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POSTPARTUM THYROID DYSFUNCTION; CLINICAL VALUATION AND PROPHETIC INFLUENCE OF TPOAB AND PSYCHIATRIC AFFECTIVE ILLNESS

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ABSTRACT
Postpartum thyroid dysfunction (PPTD) occurs in 5-7 % of women, with hypothyroidism developing in 25 % of these after 3–6 yr. Authors have determined the prophetic implication of thyroid peroxidase antibody (TPOAb), human leukocyte antigen haplotype, and postpartum thyroid status on the development of thyroid dysfunction 77–81 months after PPTD. Thyroid dysfunction occurred in 46% of group 1 vs. 4% of group 2 (P, 0.001) and 24.5% of groups 1 and 2 vs. 1.4% of group 3 (P, 0.001). Factors predictive of thyroid dysfunction included a hypothyroid form of PPTD, TSH more than 20 mU/L, and higher TPOAb levels (213.8 kIU/L in group 1 vs. 131.8 kIU/L in group 2; P, 0.002) during the postpartum period. Although TPOAb was higher in group 1 than in group 2 at follow-up (166 vs. 97.7 kIU/L; P, 0.03), there was no significant fall in TPOAb levels within either group during the period of follow-up. Human leukocyte antigen DR10 was lower in those who developed late thyroid dysfunction. These data, representing the longest follow-up of PPTD women, clearly show that the hypothyroid form of PPTD and high TPOAb levels of long term thyroid dysfunction. This compares with a relative risk of 12.9 for TPOAb- and PPTD-positive women, who remained euthyroid at the end of the first postpartum year, and 2.8 for TPOAb-positive but PPTD-negative women, all compared to TPOAb-negative women.

1. INTRODUCTION

The thyroid is a butterfly-shaped gland at the front of the oesophagus/throat that produces thyroid hormone.[1-3] Thyroid hormone helps the body to make energy, keeps body temperature regulated and assists other organs in their functions. Hypothyroidism (a deficiency of thyroid hormone) is a relatively common illness that can cause fatigue, constipation, muscle cramps and weakness, hair loss, dry skin, intolerance to cold, depression and weight gain.[4-7] Medication is with levothyroxine. Selenium is a trace element that changes the expression of selenoproteins. These act as antioxidants and appear to decrease thyroid inflammation in autoimmune thyroiditis. Pregnant women with subclinical hypothyroidism have abnormal thyroid hormone levels but no symptoms.[8-10] They are at a increased risk of miscarriage, pre-eclampsia and preterm birth with impaired neuropsychological development in the child.

Over the last decade there has been enhanced awareness of the appreciable morbidity of thyroid dysfunction, particularly thyroid deficiency. Since treating clinical and subclinical hypothyroidism may reduce adverse obstetric outcomes, it is crucial to identify which interventions are safe and effective. Postpartum thyroiditis (PPT) presents in approximately 5% of women.[11-13] Its incidence, clinical characteristics, and evolution were studied in a nonselected population of south Indian women. PPT was diagnosed in women with transient hyperthyroidism between 1 and 3 months postpartum and/or hypothyroidism between 3 and 6 months postpartum. Permanent hypothyroidism was considered if it was overt and persisted one year after diagnosis.[14-17] The incidence rate of PPT was 7.8%. Eighty-two percent of PPT patients had hormone abnormalities at the 6th month postpartum, 8.8% showed depression and 51% goiter. PPT was manifest as hyperthyroidism plus hypothyroidism in 35.5% of patients, because only.[18-22] Management of thyroid diseases during pregnancy requires special considerations because pregnancy induces major changes in thyroid function, and maternal thyroid disease can have adverse effects on the pregnancy and the fetus.[23-26] Care requires coordination among several healthcare professionals. Avoiding maternal (and fetal) hypothyroidism is of major importance because of potential damage to fetal neural development, an increased incidence of miscarriage, and preterm delivery. Maternal hyperthyroidism and its treatment may be accompanied by coincident problems in fetal thyroid function. Autoimmune thyroid disease is associated with both increased rates of miscarriage, for which the

