Neonatal and fetal effects of antithyroid peroxidase positivity in hypothyroidism in pregnancy - A hospital-based prospective analytical study

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Received - 18 January 2019 Initial Review - 10 February 2019 Accepted - 18 February 2019

ABSTRACT

Objectives: The objectives of this study were to evaluate the fetal and neonatal outcomes for pregnant women with autoimmune hypothyroidism and to compare them to hypothyroid and euthyroid women. **Methods:** A total of 309 women were included in the study. 159 hypothyroid women were categorized as "Cases" and 150 euthyroid women were "Controls." Serum thyroid-stimulating hormone (TSH) was done for all women, and in hypothyroid women, antithyroid peroxidase (TPO) was also done for the mothers. Cases were subdivided on the basis of anti-TPO positivity. Fetal and neonatal complications were noted in all three groups along with basic parameters such as baby weight and Apgar scores. Meconium aspiration, neonatal intensive care unit (NICU) admission, jaundice, intrauterine growth retardation, intrauterine death (IUD), low or very low birth weight, congenital anomalies, hypothyroidism in the newborn, and neonatal death were the parameters noted. Testing of the babies was done with serum TSH on day of life 3 and serum bilirubin whenever clinically jaundice was suspected. The study period was 2 years. **Results:** Hypothyroidism is significantly associated with an increased risk of IUD (p=0.038), NICU admissions in babies (p=0.004), neonatal jaundice (p=0.027), low or very low birth weight babies (p=0.0003), congenital anomalies in the babies (p=0.026), and neonatal deaths (p=0.007). Anti-TPO positivity is significantly associated with increased risk of IUD (p=0.044) and hypothyroidism in the newborn of hypothyroid mothers (p=0.045). **Conclusions:** Anti-TPO positivity and hypothyroidism are both significantly associated with certain fetal complications such as IUD, neonatal jaundice, increased NICU admissions, and hypothyroidism in the newborn. Mothers with hypothyroidism who are TPO positive have a higher risk of neonatal mortality and morbidity, although small. Hence, screening should be done in all hypothyroid women in pregnancy and their babies. Universal screening with serum TSH is recommended in pregnancy and in the newborn on day 3 of life.

Key words: *Antithyroid peroxidase, Autoimmune, Congenital hypothyroidism, Pregnancy, Screening, Thyroid-stimulating hormone*

The fetus is entirely dependent on transplacental maternal thyroid hormone supply until around 18 weeks of gestation [1]. Even subsequently, maternal thyroid hormone transfer to the fetus continues right up to delivery [2]. Thyroid disorders can, therefore, affect the fetal and neonatal outcomes from the beginning of pregnancy till after delivery. The most prevalent of these is subclinical hypothyroidism and autoimmune hypothyroidism. Thyroid antibody positivity has also been shown to be a risk factor for perinatal death [3]. The two important antibodies which are implicated are antithyroglobulin and antithyroid peroxidase (TPO) antibody, the latter being more significant. Mild thyroid dysfunction, characterized by increased thyroid-stimulating hormone (TSH) with normal FT4 levels, is frequently observed in the 1st month of life in neonates born from mothers affected by autoimmune thyroiditis. The majority of them undergo complete and spontaneous normalization of TSH value [4].

Psychomotor delay has been reported in the offspring of TPO antibody-positive mothers independently of thyroid dysfunction in apparently iodine-replete populations [5]. An increased incidence of neurodevelopmental deficits has also been reported in children whose mothers had subclinical hypothyroidism early in pregnancy [6]. Timely treatment of maternal hypothyroidism has shown to reduce the risk of neurodevelopmental deficits in the offspring. The stage of development, during which the lack of T4 in the fetus is most detrimental for neurodevelopment, is thought to be the first trimester [7].

