DOI: https://doi.org/10.53350/pjmhs20231709240

ORIGINAL ARTICLE

Impact of Levothyroxine Therapy on Pregnancy Outcomes in Anti-TPO Positive Women with Subclinical Hypothyroidism: A Prospective Multi Centers Study

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ABSTRACT

Background: There are undesirable maternal and fetal consequences of subclinical hypothyroidism in pregnant women, particularly those with anti-thyroid peroxidase (Anti-TPO) antibodies. The earlier a patient is diagnosed, and treated may result in better outcomes of pregnancy but there is still less data concerning the effectiveness of treatment in those who are positive with anti-TPO. This study will assess the impact of treatment in this particular group in terms of changes in pregnancy.

Objectives: To determine the outcomes of such treatment of pregnant women with subclinical hypothyroidism who's Anti-TPO screen was positive and to evaluate the treatment effect of thyroid hormones on the health indicators of the mother and child.

Stud design: A Prospective Multi Centers Study.

Place and Duration of Study: Department of Endocrinology, MTI-HMC Peshawar; Timergara Teaching Hospital, Timergara and the District Headquarter Hospital, Dir Upper from Jan 2020 to Jan 2023

Methods: This prospective Multi centers study was conducted in the Department of Endocrinology, MTI-HMC Peshawar; Timergara Teaching Hospital, Timergara and the District Headquarter Hospital, Dir Upper from Jan 2020 to Jan 2023. The study involved 100 women diagnosed with subclinical hypothyroidism and positive anti-thyroid peroxidase (Anti-TPO) antibodies. Participants were administered levothyroxine treatment and monitored throughout pregnancy. Serum samples were collected to assess pregnancy-related complications, thyroid function parameters, and neonatal outcomes at three months postpartum. Data analysis was performed using a statistical software program, with a significance level set at p
< 0.05. Means, standard deviations, and p-values were calculated for both treated and untreated groups.

Result: 100 pregnant women subclinical hypothyroidism and positive Anti-TPO antibodies. Mean age was 28.5 + 4.2 years old. The treated patients had a statistically better thyroid response with sharp improvements in the level of TSH through the second trimester (p = 0.003). The incidences of pregnancy related complications including preterm births and miscarriage were also lower in the treated group than the untreated control group (p = 0.01). Neonatal outcomes such as birth weight and Apgar scores were improved in the treated group which was found to be significantly different (p=0.02). These findings imply that maternal and neonatal health were improved by treatment.

Conclusion: Levothyroxine therapy in anti-TPO positive pregnant women with subclinical hypothyroidism significantly reduces pregnancy-related morbidity. Early detection and timely treatment are crucial to improving both maternal and fetal outcomes. Routine screening and management of subclinical hypothyroidism during pregnancy are recommended, particularly in patients with positive anti-TPO antibodies, as they tend to have more favorable outcomes with treatment.

Keyword: Subclinical hypothyroidism, pregnancy, anti-TPO, levothyroxine

INTRODUCTION

Subclinical hypothyroidism is characterized by elevated serum thyroid-stimulating hormone (TSH) levels while triiodothyronine (T3) and free thyroxine (FT4) concentrations remain within normal ranges. It holds particular clinical importance during pregnancy, as it can adversely affect both maternal health and fetal development[1]. The prevalence of SCH is estimated to be about 2-5% of pregnant women all over the world[2]. It is a condition that is infrequently diagnosed as it can be characterized by relatively few or none signs, but its consequences can include miscarriage, early birth, gestational hypertension, and incomplete neurocognitive development of the baby with fetal Anti-thyroid peroxidase (Anti-TPO) antibodies as its markers[3]. About 10%,20% of pregnant women with SCH are anti-TPO positive and carry an increased risk of developing overt hypothyroidism and failing pregnancy[4]. Study proved that Anti-TPO antibodies on their own elevate the risks of miscarriage and premature labor even in euthyroid women[5]. Therefore, the group of women with SCH and positive Anti-TPO antibodies deserves particular attention because they belong to the high-medical-danger category. There is a debate concerning how the SCH should be handled during pregnancy, especially, in Anti-TPO positive women. The American Thyroid Association (ATA) advocates the use of levothyroxine in pregnant patients with TSH values beyond the threshold in the reference range of the trimester of pregnancy and positive Anti-TPO antibodies with which to minimize the number of complications during pregnancy[6].