appropriate medical response is uncertain at this time, and postpartum thyroiditis. Fine-needle aspiration cytology should be performed for dominant thyroid nodules discovered in pregnancy.[27-28] Radioactive isotopes must be avoided during pregnancy and lactation. Universal screening of pregnant women for thyroid disease is not yet supported by adequate studies, but case finding targeted to specific groups of patients who are at increased risk is strongly supported. Factors associated with the development of hypothyroidism were high anti-microsomal antibody titre measured at 16 weeks gestation ($P < 0.01$), severity of hypothyroid phase of PPT, multiparity, and a previous history of spontaneous abortion.[29,30] The presence of microsomal antibody but no PPT in one pregnancy did not prevent the occurrence of PPT in the next pregnancy in two patients and a further five patients had PPT in two successive pregnancies. There was no association between HLA haplotype, family history of thyroid disease, smoking or frequency of oral contraception, and the development of long-term hypothyroidism after PPT. It is concluded that permanent hypothyroidism is an important sequel to PPT and patients with PPT should be followed up appropriately. Postpartum thyroid dysfunction (PPTD), which is caused by an autoimmune destructive thyroiditis, affects between 3.7–5.9% of women during the first postpartum year and is characterized by elevated thyroid peroxidase antibodies (TPOAb), thyroid ultrasound (U/S) abnormalities, and transient thyroid dysfunction. In our experience 50% of TPOAb-positive (as determined in early gestation) pregnant women develop PPTD. Although clinical and biochemical abnormalities are transient in the majority of patients, a significant number (25–30%), who have the hypothyroid form of the illness develop early permanent hypothyroidism.[31-32] Further cohorts of women who do not develop early hypothyroidism are at risk of developing hypothyroidism during long term follow-up. Therefore, it is clear that in this important group of relatively young women, the prevalence of thyroid dysfunction, with its attendant morbidity, is higher than that in the community. The natural history of anti-thyroid antibodies in subjects with or without autoimmune thyroid disease is unclear. Some reports suggest no change, and some find a decrease in the prevalence of antibodies during long term follow-up. A recent population survey in randomly selected individuals reports an increase in prevalence. Hitherto, there have been no reports of the variability of TPOAb levels in subjects with PPTD during long-term follow-up. Thyroid ultrasound hypoechogenicity correlates well with lymphocytic infiltration of the thyroid gland and thyroid dysfunction in women with PPTD. The value of this technique in the diagnosis of established autoimmune destruction in patients with PPTD has been demonstrated. TPOAb and thyroid ultrasound hypoechogenicity are surrogate markers of autoimmune thyroid destruction. The prevalence and behavior of such abnormalities during long term follow-up may provide further information on the natural history of postpartum thyroiditis. As far as we are aware, this approach has not been undertaken by previous investigators. However, a previous study demonstrated the usefulness of microsomal antibody titers at delivery in the prediction of early hypothyroidism requiring T4 replacement therapy, but concluded that antibody titers were not useful in the prediction of late thyroid dysfunction .

2. OBJECTIVES

Postpartum thyroid dysfunction (PPTD), diagnosed using biochemical criteria, is usually transient with a wide range of reported prevalence rates. The specific clinical and psychiatric morbidity associated with PPTD is still uncertain. The aims of the study were to determine the point prevalence of PPTD in South Indian women at 6 months postpartum and to assess the specific clinical and psychiatric morbidity in these women. To identify interventions used in the management of hypothyroidism and subclinical hypothyroidism in pregnancy and to ascertain the impact of these interventions on important maternal, fetal, neonatal and childhood outcomes.

3. Methodology

3.1. Study Design and Location

The present retrospective cross-sectional study was accomplished at the Medicare Group of Hospitals, Hyderabad, India between January 2020 and June'2021, Patients suffering from COVID19 were excluded from the study. Records of south Indian patients with PPTD visiting an outpatient department or admitted in internal wards in the Medicare Group of Hospitals, a Tertiary care Hospital, located Hyderabad, India were included in the study. Medical records of women who were South Indian, aged 20–45 years and 4.5–5.5 months postpartum, were considered for the study. Biochemical and psychiatric morbidity of the visiting or admitted patients' electronic records were studied. PPTD for this study was defined as TSH or free T4 outside the adult reference range.

