International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Roy S et al. Int J Reprod Contracept Obstet Gynecol. 2022 Aug;11(8):2236-2241
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20221944

Original Research Article

Pregnancy outcome in anti-thyroid peroxidase antibody negative subclinical hypothyroid women with and without treatment

Sagarika Roy[1], Babita Saha[2]*, Sajal Datta[2]

[1]Department of Obstetrics and Gynaecology, Kakdwip Superspeciality Hospital, Kolkata, West Bengal, India
[2]Department of Obstetrics and Gynaecology, Vivekananda Institute of Medical Sciences, Ramakrishna Mission Seva Pratishthan, Kolkata, West Bengal, India

Received: 25 June 2022
Accepted: 20 July 2022

***Correspondence:**
Dr. Babita Saha,
E-mail: babita.cmc@gmail.com

ABSTRACT

Background: There is insufficient evidence in the literature whether pregnancy with anti-thyroid peroxidase antibody negative subclinical hypothyroidism is benefited with treatment.
Methods: The 100 uncomplicated primigravida women before 16 weeks of gestation who were diagnosed as anti thyroid peroxidase antibody negative and subclinical hypothyroid based on serum thyroid stimulating hormone (TSH), Free T4 (FT4) and anti-thyroid peroxidase antibody (anti TPO Ab) were enrolled in this study. They were divided into case and control group having 50 patients in each arm. Case group were treated with levothyroxine therapy as per the recommended dose. Maternal and perinatal outcome were compared between the two groups.
Results: In our study we had found increased percentage of cases of antepartum hemorrhage (APH), pregnancy induced hypertension (PIH), pre-labour rupture of membrane (PROM), preterm delivery, meconium-stained liquor, intrauterine growth restriction (IUGR), low birth weight (LBW), APGAR score at 1 and 5 minutes, neonatal hyperbilirubinemia and NICU admission among women who were not treated but it was not statistically significant when compared with control group.
Conclusions: When compared between the treated and non-treated group in anti TPO Ab negative subclinical hypothyroid patients, we didn't find any significant difference in parameters studied by us. In view of inadequate literature, controversy exists whether to treat or not anti TPO negative subclinical hypothyroidism in pregnancy with levothyroxine.

Keywords: Subclinical hypothyroid, Anti thyroid peroxidase antibody, Levothyroxine

INTRODUCTION

Thyroid function undergoes immense changes during pregnancy. Hypothyroidism is common in pregnancy with an estimated prevalence of 2-3% for subclinical and 0.3-0.5% for overt hypothyroidism.[1]

A transient fall has been noted in TSH during first trimester in pregnancy because of structural homology between TSH and human chorionic gonadotrophin (hCG) molecules and their receptors allowing hCG stimulation of the thyroid gland resulting in a rise in thyroid hormone. The rise of thyroid hormone during pregnancy is partly due to high estrogenic impact on this gland as well as due to weak thyroid stimulating effect of hCG that acts like the TSH.

As high as 10-20% of women during pregnancy in their first trimester are found to have thyroid peroxidase (TPO) or thyroglobulin (Tg) antibody positive and also euthyroid.

Among these women, 16% will develop a high TSH level beyond 4.0 mIU/L during 3rd trimester and another 33%-50% will develop postpartum thyroiditis.[2]

It has been noted that presence of thyroid antibodies is not always responsible for thyroid dysfunction but has been found to be responsible for different poor outcome and makes the pregnancy high risk.[3]

In literature a term 'subclinical hypothyroidism' has been defined in condition when serum TSH is found to be high and free T4 remains within normal limits.[2] A lot of controversies noted on actual reference value of TSH to diagnose subclinical hypothyroidism.

According to ATA (american thyroid association) guideline 2011 trimester specific range of serum TSH are as follows:[2] 1st trimester-0.1-2.5 mIU/L, 2nd trimester-0.2-3 mIU/L, 3rd trimester-0.3 -3 mIU/L.

