



A RETROSPECTIVE STUDY TO EVALUATE ASSOCIATION BETWEEN THYROID PEROXIDASE ANTIBODIES AND PREGNANCY OUTCOME

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ABSTRACT

Aim: study was to compare pregnancy outcome in euthyroid women who were anti-TPO-Ab positive with those who were anti TPO-Ab negative.

Design: observational study method : comprised 500 women in the age group of 18-35 years, having normal thyroid function test normotensive, nondiabetic, singleton pregnancy attending OPD SRN Hospital Allahabad and Kamala Nehru Hospital in Prayagraj November 16 - October 17, all euthyroid pregnancy, those were already in process of abortion and those aborted in our hospital. Anti TPO-Ab level of > 50 IU/ml were considered as anti TPO-Ab positive.

Main outcome:- estimation of proportion of anti TPO-Ab in women attending OPD in hospital and comparison of maternal and neonatal outcome in anti TPO- Ab Positive and anti TPO-Ab negative euthyroid women were done.

RESULT:- increased rate of miscarriage (12.5 vs 2.39%) $p < 0.05$, LBW (27.5 vs 5.217%) $p < 0.05$, and preterm birth (17.5 vs 3.4%) $p < 0.05$, in anti- TPO-Ab positive as compared to anti- TPO- Ab negative women.

CONCLUSION- Study revealed anti-TPO- Ab is strongly associated with miscarriage, preterm birth irrespective of their gestational age, LBW is also significantly associated with anti-TPO-Ab positivity. However we did not find any correlation with other complication as found in studies by other authors.

KEYWORDS : Thyroid peroxidase antibodies, euthyroid pregnancy, Autoimmunity.

INTRODUCTION

Pregnant women with thyroid gland disorder are susceptible to hypothyroidism, accompanied with a wide range of adverse outcomes, like miscarriage, placental abruption, preterm birth, fetal growth retardation, and impaired neuro-psychological development of the offspring. Xichen et al (2016)[1] were also at high risk for post partum thyroid dysfunction and at lifelong risk for permanent thyroid failure. Maternal thyroxine is important for normal fetal brain development, especially before development of fetal thyroid gland function (Bernal, 2007) [5]. Thyroid peroxidase (TPO), is a membrane-bound enzyme, which catalyzes iodide oxidation and iodination of tyrosyl residues of thyroglobulin. Anti-TPO-antibody (anti-TPO-Ab) reacts with TPO, leading to destruction of thyrocytes. Autoantibodies to TPO are common in the euthyroid population.

Anti TPO Ab has been identified in 5% -15% of all pregnant women (Abbassi-Ghanavati, 2010)[14] and in general population of reproductive age is 10–20%. Although many types of antithyroid antibodies have been described, the most common is the group of antibodies directed against various parts of the thyroid peroxidase molecule. The detection of thyroid antibodies before or early in pregnancy can predict the development of pregnancy loss, the onset of post partum thyroiditis, and the need for thyroxine replacement therapy during pregnancy. Pregnancy alter both the physiology of the thyroid cell and the immune response to thyroid antigens. Thyroid autoantibodies are involved in both these areas.

MATERIAL AND METHODS

Observational case-control study conducted in department of Obstetrics and Gynaecology, Swaroop Rani Nehru Hospital, Motilal Nehru Medical College and Kamala Nehru Memorial Hospital Prayagraj, over a period of 1 year during years 2016-2017.

SELECTION OF CASES:-

The subjects were recruited into two study groups.

Group A- Pregnant euthyroid women with anti TPO- Antibody Positive (Ab positive)

Group B- Pregnant euthyroid women with anti TPO- Antibody (Ab Negative)

Inclusion criteria:-

Euthyroid pregnant women > 18 yrs, women who were already in process of abortion and women who aborted in our hospital. Having normal thyroid function tests, normotensive, nondiabetic and singleton pregnancy.

Exclusion Criteria:-

With abnormal thyroid functions (abnormal TSH and T4) Women having heart disease, liver disease, chronic hypertension, epilepsy, severe anaemia, anti phospholipid antibody Syndrome, anatomical abnormalities in uterus, cervix and congenitally anomalous of foetus, smoker and tobacco chewers were excluded from this study. Detailed history regarding previous pregnancy complications, gestational age at each pregnancy loss, in cases of recurrent pregnancy loss, family history of any thyroid disorder and any treatment taken for it were taken, personal history of any autoimmune disorder like diabetes mellitus, history of recent weight gain. A thorough clinical examination will be done especially thyroid enlargement. Pregnancy outcomes were noted as abortion/miscarriage, preterm delivery, term delivery (> 37 weeks), gestational hypertension, preeclampsia, placental abruption, and mode of delivery (Vaginal, LSCS). Neonatal outcomes were noted as birth weight, preterm birth, neonatal death, IUD, meconium passage, and need of admission to NICU.

