 3 reagents, calibrators and ancillary equipments. Serum samples were kept in kit and serially reagents were mixed with serum and incubated for 14 minutes and results displayed. Women with TPO Ab levels more than 34 IU/ml were considered as TPO Ab positive. Women with higher serum TSH were evaluated for FT4 levels. FT4 were also analysed in the similar manner using Cobas e 411 kit on the principle of electrochemical-luminescence.

The women diagnosed as hypothyroid were further classified as subclinical or overt hypothyroidism on the basis of FT4 levels. According to the department protocol both subclinical and overt hypothyroid women were treated as per the reference values irrespective of their TPO antibody status. The reference values were taken as: First trimester-0.1-2.5 mIU/L, Second trimester-0.2-3.0 mIU/L and Third trimester-0.3-3.0 mIU/L as per American Thyroid Association [10]. Those who were detected to be hypothyroid, were kept on levothyroxine supplement and followed. Serum TSH was repeated at interval of 4-6 weeks and dose of levothyroxine was titrated accordingly.

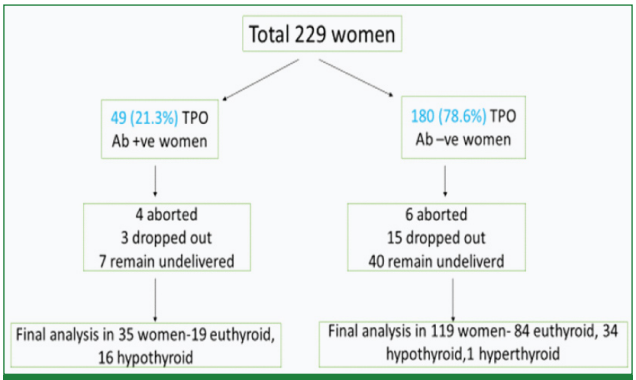
All the enrolled women were followed throughout pregnancy for obstetric and neonatal outcome. Any antepartum, intrapartum and post-partum complications were recorded. A note was made of mode of delivery, gestational age at delivery, birth weight (in centiles), sex and APGAR score of the neonate. Maternal complications like abortion (missed or spontaneous), hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia and eclampsia), intrahepatic cholestasis of pregnancy, Gestational Diabetes Mellitus (GDM), preterm labour, IUGR, post-partum haemorrhage were noted. Neonatal complications were assessed in the form of prematurity, birth weight centile, sepsis and hyperbilirubinemia.

STATISTICAL ANALYSIS

Multivariate analysis was used to determine the effect of TPO antibodies on adverse pregnancy and perinatal outcome. The study involved the categorical data hence Chi square test was used for statistical analysis. The software used in the study was Statistical Package of Social Sciences (SPSS). The confidence level of the study was kept at 95% and the p-value of 0.05 was taken as statistical significant.

RESULTS

Total 229 women were enrolled in the study and of these 49 women had TPO Ab making a prevalence of 21.3% [Table/Fig-1]. Mean age in TPO Ab positive and TPO Ab negative was similar in both groups (26.02±4.18 years and 26.29±3.99 years respectively, p=0.747). The mean BMI in TPO Ab positive and negative group was also similar (23.67±3.68 and 23.67±3.34 Kg/m^2 respectively (p=0.455). Association of thyroid status and TPO Ab is shown in [Table/Fig-2]. Among the maternal complications, there were 10 abortions in the study. Four of 35 (11.4%) women with TPO Ab had abortion as compared to 6 of 119 (5.04%) women with absent TPO Ab (RR=2.2667, CI=0.6774 to 7.5840). There



[Table/Fig-1]: Flow chart of study.

Thyroid Status	TPO Ab Positive (n=49) (Group 1)		TPO Ab Negative (n=180) (Group 2)	
	No.	%	No.	%
Hyperthyroid	0	0.00	1	0.56
Hypothyroid	24	48.98	49	27.22
Euthyroid	25	51.02	130	72.22

[Table/Fig-2]: Association of Thyroid Status and TPO Status. χ^2=8.550 (df =2); p=0.014

was no statistical difference in the incidence of hypertensive disorder of pregnancy (2.8% V/s 2.4%, p=0.11), GDM (14.2% V/s 7.5%, p=0.157) and preterm labour (20% V/s 20.1%, p=0.85) in TPO Ab positive and negative group respectively [Table/Fig-3]. There were 18 (51.43%) vaginal deliveries in TPO Ab +ve group as compared to 49 (41.18%) vaginal deliveries in TPO Ab –ve group (p=0.5). Caesarean section was done in 17 women (48.57%) in TPO Ab +ve group and 70 women (58.82%) in TPO Ab –ve group (p=0.5). There were 10 neonates who developed hyperbilirubinemia and all of them were in TPO Ab negative group (p-value=0.225). No difference in neonatal complication was noted in both the groups in terms of sex, birth weight, APGAR score and gestational age at delivery.