When maternal TSH is elevated, measurement of serum FT4 concentration is necessary to classify the patient's status as either subclinical (SCH) or overt hypothyroidism (OH).[2]

During pregnancy, subclinical hypothyroidism is defined according to the 2017 ATA guidelines, with a TSH range between 4.01 to 9.99 mU/L & normal FT4 level and overt hypothyroidism was defined as TSH of 10 mU/L or higher.[4]

During the last decades it has also been noted that subclinical hypothyroidism has an adverse effect on pregnancy.[5]

Perinatal outcome has been found to be adversely affected in both hyper and hypothyroidism states of pregnancy. Maternal hypothyroidism has been associated with adverse obstetrical outcome, such as spontaneous abortion, gestational hypertension, premature delivery.[6]

There is threefold increase risk of placental abruption and two-fold increase risk of preterm delivery (before 34 weeks of gestation) noted in both overt and subclinical hypothyroidism.[6]

Preeclampsia, eclampsia and pregnancy induced hypertension have significantly higher incidence in SCH (15%) in comparison with the incidence in general population (7.6%).[6]

Risk of developing gestational diabetes increases with increase of thyrotropin (TSH) level.[7]

The complications of pregnancies did not depend on whether the hypothyroidism was overt or subclinical but mainly on the treatment received. The adequate treatment of hypothyroidism during gestation minimizes risks and generally, makes it possible for pregnancies to be carried to term without complications.[8]

Women with SCH and thyroid auto immunity (TAI) are at an increased risk of miscarriage between four and eight gestational weeks. Pregnant women who were found to have SCH and TAI carry the highest risk of miscarriage in early part of pregnancy.

There are numerous data suggesting SCH increases the risk of pregnancy complications in anti-thyroid peroxidase antibody positive (TPOAb+) women.[9]

The risk of foetal loss was higher in women with high TSH (5.2 to 10 mIU/L) as compared to women who had normal TSH (risk of foetal loss 7.2% vs 2.2%). This risk was highest in women who were anti TPO antibody positive (15.2%).[9]

The prevalence of SCH in South East Asia especially in India is more than other parts of the world. So, keeping in mind the adverse effect of SCH on both mother and foetus, all pregnant women in the first trimester should be screened by doing TSH and FT4 followed by antithyroid antibody for diagnosis.[1]

Due to lack of randomised controlled trials there is insufficient evidence to recommend for or against universal LT4 treatment in TPO negative pregnant women with SCH.[2]

But in developing country like INDIA with low resources, estimation of antithyroid antibody is not always possible. This is not only because of cost but also due to lack of standard laboratories to estimate qualitative and quantitative assay of anti-thyroid antibody.

There are studies which have shown clinical correlation between TSH and FT4 assay with pregnancy outcome not taking in consideration of antithyroid antibody estimation.[10]

The endocrine society recommends therapy in all pregnant women presenting with SCH, irrespective of autoimmunity status (either TPOAb positive or TPOAb negative) whereas the American Thyroid Association (ATA) supports treatment only for a specific subgroup of women with SCH who are TPOAb positive (SCH-TPOAb+).[2]

In this study we have tried to compare any difference in maternal and perinatal outcome with or without treatment with levothyroxin in subclinical hypothyroid pregnant women with antithyroid peroxidase antibody negative status.

METHODS

Prospective interventional study for a period of 1 year (Jan-Dec, 2017) was conducted at VIMS, RKMSP, KOLKATA in the department of Gynaecology and Obstetrics.

Primigravida mothers with singleton pregnancy without any medical and surgical complications and booked by 16 weeks were subjected to assess serum TSH, FT4 and Anti thyroid peroxidase antibody at their 1st visit.

The 100 pregnant mothers who had subclinical hypothyroidism and were negative for antithyroid peroxidase antibody were enrolled for the study after their informed consent. These 100 mothers were divided into two groups.

Case group included 50 mothers who were treated with levothyroxine, control group included 50 mothers who were not treated with levothyroxine

Blood samples were collected again in both case and control group at the second trimester (20 to 24 weeks of gestation), and third trimester (30 of 34 weeks of gestation) to measure serum levels of TSH.

We have used levothyroxine dose according to TSH level, TSH-2.5 to 5 mIU/L treated with levothyroxine 50 µg/day, TSH-5 to 8 mIU/L treated with levothyroxine 75 µg/day and TSH->8 mIU/L treated with levothyroxine 100 µg/day.[11]

All study participants received standard prenatal care at regular intervals as recommended by prenatal guidelines and were followed up until delivery and also after delivery till their hospital stay.[12] Newborns were also followed up till their hospital stay. Adverse pregnancy outcomes were managed according to standard guidelines.

Statistical analysis

We used Epi Info (TM) 7.2.2.2 to perform the statistical analysis in our study. This is a trademark of the centers for disease control and prevention (CDC). Using this software, basic cross-tabulation and frequency distributions were prepared. Chi-square (χ^2) test was used to test the association between different study variables. To find out the significant difference between two proportions, we used Z-test (Test of proportion). T-test was used to test the significant difference between means. P<0.05 was considered statistically significant.

