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Research Article

Role of anti-thyroid peroxidase antibodies in adverse pregnancy outcomes

Abhilasha Gupta, Nishat Wajdi*, Aruna Verma, Monika Kashyap Pal

Department of Obstetrics and Gynaecology, SVBP Hospital, LLRM Medical College, Meerut, Uttar Pradesh, India

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***Correspondence:**

Dr. Nishat Wajdi,

E-mail: n.wajdi7@gmail.com

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ABSTRACT

Background: Because of the link of thyroid auto antibodies with various pregnancy related complications and anti-thyroid peroxidase antibody (TPO Ab) being most common of all of them, can be used as a surrogate marker for thyroid related adverse pregnancy outcomes. Hence, present study was designed to further elucidate any association of anti-TPO antibodies and serum thyroid stimulating hormone (TSH) levels with adverse pregnancy outcomes.

Methods: This observational study has been conducted in the department of obstetrics and gynaecology at L. L. R. M. Medical College, Meerut, Uttar Pradesh, India. Five hundred randomly selected peripartum women from 20 weeks onwards have been included and divided into two main groups, anti-TPO Ab positive (group B) and anti-TPO Ab negative (group A). Serum TSH was done only in group B. These two groups were compared for age of the patient, period of gestation, number of abortions, pregnancy outcome, maternal and fetal complications.

Results: Out of 500 women, 18.6% were anti-TPO Ab positive. Number of abortions ≥ 2 was found in 18% and 8% in group B and A whereas preterm delivery was found in 50% and 17% in the two groups respectively. In group B, 48% had increased TSH.

Conclusions: Anti-TPO Ab presence was significantly associated with preterm deliveries, recurrent abortions, increased maternal and fetal complications.

Keywords: Anti-TPO Ab, TSH, Abortions

INTRODUCTION

The maternal physiological changes that occur in normal pregnancy induce complex endocrine and immune responses. Thyroid disorders especially those of autoimmune origin are common in women of reproductive age group and approximately 1/5th of childbearing-age women are positive for the anti-thyroid peroxidase antibody (TPO-Ab) or anti-thyroglobulin antibody (TG-Ab).^{1,2}

A number of recent population studies has been conducted which suggest pregnancies with thyroid disorders may have an increased risk of pregnancy complications, including preterm delivery, placental abruption, intrauterine death, recurrent miscarriages, intrauterine growth retardation (IUGR), pre-eclamptic

toxaemia and abnormal neuropsychological development in offspring.³⁻⁸

There is evidence that thyroid autoimmunity is an important risk factor for miscarriage and preterm birth.⁹ The presence of thyroid auto antibodies is relatively common in women of reproductive age. In an unselected population of women, the prevalence ranges from 6% to 20% being even higher in women with a history of recurrent pregnancy loss, at around 17-33%, and in women with a history of subfertility, at around 10-31%.^{9,10} Because of the link of thyroid auto antibodies with continuing progression to incipient and then overt thyroid failure, it seems reasonable that such antibodies might be a surrogate marker for thyroid-related adverse pregnancy outcomes.

This study has been aimed to study the prevalence of anti-TPO Ab in peripartum period in reproductive age group women and to correlate its presence with adverse pregnancy outcomes.

METHODS

This observational study was conducted at department of obstetrics and gynaecology, LLRM Medical College, Meerut during 1st June 2014 - 31st May 2015 after ethical clearance from institutional ethical committee. It was a cross-sectional or prevalence study design. 500 randomly selected peripartum women between ages 20 to 35 years from 20 weeks onwards were included; all patients underwent a comprehensive medical evaluation including a detailed history and a thorough physical examination. Women with known autoimmune disorders, already on treatment for thyroid dysfunction, history of cervical incompetence or any uterine pathology, patient suffering from any chronic systemic illness or any critical medical illness during pregnancy were excluded from the study.

3 ml venous blood collected in vacutainer. Each blood sample analyzed for anti-TPO levels by electrochemiluminescence immunoassay (ELECSYS-2010, normal value <9 IU/ml). On the basis of anti-TPO antibody positivity, cases were divided into two groups, group A which was anti-TPO antibody negative and group B which was anti-TPO antibody positive. Serum thyroid stimulating hormone (TSH) was done in those who were anti-TPO antibody positive, (reference range - first trimester 0.1-2.5 mIU/L, second trimester 0.2-3 mIU/L, and third trimester 0.3-3 mIU/L).

