Original Article

# Pregnancy outcomes with thyroxine replacement for subclinical hypothyroidism: Role of thyroid autoimmunity

**Muthukrishnan Jayaraman, Abhyuday Verma, K. V. S. Harikumar, Meena Ugale[1], Kirtikumar Modi**

*Department of Endocrinology, Medwin Hospital, [1]Obstetrics, Kirloskar Hospital, Hyderabad, India*

## ABSTRACT

**Objective:** To study pregnancy outcomes in relation to thyroid peroxidase antibody (TPOAb) status with optimum thyroxine replacement for subclinical hypothyroidism. **Materials and Methods:** Ninety-eight women with subclinical hypothyroidism were followed up until the end of their pregnancy. TPO antibody status was performed for 59 women (positive 20, negative 39). Levothyroxine was supplemented to maintain TSH between 0.3-3 mIU/l in all patients, irrespective of TPOAb status. Pregnancy outcomes were noted as pregnancy-induced hypertension (PIH), antepartum or postpartum hemorrhage, preterm delivery, and spontaneous abortion. Outcomes were compared between 3 groups as per TPO antibody status (positive, negative, and undetermined), which were matched for age and gestational period. **Results:** Thyroid autoimmunity was noted in 34% of women screened for TPO antibody. A total of 11 adverse pregnancy outcomes were recorded (4 spontaneous abortions, 4 preterm deliveries, 3 PIH) with no significant difference between the groups. **Conclusion:** Adverse pregnancy outcomes were not different in the 3 groups with adequate thyroxine replacement for pregnant women with subclinical hypothyroidism targeting TSH in euthyroid range, irrespective of thyroid autoimmunity status.

**Key words:** Pregnancy, subclinical hypothyroidism, thyroid autoimmunity

## Introduction

Overt and subclinical hypothyroidism is known to predispose women to adverse pregnancy outcomes.[1-3] Thyroid autoimmunity with euthyroid status causes adverse pregnancy outcomes, possibly due to progressive thyroid dysfunction.[4] Thyroxine supplementation with a target TSH in recommended range should benefit pregnancy outcomes, irrespective of the thyroid autoimmunity status. Data regarding thyroid autoimmunity in pregnant Indian women and benefit of thyroxine supplementation is lacking at present.

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## Objective

To study pregnancy outcomes in relation to thyroid peroxidase antibody (TPOAb) status with optimum thyroxine replacement for subclinical hypothyroidism.

## Materials and Methods

This study was designed as an uncontrolled, prospective cohort study with thyroxine supplementation as the intervention. We included 109 pregnant women (gestation period <36 wks), referred to us with subclinical hypothyroidism (elevated TSH >5 mIU/l and normal free T4 by chemiluminiscence immunoassay) detected *de novo* in pregnancy, out of whom 98 were available for follow up until the end of their pregnancy. Where free T4 was not available, a value of total T4 up to 1.5 times upper limit of normal for non-pregnant state was taken as normal.[5] Their mean age and gestation period at inclusion in the study was 24.8 yrs and 17.6 wks, respectively. A detailed history including past

**Corresponding Author:** Dr. Muthukrishnan Jayaraman, Department of Endocrinology, Command Hospital, Chandimandir, Panchkula – 134 107, India. E-mail: jmuthukrishnan@hotmail.com