Row percentage

Total percentage of women in relation to study parameter in both the groups.

Column percentage

Total percentage of women in one study group.

RESULTS

t-test showed that there was no significant difference in mean age of the women of the two groups (t_{98} =0.206; p=0.837) (Table 1).

T test showed that there was no significant difference in mean BMI of the women of the two groups (t_{98}=0.701; p=0.485) (Table 2).

Table 1: Age distribution among the women of 2 groups, (n=50).

Age group (Years)	With treatment	Without treatment	Total
<20	3	2	5
Row%	60.0	40.0	100.0
Col%	6.0	4.0	5.0
20-24	21	25	46
Row%	45.7	54.3	100.0
Col%	42.0	50.0	46.0
25-29	20	20	40
Row%	50.0	50.0	100.0
Col%	40.0	40.0	40.0
30-34	6	3	9
Row%	66.7	33.3	100.0
Col%	12.0	6.0	9.0
Total	50	50	100
Row%	50.0	50.0	100.0
Col%	100.0	100.0	100.0
Mean ± SD	24.58±3.48	24.44±3.30	
Median	25.0	23.5	
Range	19-31	19-32	

Table 2: Distribution of BMI among women of 2 groups, (n=50).

BMI (kg/m^2)	With treatment	Without treatment	Total
Normal	25	21	46
Row%	54.3	45.7	100.0
Col%	50.0	42.0	46.0
Overweight	18	23	41
Row%	43.9	56.1	100.0
Col%	36.0	46.0	41.0
Obese	7	6	13
Row%	53.8	46.2	100.0
Col%	14.0	12.0	13.0
Total	50	50	100
Row%	50.0	50.0	100.0
Col%	100.0	100.0	100.0
Mean ± SD	25.50±3.48	25.98±3.36	
Median	25.10	26.2	
Range	19.2 - 31.6	20.2 - 31.9	

Thus, the women of the two groups were comparable in respect of their age and BMI.

T test showed that the mean level of TSH at 1st visit was significantly higher among the patients in case group than that of the patients in control group (t98=2.57; p<0.001). T test showed that the mean level of TSH at 2nd and 3rdtrimester of the patients without treatment were significantly higher than that of the patients with treatment (p<0.001) (Table 3).

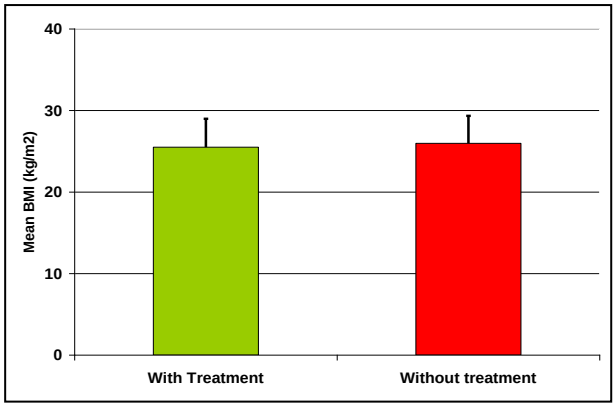

Figure 1: BMI of the women in case (with treatment) and control (without treatment) group.

Table 3: Comparison of different TSH values of the women of two groups according to trimester, (n=50).

Different parameters	Case	Control	T test, (t_{98})	P value
Level of TSH at booking (up-to 16 weeks)				
Mean ± SD	5.22± 1.23	4.68± 0.83	2.57	<0.001*
Median	5.20	4.7		
Range	3.2-7.8	3.1-6.8		
Level of TSH at 20-24 weeks				
Mean ± SD	3.01± 1.09	4.77± 1.08	8.11	<0.001*
Median	2.80	4.9		
Range	1.7-6.5	2.3-6.8		
Level of TSH at 30-34 weeks				
Mean ± SD	2.53± 0.89	4.89± 1.19	11.2	<0.001*
Median	2.55	5.15		
Range	1.1-4.9	1.3-6.9		

*Statistically significant

In both the groups, proportion of women with abortion (6.0%) was equal. Proportion of women with APH among the women without treatment (4.0%) was higher than that of the women with treatment (2.0%) but it was not significant (Z=0.82; p>0.05). Proportion of women with PIH among the women without treatment (8.0%) was higher than that of the women with treatment (1.0%) but it was not significant (Z=1.94; p>0.05). Percentage of women with GDM among the women without treatment (8.0%) was lower than that of the women with treatment (14.0%) but it was not significant (Z=1.35; p>0.05). We found no significant association in respect to PROM among women of two groups (p=0.72). Similar findings were also found when we compared the colour of liquor between the two groups at time of delivery (Z=0.55; p>0.05). We have not found any significant difference in gestational age at time of delivery between the two groups (Table 4).