Congenital hypothyroidism is also an associated consequence of maternal uncontrolled hypothyroidism in pregnancy. The incidence ranges from 1:3000 to 1:4000 neonates, but a recent Indian study has found the incidence to be about 1:1130 neonates [8]. Screening is done by measuring TSH in sample collected at 48–72 h after birth [9]. The second sampling is done at 2 weeks for premature, sick babies or babies <1.5 kg [10]. According to the American Academy of Pediatrics guidelines, neonates with serum TSH >40 mIU/L should be diagnosed with congenital hypothyroidism. In India, TSH cutoff values are >34 mIU/L during 24–48 h of life and >20 mIU/L after 48 h

on repeat filter paper TSH and >40 mIU/L at any age [10]. In general, a TSH ≥40 mIU/L on the 2–4 days of life warrants therapy, whereas values between 15 and 40 mIU/L may be carefully reassessed [11]. Therefore, we need to identify and correct hypothyroidism in pregnancy as well as screen all the newborns with serum TSH to recognize and treat congenital hypothyroidism at the earliest.

MATERIALS AND METHODS

It was a hospital-based prospective analytical study conducted over a period of 2 years from June 2016 to May 2018 in a tertiary care teaching institution of north India. All pregnant women reporting to the outpatient department in the first trimester, who did not have any of the conditions mentioned in the exclusions, were included in the study. Women with multiple pregnancies, chronic hypertension and chronic renal disease, pregnancy complicated by previous history of diabetes type 1 and type 2, TORCH infection, Rh-negative women, pregnant women whose first visit was in labor with no previous investigations of thyroid status, and known hyperthyroid pregnant women were excluded from the study.

Pregnant women, who fulfilled the criteria, were recruited in the study after taking written consent. A detailed history was taken and thorough examination was done. Serum TSH level of >2.5 μIU/L in the first trimester was considered as hypothyroidism and these patients were categorized as "Cases" and further investigated with free T4 and anti-TPO antibody. Women with TSH level <2.5 μIU/L were considered normal (euthyroid) and were categorized as "Controls." Cases and controls were taken in the ratio of 1:1. The anti-TPO test was done by IMTEC - TPO ELISA test kit - Human Diagnosis, Germany, and read on ROBONIK ELISA analyzer. Interpretation was as follows: Negative (<14.5 IU/ml), equivocal (14.5–35.5 IU/ml), or positive (>35.5 IU/ml).

All hypothyroid women were followed up for maternal and baby well-being. Baby weight at birth and 1- and 5-min Apgar was taken. The babies, born to these women, were tested on day 3 of life, for hypothyroidism, by serum TSH levels. This was repeated at 1 month of age, if indicated. Serum bilirubin was done, if clinically jaundice was noted. The data were analyzed using Chi-square test and p values were calculated. Relative risk with 95% confidence interval (CI) was also calculated. p≤0.05 was considered as statistically significant.

RESULTS

A total of 309 women were included in the study; of which, 159 hypothyroid women were categorized as "Cases" and 150 euthyroid women were taken as "Controls." Three groups were demographically comparable as seen in Table 1. Of 309 cases, 19 women had positive anti-TPO test and remaining had negative results. Demographic profile of the cases and controls is presented in Table 1.

The incidences of fetal and neonatal complications in the various groups are given in Table 2. These were analyzed in 278 women after subtracting the number of women who had IUD (22 women) and those who aborted (9 women), including 142 women in control and 136 women in the hypothyroid group. Of the hypothyroid women, n=15 in the anti-TPO-positive groups and n=121 in the anti-TPO-negative group.

According to our results, the incidence of meconium-stained liquor and intrauterine growth retardation (IUGR) was not significantly different between cases and controls and also between anti-TPO positive and negative women. The number of babies requiring neonatal intensive care unit (NICU) admission for various reasons was more in the hypothyroid group as compared to that in the control group (RR 1.8; CI 1.18–2.7, p=0.004). The incidence of low or very low birth weight was more in cases than in the control group (50% vs. 26.05%), which was statistically significant (p=0.0003, RR 1.92; CI 1.39–2.65). However, this difference not statistically significant between anti-TPO positive and negative women (RR 1.39 CI 0.93–2.08). Similarly, neonatal deaths were significantly more in cases than in the control group (p=0.007, RR 4.88 CI 1.42–16.74); however, there was no difference between anti-TPO positive and negative groups.