Maternal Complications	TPO Ab Positive (n=35)		TPO Ab Negative (n=119)		Statistical Significance	
	No.	%	No.	%	χ^2	p-value
Pre-eclampsia	1	2.85	14	11.76	2.441	0.118
GDM	5	14.2	9	7.56	2.002	0.157
Preterm labour	7	20	24	20.16	0.033	0.856
Cholestasis	2	5.71	12	10.08	0.625	0.429

[Table/Fig-3]: Distribution of women of different TPO status according to maternal complications (n=154).

Maternal Complications	Hypothyroid TPO +ve (n=16)		Euthyroid TPO +ve (n=19)		Statistical Significance	
	No.	%	No.	%	χ^2	p-value
Pre-eclampsia	1	6.25	0	0	1.222	0.269
GDM	2	12.50	3	15.78	0.077	0.782
Preterm labour	6	37.5	1	5.26	4.130	0.042

[Table/Fig-4]: Comparison of maternal complication in TPO +ve hypothyroid and euthyroid women.

In TPO Ab group there were 16 women who were hypothyroid and 19 were euthyroid. In the presence of TPO Ab, preterm labour was seen in 6 of 16 women with hypothyroidism as compared to only 1 of 19 woman who was euthyroid (p-value=0.04) [Table/Fig-4]. Pre-eclampsia was seen in only 1 woman who was hypothyroid and TPO ab positive as compared to none in euthyroid women with TPO Ab. On analysis of euthyroid women, caesarean section rates due to acute foetal distress were two times more common in presence of TPO Ab (54.45% vs 27.65%) (RR=1.97, CI = 0.96 to 4.01).

DISCUSSION

In this study the prevalence of TPO Ab in pregnant women was 21.3% which is twice the prevalence reported in general population (10-15%). The presence of hypothyroidism was found to be significantly higher in women who had TPO Ab. Relative risk of miscarriages was more in women who had TPO Ab and preterm labour was seen more often in hypothyroid women in presence of TPO Ab. Comparison of similar studies with this study is shown in [Table/Fig-5].

Similar prevalence was found in a cross-sectional study conducted at PGIMS, Rohtak over a period of one year where the prevalence of TPO Ab was found to be 27.8% in pregnant women [11]. The difference in age of women with different thyroid and TPO Ab status was not found to be statistically significant in this study (p=0.747). In 1990, Stagnaro-Green et al., screened women in the first trimester of pregnancy for thyroid autoantibodies and reported two fold increase in miscarriage rate in presence of TPO Ab (17% V/s 8.4%, p=0.011) [12]. In this study also we found a 2 fold increase in pregnancy loss in TPO Ab +ve women as compared to TPO Ab –ve women. This study was supported with similar data from several studies [13-14] who evaluated women in the first trimester of their pregnancy and reported significantly high abortion rates with presence of thyroid antibodies as compared to when antibodies were absent. However, in this study the abortion rate among euthyroid women irrespective of TPO Ab status was similar. (2.52% V/s 3.06%)

In our study there was no difference in preterm labour in TPO Ab +ve and TPO Ab –ve group (both 20%). However association between presence of TPO Ab and preterm labour was noted by Korevaar TI et al., [5] and Negro R et al., [6] and also in a meta-analysis by Thangaratinam S et al., [7]. The causative role of hypothyroidism and presence of TPO antibody in leading to preterm labour is not known. Number of women who developed preeclampsia or GDM did not vary in presence of TPO antibody in this study. An observational study by MPA Sailakshmi et al., including 1000 pregnant women also noted that only 7% women with hypothyroidism and thyroid autoimmunity had GDM (p-value <0.60) [8]. TPO antibodies were not associated with any other obstetric complication in this study.

Among TPO Ab positive group, women with hypothyroidism had more preterm labour than in euthyroid women (37.5% V/s 5.26%, p-value=0.04). On the contrary, Korevaar TI et al., found hypothyroxinemia and TPO Ab positivity associated with increased preterm delivery but this risk in TPO positive women appeared independent of thyroid function [5]. Mannisto T et al., reported that maternal thyroid disorders were associated with multiple adverse outcomes in the offspring, including sepsis, respiratory distress syndrome, transient tachypnoea, and apnoea [15]. In this study there was no difference noticed in terms of birth weight centile or other neonatal complications like sepsis, respiratory distress or hypoglycaemia. There is a contradictory body of evidence demonstrating the relationship of TPO Ab with various adverse obstetric outcome in the form of pre-eclampsia, intrahepatic cholestasis, GDM, abortion, antepartum haemorrhage, preterm labour, post-partum psychosis and adverse perinatal outcome. The exact mechanism and the magnitude of impact are still under investigation.