Applying Chi-square test no significant association was found regarding mode of delivery among women of the two groups (p=0.53). The percentage of IUGR babies were 10% in control group when compared with case group (4%) but it was not significant (Z=1.66; p>0.05). The percentage of LBW babies was more in non-treatment group (12%) when compared with treatment group (4%). This observation was not statistically significant. There was no significant association between APGAR score at 1 minute and 5 minutes among the neonates of two groups. Proportion of the neonates of the women with hyperbilirubinemia among the women without treatment (22.0%) was higher than that of the neonates of the women with treatment (12.0%) but it was not significant (Z=1.88; p>0.05). NICU admission was higher (24%) in non-treatment group when compared with treatment group (14%) but it was not statistically significant (Table 5).

Table 4: Comparison about pregnancy outcome in between women of case and control group, (n=50).

Pregnancy outcome	With treatment	Without treatment	P value
Abortion	3	3	0.99
APH	1	2	0.55
PIH	1	4	0.16
GDM	7	4	0.33
PROM	4	5	0.72
Meconium-stained liquor	3	4	0.69
LSCS	18	21	0.53
Abnormal CTG	5	7	0.53
Preterm	4	5	0.64

Table 5: Comparison of neonatal outcome among case and control group, (n=50).

Neonatal outcome	With treatment	Without treatment	P value
Low birth weight	2	6	0.14
Low APGAR score (<7) at 1 minute	5	11	0.130
Low APGAR score (<7) at 5 minutes	2	5	0.23
Hyperbilirubi-nemia	6	11	0.18
NICU admission	7	12	0.20
Neonatal death	0	0	0

DISCUSSION

There are very few studies which showed effect of LT4 therapy on anti TPO Ab negative SCH pregnant woman. In our study, we found significant lowering of TSH level below target reference range for each trimester after treatment with LT4 than women without treatment. In the literature we have found that there is wide variation of results while comparing both groups of SCH. In our study we have not found any significant differences when we

analysed antenatal and perinatal outcome of both groups of anti-TPO antibody negative SCH with and without treatment.

In a study by Maraka et al the abortion rate, APH, PIH, GDM, PROM, congenital anomaly and NICU admission rate were found to be non-significant in both the group which also has been observed in our study but they found that LBW and low APGAR score at 5 min much higher among women without treatment group when compared to treatment group which did not support our study.[8]

Another study done by Nazarpour et al in SCH with anti-TPO Ab negative women, a significant lowering of preterm delivery observed in LT4 treated group in comparison to non-treated group.[12] This observation is in contradiction to our study. But they found that there is no statistically significant association between LBW and LT4 therapy among anti-TPO negative SCH women which supports our study. Another study done by Blumenthal et al showed that there was no significant difference of abortion rate, C section rate, IUFD and APGAR score at 1 and 5 minutes among the two groups which is also supported in our study.[13]

Limitations

Major limitation of our study is small sample size. More studies with large sample size are needed in future to conclude whether LT4 therapy should be used routinely in all SCH pregnant woman. The effect of LT4 therapy on the newborn in their later life needs to be followed up in respect of IQ and neurodevelopment.

CONCLUSION

There are very few studies which showed effect of levothyroxine therapy among anti TPO Ab negative subclinical hypothyroid pregnant women. This prospective observational study showed that though there is significant lowering of TSH level seen after treatment with levothyroxine therapy but there is no statistically significant outcome difference for both mother and baby, when we compare with a group not received levothyroxine treatment. So, to reach any conclusion whether levothyroxine treatment should be given or not to a pregnant woman with anti TPO Ab negative subclinical hypothyroid status, we need a multicentric high quality randomized control trial with a large sample.

ACKNOWLEDGEMENTS

I will remain acknowledged to my guide, co-guide, my colleagues and institutional head for guiding and helping me enormously while conducting my thesis under west Bengal university of health sciences.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Roy S, Saha B, Datta S. Pregnancy outcome in anti-thyroid peroxidase antibody negative subclinical hypothyroid women with and without treatment. Int J Reprod Contracept Obstet Gynecol 2022;11:2236-41.