3.2. Measurements

Biochemical measurements were serum TSH, free T4, microsomal antibody (MsAb) and thyroid peroxidase antibody (TPOAb), and thyroid receptor antibodies (only in women with low TSH). Psychiatric assessment involved screening all participants using the General Health Questionnaire 28, followed by classifying and quantifying severity of cases using DSM-III-R categories for depression and anxiety. Clinical signs and symptoms of hypo- and hyper-thyroidism were measured using weighted standardized indices. Thyroid size was assessed by palpation.

The long term clinical outcome of postpartum hypothyroidism was investigated by follow-up studies of 44 patients (59 postpartum episodes; mean age of mothers at delivery, 28.2 yr) 5 or more yr later (mean interval after delivery, 8.7 yr; range, 5–16 yr). Forty-nine episodes (83%) in 34 women were followed by recovery within 1 yr postpartum, and those women remained

euthyroid thereafter (group A); 10 women [10 episodes (17%)] developed permanent hypothyroidism during the followup period (group B). Five women in group B recovered during the first year, but became hypothyroid again later, the other 5 women in Group B remained persistently hypothyroid. Of 9 women with postpartum hypothyroidism who had HLADRW9 and/or -B51 associated with antithyroglobulin-antibody titers of 23 × 10 or higher, 6 developed permanent hypothyroidism.

We conclude that long term follow-up is essential for women of postpartum hypothyroidism because of the risk of permanent hypothyroidism. The results suggest that some immunogenetic factors may be related to the etiology of postpartum hypothyroidism and that women with HLA-DRW9 and/or -B51 and higher titers of antithyroglobulin antibody are likely to develop permanent hypothyroidism.

4. RESULTS

Subjects

The median ages of the subjects were as follows: group 1, 35.5 yr; group 2, 35.0 yr; and group 3, 34.0 yr, respectively. The median number of pregnancies was not statistically different in the three groups.

Pregnancies after index pregnancy

The incidence of further pregnancies after the index pregnancy in each of the groups studied was the same, with no statistically significant difference.

Thyroid function at follow-up related to early postpartum status in TPOAb-positive (groups 1 and 2) and TPOAb-negative (group 3) subjects. Of the subjects who were antibody positive, 22 of 48 group1 subjects (46%),2 of 50 (4%) group 2 subjects, and 1 of 70 (1.4%) group 3 subjects had abnormal thyroid function (defined as a raised TSH level with or without low FT4/FT3 levels; Table 1). There was a significant difference in the prevalence of thyroid dysfunction between the TPOAb-positive and TPOAb-negative groups and within the former group between group 1\ and group 2 subjects (P less than 0.001). At the time of follow-up, TSH was significantly higher and FT4 levels were lower in group 1 than in group 2 subjects (P less than 0.004), reflecting the higher prevalence of thyroid dysfunction in this group.

Table 1: Thyroid function of TPOAb-positive and TPOAb-negative subjects at follow-up.

	Parameter	Group 1 (n= 5 48): TPOAb positive and developed PPTD	Group 2 (n =5 50): TPOAb positive but did not develop PPTD	Group 3 (n =5 70): TPOAb negative
S.No	TSH[mU/L;geometric mean (range)]	5.8[b](0.28-166.5)	1.4[e](0.26-11.27)	1.3[e](0.49-13.04)
1	FreeT3(pmol/L; mean ± 1SE)	4.7± 0.2[b]	5.1±0.1	4.6 ±0.1[d]
2	FreeT4(pmol/L; mean ±1 SE)	11.6±0.7[b]	15.0 ±0.5[c]	13.7 ±0.3[c]
3	Abnormal thyroid function [no. (%)]	22 (46)	2 (4)	1 (1.4)[a]

Abnormal thyroid function is defined as raised levels of TSH ([a]), and raised levels of TSH with decreased levels of free T4 or free T3 ([b]).

[a] Significant difference in the prevalence of thyroid dysfunction among the three groups (P less than 0.001).