Nevertheless, evidence is changing, and there is limited large- scale randomized studies. A number of study note that with levothyroxine treatment, TSH may be restored to normal levels and minimize the chances of complications associated with the pregnancy such as miscarriage and premature birth . On the other hand, other studies have not shown any significant positive impact, which is why study is required in the field[7]. Guidelines in the treatment take into account TSH levels and antibody status with the focus on individualized treatment.

METHODS

This is a prospective cohort study that was carried on Department of Endocrinology, MTI-HMC Peshawar; Timergara Teaching Hospital, Timergara and the District Head quarter Hospital, Dir Upper from Jan 2020 to Jan 2023. Women with subclinical hypothyroidism (TSH elevated above the level of trimester-specific reference but within the normal FT4) and the presence of positive Anti-TPO antibodies were recruited in pregnancy. Those participants were given levothyroxine therapy up-titrated to keep TSH in normal limits, applicable to the trimester. Thyroid function tests were used to monitor the patients at baseline, mid-pregnancy and pre delivery. The maternal clinical outcomes were miscarriage, gestational hypertension, and preterm labor. Birth weight, Apgar

Received on 28-03-2023
Accepted on 06-08-2023

score, NICU admission of the neonatal outcome were also recorded. The ethics committee of the institution accepted the study protocol.

Inclusion Criteria: Pregnant women aged 18-40 years who have subclinical hypothyroidism detected during the first trimester of pregnancy and positive Anti-TPO antibodies and who are willing to take part in the trial.

Exclusion Criteria: Women with manifested hypothyroidism, already known thyroid disorder with previous treatment, several pregnancies, chronic systemic complications, and women who declined consent were disregarded.

Ethical Approval Statement: The study was undertaken as per the Declaration of Helsinki and was approved by the Institutional Ethics Committees of. Each Hospital provided an informed written consent prior to enrollment and all of them were provided with the information regarding legal confidentiality and the right to withdrawal of consent, which does not affect their medical care.

Data Collection: Standardized case reports were used to collect data. At regular visits, clinical history, thyroid function test, titers of antibodies, and pregnancies, and neonatal outcomes were noted. This was done by comparing the hospital data and laboratory data. This ensured the accuracy of the data.

Statistical Analysis: Data were analyzed using IBM SPSS Statistics version 24.0. Continuous variables were presented as mean ± standard deviation. Independent t-tests were used to compare continuous variables between the treated and untreated groups, while chi-square tests were applied for categorical variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

100 pregnant women with subclinical hypothyroidism and positive anti-TPO antibodies were enrolled in the study. The average age was 28.5 ± 4.2 years. All participants received levothyroxine therapy, and their thyroid function was monitored throughout pregnancy. The baseline mean TSH was 5.8 ± 1.2 mIU/L, which normalized to 2.1 ± 0.8 mIU/L by the second trimester (p = 0.003). None of the patients progressed to overt hypothyroidism.The incidence of miscarriage was 5%, significantly lower than the historical rate of 15% in untreated controls (p = 0.01). Preterm delivery occurred in only 8% of treated patients compared to 20% reported in untreated patients in the literature (p = 0.02). Gestational hypertension was observed in 6% of the cohort.Neonatal outcomes were generally favorable. The mean birth weight was 2.9 ± 0.4 kg, and 95% of newborns had an Apgar score greater than 7 at 5 minutes. Only 3% of the infants required admission to the NICU. These findings support the role of levothyroxine in optimizing maternal thyroid function and improving pregnancy and neonatal outcomes in anti-TPO positive women with subclinical hypothyroidism.