obstetric history was obtained. Goiter was graded as per modified WHO grading.[6] The gestation period was noted from last menstrual period as reported by the patient and confirmed by fetal ultrasound. Women with pre-existing hypothyroidism, non-thyroidal autoimmune diseases, hypertension, diabetes mellitus and any other condition contributing to adverse pregnancy outcome, noted initially or at any time during the study period, were excluded. All women on inclusion were advised TPOAb testing. TPOAb test reports as per method used (Hemagglutination assay reported as positive >1:1600 and chemiluminescence immunoassay reported as positive >75 IU/l) were recorded. TPO Ab testing was performed on 59 women (20 +ve and 39 –ve). The remaining 39 women with undetermined TPOAb status were also adequately treated with thyroxine and included for analysis. The past history of at least one spontaneous abortion and visible goiter was noted with greater frequency in TPOAb +ve women. Baseline characteristics are noted in Table 1. All these women were advised tablet levothyroxine with a starting dose based on their baseline TSH (TSH 3-5 mIU/l – 25 mcg, 5.1-15 mIU/l– 50 mcg). Serum TSH was repeated at 8 weeks interval, and the dose of levothyroxine was adjusted to target the TSH between 0.3 to 3 mIU/l. Pregnancy outcomes were recorded *via* self-reporting by the patient and from the obstetricians' notes as mode of delivery (normal delivery or cesarean section), preterm delivery (gestation <36 wks), or spontaneous abortion (gestation <28 wks). These adverse pregnancy outcomes were chosen based on existing knowledge in literature about increased predisposition with thyroid dysfunction to these outcomes.[7,8] Complications like gestational hypertension (persistent BP >130/80 mmHg or requiring anti-hypertensives or termination of pregnancy), ante-partum or postpartum hemorrhage requiring blood transfusion were recorded. All women who had at least one follow up visit with serum TSH in the target range (0.3-3.0 mIU/l), irrespective of whether TPOAb testing was done, were included for analysis. Three groups (TPOAb positive, negative, and status undetermined) were analyzed for pregnancy outcomes. Fisher's exact test to assess the significance of difference in frequency of adverse pregnancy outcomes, and paired T-test for comparison of means were applied. *P* value of less than 0.05 was taken as significant.

## Results

Mean age and gestation period at start of therapy were comparable in the 3 groups. Mean TSH was higher in TPOAb +ve women compared to the other two groups. A total of 11 adverse pregnancy outcomes were noted. Their frequency in each group was not statistically different [Table 2].

**Table 1: Baseline characteristics of the study population (*N*=98)***

| Parameter | TPOAb +ve (*n*=20) | TPOAb –ve (*n*=39) | TPOAb undetermined (*n*=39) |
|---|---|---|---|
| Age (yrs) Mean±SD | 25.9±4.1 | 25.8±3.1 | 24.2±3.5 |
| Gestation period (wks) Mean±SD | 16.1±2.6 | 17.6±1.7 | 16.8±1.9 |
| Past h/o of spontaneous abortions (No.) | 6 | 8 | 2 |
| Goiter present (No.) | 5 | 4 | 7 |
| TSH (mIU/l) Mean±SD | 5.82±3.1 | 4.37±2.4 | 4.65±1.9 |

**P*>0.05 for all values, TPOAB: Thyroid peroxidase antibody, TSH: Thyroid stimulating hormone

**Table 2: Mode of delivery, pregnancy outcomes, and adverse events noted in the studied**

| Pregnancy outcome | TPO Ab+ve (*n*=20) | TPO Ab–ve (*n*=39) | TPOAb undetermined (*n*=39) |
|---|---|---|---|
| Full term normal delivery | 8 | 7 | 12 |
| Caesarean section | 11 | 28 | 22 |
| Preterm delivery | 1 | 1 | 2 |
| Spontaneous abortion | 0 | 2 | 2 |
| Pregnancy induced Hypertension | 1 | 2 | 0 |
| Ante partum/ postpartum hemorrhage | 0 | 0 | 0 |

Cohort. (*N*=98) @; @ *P*>0.05 for all values, TPOAB: Thyroid peroxidase antibody

## Discussion

We studied the differences in adverse pregnancy outcomes between groups of women with or without thyroid autoimmunity after thyroxine supplementation. A third cohort of women in whom TPOAb testing was not done due to various reasons, but who received adequate thyroxine replacement was also included for analysis. These 3 groups were well-matched for their age and gestation period, at which thyroxine was started. No difference in the frequency of adverse pregnancy outcomes was noted between these groups.