In our study, 16 (5.18%) neonates had different congenital anomalies with an incidence of 7.54% in cases as compared to 2.66% in the control group (RR 2.83; CI 0.93–8.5). However, it was not significant between anti-TPO positive and negative groups (Table 3). The incidence of intrauterine death (IUD) was also more in cases than in controls (p=0.038, RR 2.51; CI 1.01–6.25).

Out of the babies of 159 hypothyroid mothers, serum TSH levels on the day of life 3 could be done for 137, and out of them, 6 (4.37%) babies were hypothyroid requiring further evaluation (p=0.045, RR 3.68; CI 0.72–18.77) as shown in Table 4.

DISCUSSION

Hypothyroidism in pregnancy has been shown to be associated with NICU admission and lower intelligence scores [12,5].

Table 1: Demographic profile of the study population

Demographic character	Groups		
	Control	Anti-TPO positive	Anti-TPO negative
Age (years)	150	19	140
18–20	2	1	5
21–30	134	11	114
31–40	14	7	21
Mean age (years)	25.87±3.56	29.26±4.71	26.34±4.35
Parity			
Primigravida	55	4	35
Multigravida	92	14	103
Grand multipara	3	1	2
Mode of delivery			
Abortion	2	0	9
LSCS	47	4	102
Vaginal	101	15	198

TPO: Thyroid peroxidase

Table 2: Various fetal complications in different groups

Fetal effects	Control (%)	Cases			Total (%)	p value	
		Anti-TPO positive (%)	Anti-TPO negative (%)	Total cases (%)		Control versus cases	Anti-TPO +ve versus -ve
Number	142	15	121	136	278	-	-
Meconium	16 (11.26)	1 (6.67)	15 (12.39)	16 (11.76)	32 (11.51)	0.896	0.515
NICU admission	26 (18.3)	4 (26.67)	41 (33.89)	45 (33.09)	71 (25.54)	0.004	0.575
Jaundice	18 (12.6)	2 (13.34)	27 (22.31)	29 (21.32)	47 (16.9)	0.027	0.423
IUGR	6 (4.22)	2 (13.34)	9 (7.43)	11 (8.09)	17 (6.11)	0.180	0.429
LBW/VLBW	37 (26.05)	10 (66.67)	58 (47.93)	68 (50)	105 (37.76)	0.0003	0.170
Neonatal death	3 (2.11)	1 (6.67)	12 (9.91)	13 (9.55)	16 (5.75)	0.007	0.689

TPO: Thyroid peroxidase, IUGR: Intrauterine growth retardation, NICU: Neonatal intensive care unit, LBW/VLBW: Low birth weight/very low birth weight

Table 3: Various fetal complications in different groups

Fetal effects	Control	Cases			Total	p value	
		Anti-TPO positive	Anti-TPO negative	Total cases		Control versus cases	Anti-TPO +ve versus −ve
Number	150	19	140	159	309	-	-
Congenital anomaly	4 (2.66)	2 (10.52)	10 (7.14)	12 (7.54)	16 (5.18)	0.026	0.603
IUD	6 (4.00)	4 (21.05)	12 (9.02)	16 (10.06)	22 (7.12)	0.038	0.044

TPO: Thyroid peroxidase, IUD: Intrauterine death

Table 4: Distribution of hypothyroid babies in various groups

	Anti-TPO positive	Anti-TPO negative	Total hypothyroid mothers	p value
Number of mothers	19	140	159	
TSH done on day 3 (%)	16 (84.21)	121 (86.43)	137	0.729
Hypothyroid babies (%)	2 (12.5)	4 (3.30)	6 (4.37)	0.045

TSH: Thyroid-stimulating hormone, TPO: Thyroid peroxidase

In our study, the incidence of NICU admissions was more in the hypothyroid group as compared to the euthyroid group (33.09% vs. 18.3%; p=0.004), but anti-TPO positivity was not an independent risk factor for the same.