Data was recorded in a predesigned proforma and maternal and fetal outcomes were noted and compared in both the groups.

Statistical analysis

The sample size for a study of prevalence was calculated to an accuracy of 95% (5% error), assuming a prevalence estimate of 10% (prevalence internationally reported), with a confidence level of 95% (5% alpha error), yielding a sample size of 477 women. Unpaired t test was used for normal data and Mann-Whitney U test was used for non-normal data. To analyze the dichotomous data, odds ratio or Fisher's exact test was used.

Multivariate analysis was carried out to determine the effect of TSH and anti - TPO Ab on percentage of live birth per individual. The covariates included for multivariate analysis were age, weight, TSH, anti-TPO titre, period of gestation and haemoglobin level of the patients. A p value of <0.05 was considered significant.

RESULTS

Out of 500 women, 407 women were anti-TPO Ab negative i.e. 81.4% (group A) and 93 women were found

to be anti-TPO Ab positive. Thus, prevalence of anti-TPO Ab presence found to be 18.6% (group B). Maximum patients were in the age group 25-29 years (54.3%). Age had no significant association with anti-TPO Ab positivity (p-value 0.301). But as the age increased the odds of having anti-TPO Ab presence increased. Both the groups were comparable in age distribution.

In group A and B, patients having no abortion were 373 (91.6%) and 65 (69.8%), 1 abortion were 26 (6.3%) and 13 (13.9%), 2 abortions were 7 (1.7%) and 10 (10.7%), ≥ 3 abortions are 1 (0.2%) and 5 (5.3%) respectively. There was a statistically significant association between number of abortions and anti-TPO Ab positive status (p-value <0.001) and there was a significant correlation between these auto antibodies and number of abortions as depicted by the successive increase in odds ratio of having these auto antibodies as the number of abortions increase.

The prevalence of thyroid autoimmunity was higher in pregnant women with a history of recurrent abortion. There was no absolute difference in the prevalence of miscarriage between subclinical hypothyroid and euthyroid pregnant women irrespective of TPO status.

Table 1: Various adverse maternal occurrences in group A and group B.

Maternal complications	Anti-TPO Ab titre		p - value (chi-square test)
	Negative N = 407 group a	Positive N = 93 group b	
No complication:	299 (73.46%)	55 (59.14%)	0.15
H/o previous abortion	34 (8.36%)	28 (30.11%)	<0.001
Hypertensive complications	35 (8.59%)	19 (20.44%)	0.001
Preterm labour	74 (18.18%)	48 (51.62%)	<0.001
Gdm*	0 (0.00%)	1.0 (1.08%)	0.01
Prom	55 (13.50%)	16 (17.20%)	0.05
Aph*	6.0 (1.47%)	4.0 (4.30%)	0.03
Postdatism	60 (14.74%)	5.0 (5.38%)	0.25

*As the cases were so small in number, even though p-value came out to be <0.05, so the results cannot be generalized on the entire population. P - value has been calculated by Fisher's Exact test.

When compared for maternal complications, in group B, 44% patients landed up in preterm delivery in comparison to only 8.3% patients in group A (p-value<0.001). In group A and group B, 8.36% and 30.11% patients had history of previous abortions, 8.59% and 20.44% had hypertension or its complications, 18.18% and 51.62% patients had preterm labour, 13.5% and 17.20% patients had preterm premature rupture of membranes, 1.47% and 4.3% had antepartum haemorrhage, 0% and 1.08% had gestational diabetes mellitus respectively (Table 1).

Table 2: Various adverse perinatal occurrences in group A and group B.

Perinatal outcome	Anti - tpo ab titre		P-value (chi square test)
	Negative group A (81.4%)	Positive group B (18.6%)	
Prematurity	74 (18.18%)	48 (51.62%)	<0.001
IUD	11 (2.7%)	19 (20.43%)	<0.001
IUGR*	2 (0.49%)	2 (2.15%)	<0.001
LBW	123 (30.22%)	51 (54.84%)	<0.001
Congenital anomaly *	0 (0.00%)	2 (2.15%)	<0.001
Need for NICU admission	73 (17.94%)	45 (48.39%)	<0.001

*p-value calculated by Fisher's Exact test.

