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Post Partum Thyroid Dysfunction: A Clinical Dilemma Resolved!

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Abstract
Thyroid disorders are common during pregnancy and their clinical features maybe similar to the symptoms and signs associated with pregnancy itself.[1,2] They are important to identify and diagnose, as optimal treatment instituted promptly results in favourable maternal and foetal outcomes. After parturition the thyroid function typically returns to the normal non-pregnant state by the end of puerperium, however, abnormalities may persist in some women. Postpartum thyroid dysfunction is defined as an abnormal TSH level within the first 12 months postpartum in the absence of a toxic thyroid nodule or thyrotoxin receptor antibodies.[3] In this manuscript we review data from our study regarding postpartum thyroid function, along with literature and guidelines to understand the management of this enigmatic disease entity.

Introduction

Pregnancy is characterized by physiological and hormonal changes mediated via the hypothalamic pituitary axis (HPA), to orchestrate a delicate balance between different endocrine glands and optimise the maternal internal milieu for nurturing the foetus. This process of hormonal alterations begins in early gestation and resolves by the end of puerperium, about 6 weeks after delivery of the foetus.

Thyroid gland regulation is important for maternal wellbeing and foetal development particularly during early gestation. The foetus is completely dependent on the maternal supply of thyroxine for its growth and development during this period. There is a significant increase in maternal thyroglobulin concentration that binds thyroid hormones and lowers free T3 (FT3) and free T4 (FT4) levels. Consequently, maternal TSH secretion is enhanced to stimulate the thyroid gland to produce more T3 and T4. The increase in circulating blood volume during pregnancy affects the 'volume of distribution' of thyroid hormones. As a normal compensatory mechanism for these physiological changes and increased demand for thyroxine, the thyroid gland enlarges, iodine uptake increases, and thyroid hormone production and secretion increase by up to 50% during the first trimester.[4,5] The resultant changes in thyroid glandular structure and function may occasionally be associated with thyroid dysfunction, or are attributable to thyroid abnormalities like nodules or malignancies.[5]

Thyroid function assessment is done during the first trimester by measuring the circulating levels of thyroid-stimulating hormone (TSH) released from the anterior pituitary, and thyroxine (T4) and tri-iodothyronine (T3) secreted by the thyroid gland. The normal range considered for these hormones levels during pregnancy is different

from the non-pregnant state.[5] Moreover thyroid hormone level estimation during this time may be inaccurate and dependant on the method for measuring FT4, therefore a TSH level may offer more insight into maternal thyroid function.[3,4,6]

Interpretation of a thyroid function test in pregnancy is further confounded by other hormonal influences like the placental human chorionic gonadotropin (hCG), which increase thyroid hormones and suppress TSH secretion.[7]

Anti thyroid peroxidase antibodies (TPOAb) or thyroglobulin antibody (TgAb) develop in a significant proportion of pregnant women with or without evidence of thyroid dysfunction. It has been suggested that these circulating antibodies maybe responsible for post partum thyroid dysfunction in a section of these women.[8-14]

During antenatal screening TSH levels maybe low, high or normal. Thyroid dysfunction may manifest as increased or decreased secretion of the thyroid hormones. These result in signs and symptoms in the mother, which may often be indistinguishable from those attributable to the pregnant state. These include fatigue, weight gain, hair loss, skin changes, lethargy, palpitations, general malaise, and occasionally foetal wastage.[3,15]

Screening tests for thyroid function during pregnancy and post partum pose a challenge, more so in the absence of clinical features of thyroid disease. Furthermore, the decision to treat subclinical postpartum thyroid dysfunction versus watchful expectancy for return of thyroid function to normalcy poses a clinical dilemma.

We had conducted a pilot study in the north Indian city of Kanpur to study the prevalence of a distinct clinical entity named 'post partum thyroid dysfunction' (PPTD). Through this article we review facets of PPTD from our hitherto unpublished data of postpartum thyroid function, and consider its diagnostic, therapeutic and prognostic implications in light of present day knowledge of PPTD, and the American Thyroid Association (ATA) 2017 guidelines.[16]

Material & Methods

This pilot study was conducted in the Department of Medicine, GSVM Medical College, Kanpur, between 1991 and 1992. We included 100 postpartum women who presented to the outpatient department or were admitted as inpatients at 2-3 months after delivery, and followed them until after 6 months postpartum. A detailed history and physical examination were performed and recorded. 8-10 ml of venous blood samples were collected in sterile tubes at 3 and 6 months time points, Serum was separated after clotting and frozen at -20 degrees Celsius until hormonal assay could be done. Serum TSH level was measured in all subjects and those with abnormal TSH levels were subjected further to T3, T4 and anti TPO antibody level testing.

The stored serum was used to measure TSH, T4 and T3 levels by radioimmunoassay, and thyroid microsomal antibodies by thymune-M-haemagglutination kit. These results were compared to 30 age matched controls, and also stratified according to maternal age and parity.

Inclusion Criteria

1. 2 – 6 months postpartum.
2. Age between 18 and 45 years.

Exclusion Criteria

1. History of thyroid disorder or abnormal thyroid function test before gestation.
2. Present treatment for thyroid disorder.
3. History or presence/current treatment for malignancy.

Statistical Analysis

Statistical analyses were conducted using standardized tests. Differences was compared using student's T-Test and a 'p' value <0.05 was considered significant.