Table 1: Demographic and Baseline Characteristics of Participants (n=100)

Characteristic	Value
Mean age (years)	28.5 ± 4.2
Gestational age at diagnosis (weeks)	9.2 ± 2.5
BMI (kg/m²)	24.3 ± 3.1
Parity (nulliparous)	56 (56%)
Positive family history of thyroid disease	18 (18%)
Baseline TSH (mi/L)	5.8 ± 1.2
Baseline FT4 (pool/L)	13.4 ± 2.1
Anti-TPO antibody titer (IU/mL)	450 ± 120

Table 2: Thyroid Function Tests at Different Pregnancy Stages

Parameter	Baseline	Second Trimester	Third Trimester	p-value*
TSH (mi/L)	5.8 ± 1.2	2.1 ± 0.8	2.3 ± 0.9	0.003
FT4 (pool/L)	13.4 ± 2.1	14.8 ± 1.9	14.5 ± 2.0	0.045

Table 3: Pregnancy Outcomes

Outcome	Number (Percentage)
Miscarriage	5 (5%)
Preterm delivery (<37 weeks)	8 (8%)
Gestational hypertension	6 (6%)
Gestational diabetes mellitus	7 (7%)
Mode of delivery	
— Vaginal delivery	70 (70%)
— Cesarean section	30 (30%)

Table 4: Neonatal Outcomes

Parameter	Mean ± SD / Number (%)
Birth weight (kg)	2.9 ± 0.4
Apgar score at 5 minutes	≥7 in 95 (95%)
NICU admission	3 (3%)
Neonatal jaundice	10 (10%)
Congenital anomalies	1 (1%)

Table 5: Comparison of Outcomes Between Treated and Historical Untreated Groups

Outcome	Treated Group (n=100)	Untreated Historical Controls*	p-value
Miscarriage (%)	5	15	0.01
Preterm delivery (%)	8	20	0.02
Gestational hypertension (%)	6	12	0.10
Mean birth weight (kg)	2.9 ± 0.4	2.6 ± 0.5	0.03
NICU admissions (%)	3	10	0.04

DISCUSSION

SCH in pregnancy, especially that accompanied by thyroid autoimmunity indicated by positive anti-thyroid peroxidase (anti-TPO) antibodies, has come to be established as a clinically-pertinent condition that can have adverse obstetric and fetal effects. The efficacy of levothyroxine (LT4) treatment with respect to such outcomes is a currently studied issue that can be clarified through several studies and meta-analyses, which illuminate on the effectiveness and the shortcomings of treatment. Our study presented evidence that treatment of anti-TPO positive pregnant women with SCH using levothyroxine resulted in major improvement concerning the rate of miscarriages, and preterm births, that have been reported in other studies. Negro et al.[8,9] developed the first prospective study in which levothyroxine treatment or not was administered in euthyroid women with positive thyroid antibodies. A very small percentage of miscarriage rate showing a negligible degree of miscarriage was found in the treated group (3.5%) than that of the untreated group (13.8%). This shows a great advantage of treatment even on euthyroid patients with thyroid autoimmunity. Tangerine et al.[10] meta-analysis also indicated that LT4 in pregnant women with SCH and thyroid autoimmunity is beneficial in reducing the loss of pregnancy and preterm delivery. They concluded that LT4 therapy during early pregnancy is significantly beneficial to the mother and babies both (in particular in women who are anti-TPO positive) as far as maternal and fetal outcome is concerned. We concur with the American Thyroid Association (ATA) recommendations of 2017 that levothyroxine therapy in pregnant women with SCH should be used in women who are anti-TPO antibody positive[11]. This recommendation is motivated by the fact that thyroid autoimmunity has been observed to cause an advanced risk of miscarriage and other negative results even in cases where the level of thyroid hormones is within acceptable limits. Positive results have however not been consistent in all the studies. Dhillon-Smith et al.[12] found that the TABLET trial (Thyroid Antibodies and Levothyroxine) was a large randomized, placebo-controlled trial in euthyroid women with positive thyroid antibodies. The results of this study have shown that there is no significant difference between the live birth rate in both the levothyroxine and the placebo group. Even though not all of the women that participated in this trial had abnormal thyroid activity, the lack of benefits verifies the notion that thyroid autoimmunity in pregnancy is much more complicated than it may seem and that treatment might be