METHOD

Serum free T3, free T4, and TSH levels were done. Out of these, euthyroid patients were selected on the basis of normal serum TSH and T4 level, antiTPO-antibody levels were measured, and the patients were divided into antiTPO- antibody positive and anti negative groups and compared for any adverse maternal and neonatal outcome.

Approx 5ml of venous blood samples were collected blood was allowed to clot, centrifuged for three minutes and then serum was separated, aliquoted and stored at -20°C till analyzed. Measurement of serum TSH level and free T4 concentration. Serum aliquots were analyzed for thyroid peroxidase antibody concentration using a chemiluminescent microparticle immunoassay (CMIA) -for quantitative measurements of T4, TSH, and anti-TPO Ab in our central lab. Those who were normal for TSH and T4 were assayed for anti-TPO-Ab concentration using chemiluminescent microparticle immunoassay (CMIA). The analytical sensitivity of thyroid peroxidase assay is ≤ 1.0 IU/ml. The ARCHITECT Anti-TPO assay is

designed to have an assay precision of < 10% total CV for samples > 5.61 IU/ml. Anti-TPO-Ab level more than 50 IU/ml considered as antithyroid peroxidase antibody positive.

Standard reference ranges in non-pregnant women.

Serum Free T3 - 1.71-3.71 pg/ml
 Serum Free T4 - 0.70-1.48ng/ml
 Serum TSH - 0.5-4.94 μIU/ml

Standard reference range in pregnant women

1st trimester : 0.1-2.5mIU/L
 2nd trimester : 0.2-3.0mIU/L
 3rd trimester : 0.3-3.0mIU/L
 Free Thyroxine (T4, reference range 0.93-1.7 ng/dl)
 Free Triiodothyronine (T3, reference range 2.5-4.3pg/ml)

Statistical Analysis

The qualitative data were analyzed using chi-square test, and quantitative data (mean and standard deviation) were compared using T test and Z test by GraphPad Prism 7 software.

RESULT

Out of 500 euthyroid antenatal women in the study 40(8%) were positive for TPO antibodies and 460 (92%) were negative for TPO antibodies. Thus prevalence of anti TPO-Ab positive found to be 8%.pregnant women with Tpo-Ab level of more than 50 IU/ml termed as anti-Tpo – Ab Positive.

Table1: Distribution Of Cases According To Anti-Tpo- Ab Status



most of the women were in the age group of 23-27 years. Mean maternal age in our study were 26.6±3.73 years in anti TPO- Ab positive group and 25.07±3.34 years in anti TPO- Ab negative group.

In present study more than 5 fold increased rate of abortion in antiTPO-Ab positive women as compared to antiTPO-Ab negative women[5(12.5%)vs 11(2.23%),p=0.000494]

And more than 5 fold increased rate of preterm deliveries in antiTPO-Ab positive women compared to AntiTPO-Ab negative women[7(17.5%)vs 16(3.4%),p=0.000049] the incidence of prematane rupture of membrane were approximately same in both anti TPO-Ab positive and negative women [2(5%) vs 19(4.13%),p=0.79].

NO significant difference were noted in incidence of caesarean rate,rate of placental abruption, gestational hyper tension and incidence of preeclampsia among anti TPO-Ab positive and negative women [11(27.5%) vs 106(23.04%),p=0.52],[1(2.5%) vs 9(1.95%) p=0.81],[3(7.5%) vs 30 (6.52%) p=0.81],[1(2.5%) vs 13(2.82%) p=0.90]. There were more than 5 fold increased rate of preterm deliveries in antiTPO-Ab positive women compared to AntiTPO-Ab negative women.