[b] Values shown are for 44 subjects, as 4 were receiving T4 replacement therapy at the time of sampling.

[c] Significant difference in levels of free T4 between groups 1 vs. 2 (P , 0.004) and groups 2 vs. 3 (P less than 0.02).

[d] Significant difference in levels of free T3 between groups 2 vs. 3 (P less than 0.05).

[e] Significant difference in levels of TSH between groups 1 vs. 2 and 3 (P less than 0.001).

Table 2: TPOAb levels in Group 1 and Group 2 subjects.

	Peak postpartum TPOAb levels (geometric mean ± 1 SD)	TPOAb levels at follow-up (geometric mean ± 1 SD)
Group1	213.8 (109.6–416.9)[a]	165.9 (70.8–389)[b]
Hypo E[c]	245.5 (147.9–407.4)	208.9 (120.2–345.7)
Hypo L[d]	239.9 (162.2–338.8) 177.8 (55–549.5)	239.9 (162.2–338.8) 177.8 (55–549.5)
Euthyroid[e]	186.3 (85.9–416.9) 141.3 (46.8–363.1)	186.3 (85.9–416.9) 141.3 (46.8–363.1)
Group2	131.8 (51.3–323.6)[a]	97.7 (25.7–371.5)[b]

The prevalence of PPTD in the participants was 11.5% (95% CI 9.2–13.8%), giving a minimum prevalence for the randomly selected sample of 4.7% (95% CI 3.7–5.7%). In the PPTD women, 54% had an elevated TSH, 30% had a suppressed TSH and the remainder had a low fT4 and normal TSH. Positive thyroid autoantibody titres in the PPTD group were 46.5% for microsomal antibody (MsAb) and 63.9% for thyroid peroxidase antibody

(TPOAb), and in the non-PPTD group were 1.7% and 4.9%, respectively. The 6 month point prevalence rates of depression, generalized anxiety disorder and panic disorder and/or agoraphobia were 9.4%, 1.4% and 3.1%, respectively. No relationship was found between PPTD status and the diagnosis of current depression or between thyroid antibody status and current depression. In women who were diagnosed as anxious at the time of assessment, the number of anxiety symptoms was higher in the PPTD group ($P<0.05$). There was no difference in signs and symptom scores for the hypo- and hyper-thyroid clinical indices between PPTD women and their controls.