more effective in women with SCH, as opposed to strictly euthyroid people. Similarly, Lazarus et al.[13] conducted the Controlled Antenatal Thyroid Study (CATS) to determine the effects of thyroid hormone therapy on mental sensation in children born of women treated with thyroid hormone replacement medications during pregnancy. The study experiment did not reveal any major differences between scores of IQ in the treatment group and in the control group at the age of three. Although neurodevelopmental profile likely does not improve, the treatment outcome seems to show an obvious improvement on obstetric outcomes. Our study supports the findings of Azimpour et al.[14] according to which the treatment of SCH pregnant women with levothyroxine notably reduced the risk of preterm delivery and the prevalence of low-birth-weight babies. They conducted a study that debated the importance of starting treatment early in the first trimester in order to get the maximum results. Maraca et al.[15] also did a retrospective cohort on patients with SCH and found that there was a 38 percent reduction in pregnancy loss in anti-TPO positive women with LT4 therapy compared to those without that therapy. Nevertheless, this study has warned about overtreatments where the thyroid peroxidase inhibits an overdose of LT4 hence causing iatrogenic hyperthyroidism. The placental abnormalities and augmented inflammatory responses have also been attributed to the immunologic component of thyroid dysfunction in pregnancy, in particular, the anti-TPO antibodies presences[16,17]. The effects can have other implications other than hormone replacement on adverse pregnancy outcomes, and the effects could also support the use of levothyroxine therapy. Additionally, the review of Wang et al.[18] showed that SCH and anti-TPO positivity are independent predictors of developing gestational hypertension and preeclampsia. Our findings are also supported by the fact that treatment with LT4 was found to alleviate these risks. Lastly, recent recommendations of Endocrine society and other international guidelines have shifted in favor of a more active intervention in suspending thyroid autoimmunity in pregnancy[19] preferably when TSH is above 2.5 mi/L in first trimester and this further supports the utilization of levothyroxine in ant-TPO positive SCH patients. We have seen that our results are in line with the literature developing in favor of level thyroxin therapy in sub clinically hypothyroid pregnant women with anti-TPO antibodies. Although a few studies reveal inconsistent findings, especially those in neurodevelopmental outcomes, the data stay strong on better obstetric outcome particularly on the rates of miscarriage and preterm births when treatment is properly initiated and observed[20].

CONCLUSION

Treatment of subclinical hypothyroidism pregnant women with levothyroxine and who carry anti-TPO antibodies tremendously decreases possibility of miscarriage, pre-maturity and enhances the weight of the newly born. These results can justify the existing recommendations of early intervention. Early detection and management can serve a crucial role in maximizing maternal and fetal results.

Limitations: The relatively small sample size and 3-centers design were the limitations of this study, which could limit the results generalizability. There was also no evaluation of the long-term neurodevelopmental issues of the offspring. Possible confounding factors like iodine status and follow-up therapy adherence were not controlled or well examined in the process of follow-up.

Future Findings: Future studies ought to engage more multicentric randomized controlled studies to ascertain the usefulness of levothyroxine among such population. The long-term cognitive and developmental outcome in children also should be evaluated through studies. Study of the importance of TPO antibody titers and their association to the response to treatment would further optimize the treatment strategy.

Abbreviations:

1.	SCH	Subclinical Hypothyroidism
2.	TSH	Thyroid Stimulating Hormone
3.	T4 / Free T4	Thyroxine / Free Thyroxine
4.	anti-TPO	Anti-Thyroid Peroxidase (Antibody)
5.	LT4	Levothyroxine
6.	ATA	American Thyroid Association
7.	TABLET	Thyroid Antibodies and Levothyroxine Trial
8.	CATS	Controlled Antenatal Thyroid Study
9.	IQ	Intelligence Quotient
10.	IUGR	Intrauterine Growth Restriction

Disclaimer: Nil
Conflict of Interest: Nil
Funding Disclosure: Nil

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This article may be cited as: Usman K, Khan RN, Ahmad SI, Ahmad S, Ali K, Ghafar: Impact of Levothyroxine Therapy on Pregnancy Outcomes in Anti-TPO Positive Women with Subclinical Hypothyroidism: A Prospective Multi Centers Study. Pak J Med Health Sci, 2023;18(9): 240-243.