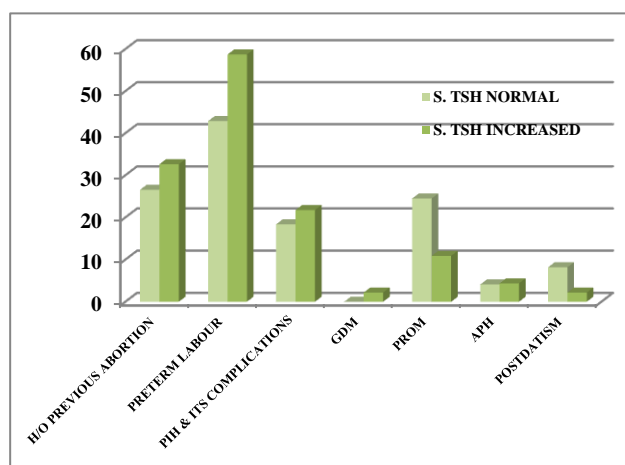


Figure 1: Distribution according to percentage of maternal complications based on serum TSH values.

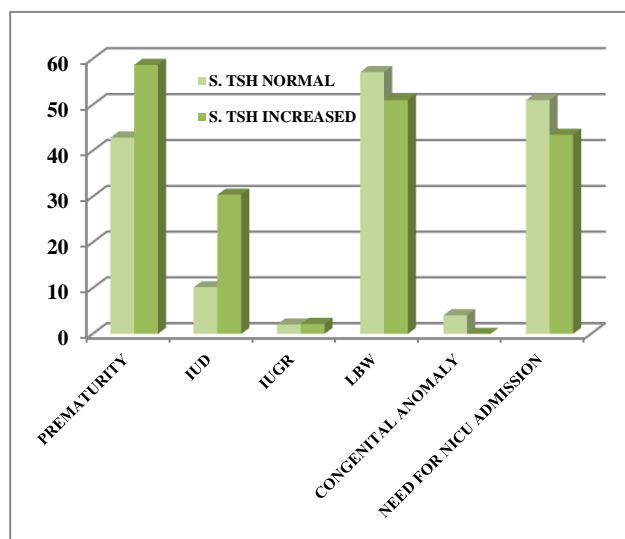


Figure 2: Distribution according to percentage of fetal complications based on serum TSH values.

When compared for perinatal complications, group A and group B, 18.18% and 51.62% were preterm neonates, 2.7% and 20.43% were intrauterine dead (IUD), 30.22%

and 54.84% were low birth weight, 17.94% and 48.39% neonates needed neonatal intensive care unit (NICU) admission, 0.49% and 2.15% patients were intrauterine growth restricted (IUGR), 0% and 2.15% patients had congenital anomalies respectively (Table 2).

Serum TSH was done in group B only and 51.61% patients had normal TSH and 48.39% patients had raised TSH. Presence of Anti-TPO Ab had a significant association with raised serum TSH (p-value<0.001). Various maternal complications were comparable in both the groups having normal TSH and raised TSH (Figure1). Perinatal outcomes were also comparable in both the groups (Figure 2).

DISCUSSION

Autoimmune thyroid disease (AITD) is by far the most frequent cause of hypothyroidism in women of reproductive age. The prevalence of hypothyroidism in the general population of reproductive age is ~2-3%. This study was planned to study the prevalence of anti-TPOAb in peripartum period and to correlate the prevalence of anti-TPO Ab with adverse pregnancy outcome.

In this study, prevalence of thyroid autoimmunity has been found to be 18.6%. The national health and nutrition examination survey (NHANES) data from the USA reviewed in 2002, examining 17,353 people, showed TPO-Ab in 13%.

In this study, age had no significant association with anti-TPO Ab positivity. But as the age increased the odds of having anti-TPO Ab positivity increased. In all the age groups of group A and group B the difference was statistically not significant (p - value 0.301), and both the groups are comparable in age distribution.