Prevalence of autoimmune thyroid disease is increasing in young Indian women after the introduction of universal iodine supplementation.[9] Various studies show the prevalence of subclinical hypothyroidism in pregnant Indian women to vary from 2% to over 6% with thyroid autoimmunity being seen in about 60% of them. Prevalence of autoimmunity has been noted in 7% of euthyroid pregnant women.[10,11] Western data show similar prevalence of subclinical hypothyroidism with greater frequency of thyroid autoimmunity in them (near 100%).[12] Thyroid autoimmunity *per se* is known

to lead to adverse pregnancy outcomes, even with euthyroid status.[12] Progressive hypothyroidism during pregnancy in those with thyroid autoimmunity, despite baseline euthyroid status and TPOAb as a marker of generalized autoimmunity, is implicated in contributing to this adverse pregnancy outcome. Levothyroxine supplementation has been shown to mitigate this risk.[4] In India, TSH assays are widely available at an affordable cost with reliable results. However, the use of TPOAb assay is restrictive because of its high cost, poor availability, and as this test is infrequently done, its standardization and reliability is often questionable.

We hypothesized that adequately supplementing thyroxine and targeting optimum TSH levels should benefit pregnancy outcomes, irrespective of thyroid antibody status. Although a small single-center study, it highlights the greater prevalence of thyroid autoimmunity in pregnant Indian women with mild thyroid dysfunction (34%). A greater prevalence of goiter, worse thyroid function, and greater frequency of spontaneous abortions in those with TPOAb positivity is similar to earlier studies on this subject.[3] That there were no significant differences in adverse pregnancy outcomes in the present study amongst the 3 groups suggests the possible benefit of thyroxine supplementation, irrespective of thyroid autoantibody status. Based on this, we suggest the importance of a TSH- targeted approach during pregnancy. In a clinical practice setting, restricted by the cost, reliability, and availability of TPOAb testing, TSH alone may be sufficient for treatment during pregnancy. However, the relevance of TPOAb status in predicting postpartum thyroid dysfunction is undisputable although this issue was not addressed in this study.

Increased predisposition to adverse pregnancy outcomes and other events studied by us is a well-known association with hypothyroidism of any degree. This study adds to the existing knowledge on this subject from India.[11] In view of a large population of Indian women with hypothyroidism and its increasing prevalence following universal iodine supplementation, data from India has greater relevance. In addition, due to the benefits noted irrespective of the thyroid autoimmunity status, the findings of this study hint at a possible relevance even in settings where thyroid autoimmunity has not been assessed. This issue needs further assessment in a larger study.

Our study is limited by the low number of subjects and few adverse events which occurred in them, restricting the power of statistical analysis. Reporting bias in TPOAb-positive women may have contributed to the greater frequency of TPOAb positivity noted in our study. A larger study is intended for addressing this important issue and for strengthening our conclusions. Lack of a control population of untreated pregnant women with subclinical hypothyroidism due to ethical reasons restricts the strength of this study in concluding definitively regarding the benefit of thyroxine supplementation. However, few adverse pregnancy events in the cohorts studied, which is below the known frequency of these events in general population, suggests the benefit. A subset of women, although compliant with thyroxine, did not get their TPOAb testing done due to various reasons. Although a limitation in an experimental setting, it highlights the practical problem in clinical practice and thus demonstrates the relevance of our findings in this setting. Screening for thyroid dysfunction and autoimmunity in pregnancy is recommended only in high-risk women.[5] In Indian setting, cost concerns, lack of well-standardized testing centers for thyroid function and antibodies, and scarce data in local population makes the case for universal screening even less strong. However, in view of a large number of women affected by this disorder, we must continue to aggressively screen high-risk pregnant women to improve perinatal health.

In conclusion, we emphasize the need for the screening of pregnant women with TSH, as per existing guidelines, and an aggressive treatment approach targeting TSH in the euthyroid range for optimum benefits, irrespective of the thyroid autoimmunity status.

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