Table 2: pregnancy outcome

PREGNANCY OUTCOME	TPO-Ab NO OF CASES	POSITIVE PERCENT AGE	TPO-Ab NEGATIVE NO OF CASES	NEGATIVE PERCENT GE	P-value
Abortion	5	12.5%	11	2.39%	0.00494
Preterm delivery	7	17.5%	16	3.47%	0.000049
PROM	2	5.0%	19	4.13%	0.792568
Caesarean	11	27.5%	106	23.04%	0.523113
Placental Abruption	1	2.5%	9	1.95%	0.813826
Gestational Hypertension	3	7.5%	30	6.52%	0.811091
Preeclampsia	1	2.5%	13	2.82%	0.904557

Delivered at term	10	25%	256	55.65%	0.000194
Total	40	100%	460	100%	

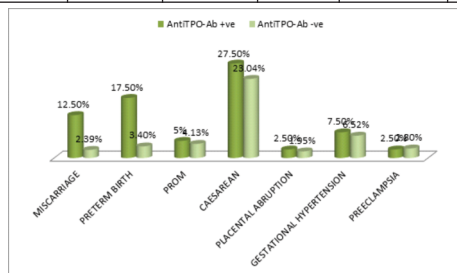


figure1:correlation of pregnancy outcome with TPO-Ab status .

Incidence of low birth weight(LBW) babies were significantly higher in anti TPO-Ab positive women compared to negative women [11(27.5%)vs 24(5.21%),p<0.05]

No significant differences were noted in anti-TPO-Ab positive and negative group with respect to intra uterine fetal demise (IUD) [1(2.5%) vs 11 (2.39%), p=0.95],neonatal intensive care unit (NICU) admission [6(15%) vs 73 (15.87%),p=0.88] and passage of meconium [5 (12.5%) vs 64 (13.91%),p=0.80].

Table 3: Cases Distribution According to neonatal outcome in TPO-Ab positive and TPO-Ab negative

NEONATAL OUTCOME	TPO-Ab NO OF CASES	POSITIVE PERCE NTAGE	TPO-Ab NEGATIVE NO OF CASES	NEGATIVE PERCE NTAGE	P-Value
Low birth weight	11	27.5%	24	5.217%	< 0.05
IUD	1	2.5%	11	2.36%	0.955635
Need for NICU Admission	6	15.0%	73	15.87%	0.885007
Passage of Meconium	5	12.5%	64	13.91%	0.803721
Delivered at term	17	42.5%	288	62.60%	0.012385
Total	40	100%	460	100%	

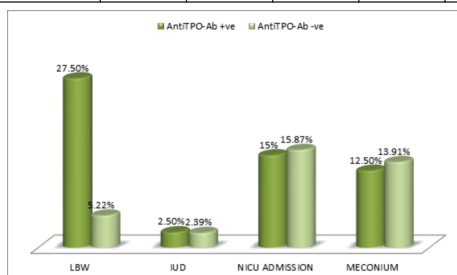


figure 2: correlation of neonatal outcome with tpo-ab status

DISCUSSION

.The increased need of thyroid hormone is approximately 30%-40% due to increased placental uptake, higher thyroid binding globulin level and greater blood volume.

Prevalence of anti TPO- Ab during gestation is depends on different factor including genetic makeup, environmental conditions and demographic characteristics of populations[72] .The high degree of variability may be due to ethnic and geographical factors.

In the present study, antiTPO-Ab positive women were40 (8%) and rest 92% were anti TPO-Ab negative consistent with Sieiro Netto et al (2004) 5.43% [4], Negro et al (2006) 6.25% [5] .

In our study age had no significant association with anti TPO-Ab positivity but slightly higher age observed in anti TPO –Ab positive group compared to negative group (mean age 26.6±3.73 vs 25.07±3.34years p=0.795) .

There were no significant association find in anti TPO-Ab positive group and negative group with respect to socioeconomic status ,education, residence ,and occupation .This may be due to the fact that

India is a developing country and majority of our population is from the middle socioeconomic status.

Non awareness of rural population about antenatal check-up and negligent attitude toward health showed that majority of population from the urban area. Almost two third population included in study were housewife.

Stagnaro-Green et al(1990) [6] reported a doubling of the miscarriage rate in women who were antibody positive in the first trimester as compared to an antibody negative cohort (17% vs 8.4%, $p=0.011$).

In present study also more than 5 fold increased rate of abortion in antiTPO-Ab positive women as compared to antiTPO-Ab negative women (12.5% vs 2.23% , $p=0.000494$) similar with Ghafoor *et al.*, (O.R 49.2) (2006) [7].