In our study, the incidence of low birth weight (LBW) was found to be significantly more in the hypothyroid mothers (50% vs. 26.05%; p=0.0003). Anti-TPO-positive mothers did have more LBW infants as compared to anti-TPO-negative mothers (66.67% vs. 47.93%), but it was not statistically significant. Hence, hypothyroidism predisposes the babies to LBW, but the risk is not increased with anti-TPO positivity. In a study was done by Shameel *et al*. [13], the incidence of LBW babies was more in the uncontrolled hypothyroid group (p<0.005). Nazarpour *et al*. [14] have also reported a higher incidence of LBW in mothers with clinical hypothyroidism. Chen *et al*. [15]reported a significant association between subclinical hypothyroidism and the risk of having an LBW baby (p<0.001).

In our study, another significant association was with neonatal death (9.55% in hypothyroid mothers vs. 2.11% in the controls, p=0.007). Anti-TPO positivity did not have any added risk for neonatal death. We also found that the risk of IUD was more in the hypothyroid mothers as compared to euthyroid mothers (10.06% vs. 4%; p=0.038). Anti-TPO-positive mothers had an even greater risk of IUD. Hence, both hypothyroidism and anti-TPO positivity raise the risk of IUD. We found that 5.18% of women had babies with various congenital anomalies such as renal agenesis, congenital talipes equinovarus, anencephaly, and gastroschisis. The incidence was more in the hypothyroid women (7.54% vs. 2.66%; p=0.026); however, anti-TPO positivity did not have an increased risk. The risk of stillbirth and congenital malformation was not found to be increased in women with subclinical hypothyroidism in a study by Chen *et al*. [15].

In our study, hypothyroidism in the babies was also looked for and screening was done by checking day 3 TSH in all the babies of hypothyroid mothers. A total of 4.37% of the babies had a raised TSH which needed further evaluation. Anti-TPO-positive mothers had 12.5% of babies with raised TSH as compared to 3.30% in the anti-TPO-negative group (p=0.045). Hence, anti-TPO positivity was a risk factor for hypothyroidism in the newborn which could be congenital hypothyroidism. Hence, we suggest that all women with hypothyroidism should have their babies screened with TSH levels, and even more so if the mother is anti-TPO positive. Rovelli *et al*. [4] conducted a study on 129 neonates of mothers with autoimmune thyroiditis and found that transient mild elevation of serum TSH above the normal reference value for age is frequently observed in the 1st month of life in these infants. Persistent hyperthyrotropinemia requiring replacement therapy was observed in 2.2% of these neonates.

Hypothyroidism is significantly associated with an increased risk of IUD, NICU admissions, neonatal jaundice, LBW,

congenital anomalies, and neonatal deaths. Hypothyroidism may be associated with an increased risk of IUGR, although it was non-significant. Anti-TPO positivity may be associated with IUGR, LBW, and congenital anomaly, but they were not statistically significant in our study. We recommend all hypothyroid women should be tested for the presence of anti-TPO antibodies.

Strength of the study was that antenatal data were also available and babies were followed up from fetal till neonatal period. Hence, we knew about the effects of hypothyroidism right from conception till delivery and even later. Limitation of our study was a small sample size and no anti-TPO testing done for the babies. However, studies with a larger sample size are needed to confirm our findings and provide further evidence of the importance of anti-TPO positivity in pregnancy and its effects on the newborns.

CONCLUSIONS

We found that anti-TPO positivity is significantly associated with increased risk IUD and hypothyroidism in the newborn of the hypothyroid mother. Hence, screening with serum TSH is recommended in all babies of hypothyroid women.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Gupta T, Mani P, Gupta A, Yadav L. Neonatal and fetal effects of antithyroid peroxidase positivity in hypothyroidism in pregnancy - A hospital-based prospective analytical study. Indian J Child Health. 2019; 6(2):79-82.

Doi: 10.32677/IJCH.2019.v06.i02.007