Name of Author and Sample Size (n)	Year of Study	Nature of Study	Prevalence of TPO Ab	Miscarriage Rate TPO Ab +ve V/s -ve	Preterm Labour TPO Ab +ve V/s -ve	Other Complications
Korevaar TI et al., [5] (5971)	2013	Generation R	-	-	1.7 fold increased (p=0.01)	-
Negro R et al., [6] (984)	2006	Prospective	11.7	13.8 V/s 2.4 (p<0.05)	22.4 V/s 8.2 (p<0.01)	-
Thangaratinam S et al., [7] (31) studies	2011	Meta-analysis of evidence		Cohort- OR-3.9 Case control- OR- 1.8	OR-2.07	-
Sailakshmi MPA et al., [8] (1000)	2014	Observational study	12.8	-	-	46% pre-eclampsia (p-value<0.01) 7% GDM(p value<0.6) 15.4% IUGR (p-value-0.033)
Rajput R et al., [11] (461)	2015	Cross-sectional	27.8	-	-	-
Stagnaro-Green A et al., [12] (552)	1990	Prospective cohort	19.6	17% V/s 8.4%	-	-
Bhattacharya R et al., [13] (400)	2015	Prospective	11.5	-	-	-
Present study, (229)	2015	Prospective cohort study	21.6	11.4 V/s 5.04 (RR=2.2667,CI=0.6774 to 7.5840)	20% V/s 20.1% (p=0.85)	No difference noticed in terms of pre-eclampsia, IUGR, GDM

[Table/Fig-5]: Comparison of similar studies with this study.

LIMITATION

This study was conducted in limited number of antenatal women and the results hence cannot be extrapolated to a larger population. Only TPO Ab was considered for evaluation and not other anti-thyroid antibodies like thyroglobulin. Hence, there is need of a larger study to confirm and validate the findings of this study.

CONCLUSION

The study shows that there is high prevalence of TPO Ab in antenatal women coming to tertiary care centre and there is positive association of presence of TPO Ab with hypothyroidism. Women with TPO Ab and hypothyroidism were also more predisposed to preterm labour. Women in the presence of TPO Ab irrespective of their thyroid function status were found to be at two fold increased risk of foetal distress leading to caesarean section.

REFERENCES

[1] Singh A, Reddy MJ. Prevalence of thyroid dysfunction in pregnancy and its implications. Int J Med Sci Public Health. 2015;4:1247-50.

[2] Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5-5μIU/ml in the first trimester of pregnancy. J Clin Endocrinol Metab. 2010;95(9):E44-48.

[3] Benhandi N, Wiersinga WM, Reitsma JB, Vrijkotte TG, Bonsel GJ. Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. Eur J Endocrinol. 2009;160:985-91.

[4] Lata K, Dutta P, Sridhar S, Rohilla M, Srinivasan A, Prashad GR et al. Thyroid autoimmunity and obstetric outcomes in women with recurrent miscarriage: a case control study. Endocrine Connections. 2013;2:118-24.

[5] Korevaar TI, Timmermans SS, Rijke YB, Visser WE, Visser W, Schrama MK, et al. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. J Clin Endocrinol Metab. 2013;98(11):4382-90.

[6] Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab. 2006;91(7):2587-91.

[7] Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid auto-antibodies and miscarriage and preterm birth; meta-analysis of evidence. BMJ. 2011;342:d2616.

[8] Sailakshmi MPA, Pavana Ganga A, Rekha BR, Akash SS. Autoimmune thyroid disease in pregnancy. Int J Reprod Contracept Obstet Gynecol. 2014;3:321-24.

[9] Sahu MT, Das V, Mittal S, Agarwal A, Sahu M. Overt and subclinical thyroid dysfunction among Indian pregnant women and its effect on maternal and fetal outcome. Arch Gynecol Obstet. 2010;281(2):215-20.

[10] Garber J, Cobin R, Gharib H, Hennessey J, Klein I, Mechanick J, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract. 2012;18(6):988-1028.

[11] Rajput R, Goel V, Nanda S, Rajput M, Seth S. Prevalence of Thyroid dysfunction among women during the first trimester of pregnancy at a tertiary care hospital in Haryana. Indian J Endocr Metab. 2015;19:416-19.

[12] Stagnaro-Green A, Roman SH, Cobin RH, el-Harazy E, Alvarez-Marfany M, Davies TF. Detection of at risk pregnancy by means of highly sensitive assays for thyroid autoantibodies. JAMA. 1990;264(11):1422-25.

[13] Bhattacharyya R, Mukherjee K, Das A, Biswas MR, Basunia SR, Mukherjee A. Anti-TPO antibody positivity during early pregnancy is associated with pregnancy complications and maternal morbidity in later life. J Nat Sci Biol Med. 2015;6(2):402-05.
[14] Mehran L, Tohidi M, Sarvghadi F, Delshad H, Amouzegar A, Soldin O, et al. Management of TPO antibody euthyroid women in pregnancy: comparison of the American Thyroid Association and the Endocrine Society Guidelines. Journal of Thyroid Research. 2013;2013:01-06.
[15] Mannisto T, Vaarasmaki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, et al. Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. J Clin Endocrinol Metab. 2009;94:772-79.

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