Ghafoor *et al.*, (2006) [7] reported that TPO-Ab positive women had a significantly higher rate of preterm delivery compared with women who were TPO-Ab negative (26.8 vs. 8.0 %, $P < 0.01$).M.Abbassi - Ghanavati *et al*(2010) [3].found no association between thyroid peroxidase antibody status and preterm delivery In the present study there were more than 5 fold increased rate of preterm deliveries in antiTPO-Ab positive women compared to AntiTPO-Ab negative women(17.5% vs 3.4% $p=0.000049$).

found no association between thyroid peroxidase antibody status and prematurely ruptured In this study, the incidence of premature rupture of membrane was approximately same in both antiTPO-Ab positive women and antiTPO-Ab negative women (5% vs 4.13%, $p=0.07$) Similar to Abbassi Ghanavati *et al*(2010)[3]

Negro *et al.*,(2011) [8] also noted no significant difference in incidence of caesarean among antibody positive and negative women. Finding of the present study are consistent with the above study(27.5 vs 23.04 $p=0.52$).

Stagnaro- Green *et al.*, (1990) [6] stated that the risk of placental abruption was increased in antiTPO-Ab positive women. Prummel *et al*(2004) [9] stated that the risk of placental abruption was increased in antiTPO-Ab positive women.However Chen *et al.*, (2014) [10] reported that TPO-Ab was not associated with placental abruption.

In this study, no significant difference was observed in rate of placental abruption in antiTPO-Ab positive women compared to antiTPO-Ab negative women (2.5% vs 1.95%, $p= 0.81$), Stagnaro- Green *et al.*, (1990) [6] stated that the risk of gestational hypertension, preeclampsia and Eclampsia was increased in antiTPO-Ab positive women. Moncef Feki *et al.*, (2008) [11] reported that women with positive anti-TPO have a trend toward higher prevalence of gestational hypertension. However Chen *et al.*,(2014) [10] reported that TPO-Ab was not associated with gestation hypertension.

In the present study no significant difference were noted in the incidence of gestational hypertension and preeclampsia among antiTPO-Ab positive and antiTPO-Ab negative women(7.5% vs 6.52% $p=0.81$),(2.5% vs 2.8% $p=0.09$).

Abbassi-Ghanavati *et al.*, (2010) [3] found no difference in low birth weight babies among anti-TPO antibodies positive and negative women. Karakosta *et al.*,(2012) [12] reported 3-fold increased risk for low birth weight neonates (RR 3.1, 95% CI 1.2-8.0) in thyroid autoimmune patient. Chen *et al.*,(2014) [10] also reported that TPO-Ab was associated with LBW.

In the present study, presence of thyroid peroxidase antibodies significantly affected birth weights of newborns according to gestational age. Incidence of low birth weight babies were significantly higher in antiTPO-Ab positive women compared to antiTPO-Ab negative women(27.5% vs 5.21% , $P<0.05$).

Moncef Feki *et al.*, (2008) [11] reported that women with positive anti-TPO have a trend toward higher prevalence of foetal death. Mannistö *et al.*,(2010) [12] found an increase in perinatal death in anti-TPO Ab positive women compared with anti-TPO Ab negative women.

In the present study no significant difference was noted in IUFD among antiTPO-Ab positive and antiTPO-Ab negative women (2.5%

vs 2.39%, $p=0.95$).

Negro *et al.*, (2011) [8] noted no significant difference in incidence of NICU admission.

In this study, no statistically significant difference was noted regarding neonatal ICU admission in antiTPO-Ab positive and negative women(15% vs 15.87% $p=0.88$)

With regard to meconium passage there were no significant difference noted among anti TPO-Ab positive and negative group (12.5% vs 13.91% $p=0.8$).

CONCLUSION

anti TPO-Ab are associated with some adverse pregnancy outcomes.antiTPO-Ab are strongly associated with abortion, low birth weight and preterm deliveries.

No significant association were noted among antiTPO-Ab positive and pregnancy induced hypertension, placental abruption, intrauterine death, meconium passage, premature rupture of membrane, caesarean section, preeclampsia and need for NICU admission.

No correlation with other complications was found as observed by other authors.

thyroid autoimmunity has its effect on obstetric outcomes. Thyroid antibodies detected in early pregnancies seem to predict pregnancy complication and later thyroid disease morbidity of the mother. Hence, screening should include an anti TPO-Ab titre and TSH level, as the presence of antibody identifies women with much increased risk of developing pregnancy complications and postpartum thyroiditis.

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