5. DISCUSSION

The prevalence of thyroid dysfunction (i.e. hypothyroidism) at follow-up was significantly different in the TPOAbpositive group between subjects who had PPTD (group 1) and subjects who did not have PPTD (group 2). The occurrence of PPTD, therefore, clearly confers an added risk for the development of long term thyroid dysfunction. A significantly higher proportion of group 1 subjects who were euthyroid at the end of the first postpartum year (compared to such group 2 subjects) continue to have autoimmune thyroid damage and a decline in thyroid function. Overall, the high prevalence of thyroid dysfunction (24.5%) in this relatively young (35–35.5 yr, respectively) group of TPOAb-positive subjects contrasts with a prevalence of 7.7% and a mean age at diagnosis of 59 yr reported in a community survey. Furthermore, in subjects who developed PPTD (group 1), the hypothyroid form of the illness and its severity (TSH .20 mU/L postpartum) were markers for long term thyroid dysfunction. Ninety-two percent of subjects who developed early permanent hypothyroidism had developed a hypothyroid phase in their illness. There have been 4 studies of long term outcome in women with PPTD. Nikolai et al. found a prevalence of hypothyroidism of 12% (27 subjects) at the end of 3 yr . Tachi et al., in a study concentrating mainly on HLA status, found a prevalence of hypothyroidism of 23% (44 subjects) at a mean follow-up of 8.7 yr (6). Jansson et al., in another study, found a prevalence of hypothyroidism of 30% (47 subjects) at the end of 5 yr (18). Our own previous study established a prevalence of hypothyroidism of 23% (43 subjects) at a mean period of follow-up of 3.5 yr (5). These studies did not examine the behavior and influence of surrogate markers of thyroid damage on long term outcome. The current study, therefore, represents the largest cohort of TPOAb-positive subjects (48 who developed PPTD and 50 who did not develop PPTD) studied for a median period of 77–81 months, respectively. We have presented a comprehensive picture of long term outcome after PPTD, with particular attention to markers of autoimmune thyroid damage, such as the levels and behavior of TPOAb, thyroid U/S hypoechogenicity, and HLA status. TPOAb is a marker for the development of PPTD when measured in early pregnancy. The higher peak postpartum TPOAb level in group 1 subjects was a marker of the severity of the postpartum immune rebound phenomenon and resultant immune-mediated thyroid destruction. A persistent elevation of TPOAb occurred in both groups of TPOAb-positive subjects. The natural history of anti-thyroid antibodies in subjects with and without autoimmune thyroiditis is unclear. Several reports suggest no change in prevalence/titers, and some find a decrease during long term follow-up. The effect ofT4 replacement therapy was variable. A recent study of randomly selected individuals in the north of England showed an increase in prevalence of antithyroid antibodies from 9% to 26% in women and from 2% to 9% in men during a 20-yr follow-up. The current study in TPOAb-positive postpartum women demonstrated a persistent elevation in TPOAb levels after an initial postpartum rise. Although there was a tendency toward a reduction in levels, this did not reach statistical significance. Aclear cut-off level of TPOAb predictive of long-term outcome was not evident in this study. In our subjects, destructive thyroiditis, as evidenced by U/S hypoechogenicity, was maximal at the time of postpartum thyroiditis, with gradual improvement to a lesser grade over the period of follow-up. However, persistence of hypoechogenicity in the majority of group 1 subjects (significantly different prevalence when compared to group 2) would indicate an on-going process of destructive thyroiditis. The value of thyroid ultrasound hypoechogenicity as a surrogate marker of autoimmune thyroiditis has been demonstrated. However, its use in the follow-up of PPTD is not well documented. We are unable on the basis of this study to comment on its value as a predictor of long term thyroid dysfunction in view of the small numbers available for study, but such data as there are suggest no clear-cut predictive pattern. We have shown a weak association between a reduced frequency of HLA-DR15 and DQ6 and an increased frequency of HLA-DR5 and DQ7 and PPTD. However, in our previous follow-up study, we were not able to demonstrate a link between HLA and PPTD. The current follow-up study in a larger group of subjects confirmed this lack of association between HLA antigens and long-term outcome after PPTD. The clinical significance of the low frequency of HLA-DR10 in subjects with late thyroid dysfunction is unclear. The number of subjects was too small for any meaningful comparisons. Finally, the current study makes it clear that the effects of PPTD are not confined to the immediate postpartum period, and it underlines the need for long term surveillance of TPOAb-positive subjects who develop PPTD (a relative risk of developing long-term thyroid dysfunction of 32 compared to TPOAb-negative subjects). The early development of permanent hypothyroidism in one third of them and the tendency for a further cohort to develop thyroid dysfunction over several years (a relative risk of 12.9 for subjects who developed PPTD, but were euthyroid during the first postpartum year), make regular follow-up necessary. There is also the risk of developing PPTD after subsequent pregnancies. Long term follow-up of TPOAb-positive subjects who do not develop PPTD (a

relative risk of 2.8 of developing thyroid dysfunction compared to TPOAb-negative subjects) does not seem to be as important, although they too may develop PPTD after subsequent pregnancies.

6. CONCLUSION

This study has shown a high prevalence of postpartum thyroid dysfunction but there was no difference in the clinical and psychiatric signs and symptoms between cases and controls. In the social, psychological, physical and endocrine setting of the postpartum period, women with postpartum thyroid dysfunction are identifiable by the attending physician only by their abnormal thyroid function tests. Postpartum thyroiditis has been suggested as a cause of psychosis following pregnancy. However, 30 hospitalized psychotic postpartum women and 30 control subjects matched for age and time since delivery showed no significant differences in thyroid function or the presence of thyroid antibodies.

7. CONFLICT OF INTEREST

Authors declare no conflict of interest.

8. ACKNOWLEDGMENT

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