A meta-analysis by Prummel et al showed that TPO Ab was associated with a twofold increased risk of miscarriage as shown in this study.¹¹ Similar results were found by Negro et al who found the miscarriage rate in the TPO Ab group supplemented with levothyroxine 4 (T4) was comparable to healthy controls (3.5 versus 2.4%).¹² Although multiple studies had demonstrated a risk of miscarriage in patients with AITD, the cause has yet to be established. TPO Ab is one of the markers of recurrent miscarriage. However, more evidence is needed before dismissing antibody positivity as a cause of adverse pregnancy outcome. The association of thyroid autoimmunity and miscarriage could be due to heightened autoimmune imbalance that in turn leads to a greater rejection rate of the foetal graft, and TPO Ab positive women would tend to become pregnant at an older age (3-4 years older on average), and older women are more prone to pregnancy loss.^{13,14}

Women with hypothyroidism have decreased fertility, even if they conceive; the risk of miscarriage is increased.

The risk of gestational hypertension, preeclampsia and eclampsia, abruption placentae, post-partum haemorrhage, premature delivery and IUGR is increased.^{14,15} These risks are increased in the whole spectrum of hypothyroidism, including isolated TPO positivity, subclinical hypothyroidism and overt hypothyroidism. In a study by Negro et al there was a positive association between thyroid autoimmunity with preterm delivery and neonatal respiratory distress syndrome in euthyroid women.

In this study anti-TPO Ab presence had a significant association with various maternal complications like preterm delivery, recurrent abortions, pre-eclampsia or its complications, antepartum haemorrhage, preterm rupture of membranes (p-value <0.001).

Various adverse perinatal outcomes had a significant association with anti TPO Ab positive status. Those who were positive for anti-TPO Ab 51.02% were premature, 20.43% were IUD, 54.84% were low birth weight (<2.5 kg), 48.39% needed NICU admission, 2.15% were IUGR, 2.15% had congenital anomaly (p-value <0.001).

A meta-analysis done in 2011 involving 30 articles with 31 studies (19 cohort and 12 case-control) involving 12,126 women assessed the association between thyroid auto antibodies and miscarriage. Five studies with 12,566 women evaluated the association with preterm birth. Of the 31 studies evaluating miscarriage, 28 showed a positive association between thyroid auto antibodies and miscarriage. Meta-analysis of the cohort studies showed more than tripling in the odds of miscarriage with the presence of thyroid auto antibodies (odds ratio 3.90, 95% confidence interval 2.48 to 6.12; P <0.001). For case control studies the odds ratio for miscarriage was 1.80, 1.25 to 2.60; P = 0.002). There was a significant doubling in the odds of preterm birth with the presence of thyroid auto antibodies (2.07, 1.17 to 3.68; P = 0.01).

The frequent presence of thyroid auto antibodies in several non-thyroidal autoimmune diseases supports a hypothesis of global immune dysfunction being relevant to these clinical outcomes.¹⁶ There is evidence that there is an alteration in cytokine expression by peripheral T lymphocytes in women positive for thyroid antibodies outside of pregnancy.¹⁷ Pregnancy is an inflammatory process involving a shift in the regulation of cytokine networks within the local placental decidual environment.

Thyroid hormones can directly influence angiogenic growth factor and cytokine production as well as trophoblast proliferation, survival, and invasion. Furthermore, the presence of thyroid autoantibodies might be a marker of underlying subtle alteration in thyroid reserve which could be associated with reduced adaptation to the physiological changes of pregnancy and could contribute to minor changes in circulating thyroid hormone concentrations within the reference range.¹⁸

CONCLUSION

Pregnancy complicates both the physiology of the thyroid cell and the immune response to thyroid antigens. Thyroid auto antibodies are involved in both these areas and are associated with major alterations in the course of pregnancy affecting the mother, the fetus, and the neonate. Thyroid antibodies can serve as useful clinical predictors of thyroid dysfunction, for example, TPO Ab and post-partum thyroiditis and TSH receptor antibodies (TSHR-Abs) and neonatal hyperthyroidism. Our study has demonstrated that various adverse maternal and perinatal outcomes had a significant association with anti-TPO Ab positivity irrespective of serum TSH levels. So this antibody can be used as a surrogate marker of adverse pregnancy outcomes. Hence, screening in high risk group along with levothyroxine 4 (LT4) supplementation in future might prevent even some of these adverse perinatal occurrences.

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