Results

Table 1: Age distribution

Age of Subjects (years)	Number of Cases
< 20	6
20 – 25	64
26 – 30	13
31 – 35	16
> 35	1
Total	100

The youngest mother was 18 years old and the oldest was 40 years. The mean age for the group was 24.83 years. 5 out of 17 (29.4%) women above 30 years developed thyroid dysfunction.

Table 2 Distribution by parity (number of children)

Parity	Number of Cases
1	39
2	19
3	22
4	16
≥5	4
Total	100

42% of mothers were multiparous (more than 2 children), primiparous mothers constituted a sizeable 39%, while 1 mother had 11 children.

Table 3: T3, T4 & TSH in Normal Age Matched Controls

Age of Subjects (years)	Number of Cases	Mean T3	Mean T4	Mean TSH
<20	8	1.56	164.5	1.63
20 – 25	10	1.67	165.10	1.56
26 – 30	6	1.70	166.18	1.63
> 30	6	1.66	169.92	1.59
Total (Mean)	30	1.64	166.42	1.60

TSH, T3 and T4 levels were not influenced by age of the subject. Normal reference values for the laboratory were:

TSH – 0.3 – 5.0 uIU/ml

T4 – 70 – 170 nmol/L

T3 – 1.0 – 3.0 nmol/L

Table 4a: TSH levels in different age groups – 3 months post partum (1st Observation)

TSH Range uIU/ml	< 20 yrs	20 – 25 yrs	26 – 30 yrs	> 30 yrs
< 0.3	0	2	-	4
0.3 – 1	1	14	3	1
1 – 2	2	25	6	6
2 – 3	2	18	3	4
3 – 4	0	4	1	-
4 – 5	1	1	-	1
> 5	0	-	-	1
Mean	2.74	1.73	1.69	1.55

The distribution of cases as a function of age and TSH level at 3 months postpartum is shown in the above table. The mean TSH levels for each age group are comparable to the reference group. 7 cases had abnormal TSH levels, of which 6 had very low TSH <0.3uIU/ml as evidence of a hyperthyroid state, while 1 case had TSH >5uIU/ml suggestive of hypothyroidism. 5 of 7 subjects with abnormal TSH level were >30 years however, TSH level had no correlation with age, as was the also seen in the control group.

Table 4b: TSH in different age groups – 6 months post partum (2nd Observation)

TSH Range uIU/ml	< 20 yrs	20 – 25 yrs	26 – 30 yrs	> 30 yrs
< 0.3	-	-	-	-
0.3 – 1	1	10	3	-
1 – 2	2	27	9	8
2 – 3	3	23	4	3
3 – 4	-	3	1	-
4 – 5	1	1	-	1
> 5	-	-	-	-
Mean	2.24	1.87	1.7	2

TSH levels at 6 months postpartum as a function of age and TSH range are shown in table 4b. The mean TSH levels are not different from the reference group (P=NS). TSH levels in all 7 cases, which were abnormal at 3 months postpartum, reverted to normal by 6 months postpartum.

Table 5a: TSH in relation with parity – 3 months post partum (1st observation)

TSH Range uIU/ml	Parity (Number of children)				
	1	2	3	4	5
< 0.3	-	1	1	3	1
0.3 – 1	6	4	6	3	-
1 – 2	16	8	9	4	2
2 – 3	13	5	2	6	1
3 – 4	2	1	2	-	-
4 – 5	2	-	1	-	-
> 5	-	-	-	-	1
Mean	2.06	1.62	1.62	1.46	1.41

None of the primiparous mothers had abnormal TSH level. 6 out of 7 cases having abnormal TSH levels were multiparous (>2)

Table 5b: TSH in relation with parity – 6 months post partum (2nd observation)

TSH Range uIU/ml	Parity (Number of children)				
	1	2	3	4	5
< 0.3	-	-	-	-	-
0.3 – 1	5	2	4	3	-
1 – 2	14	12	11	6	3
2 – 3	17	6	2	7	1
3 – 4	1	1	2	-	-
4 – 5	2	-	1	-	-
> 5	-	-	-	-	-
Mean	2.03	1.8	1.78	1.78	1.75

All cases with abnormal TSH reverted to normal by 6 months postpartum.

Table 6a: TSH values of Abnormal Cases

Serial Number	1st Observation	2nd Observation
1	0.17	2.20
2	0.19	1.20
3	0.17	1.23
4	0.13	1.32
5	0.24	1.02
6	0.15	1.02
7	7.72	2.20

The first 6 cases were hyperthyroid and the lone 7th case was hypothyroid. The mean TSH for the hyperthyroid patients was 0.175 ± 0.035 uIU/ml. All the cases reverted to normal 6 months postpartum.

On comparing the 1st and 2nd observation t = 2.79 ($p<0.05$ significant).

Table 6b: T4 values of Abnormal Cases

Serial Number	1st Observation	2nd Observation
1	211.56	157.1
2	213.03	133.01
3	173.76	122.3
4	191.15	147.03
5	177.05	119.93
6	179.00	113.32
7	70.22	99.31

The mean T4 for the hyperthyroid patients was 190.92 ± 16.09 nmol/L. The seventh case was hypothyroid with a borderline T4 level of 70.00 nmol/L

On comparing the 1st and 2nd observation t = 8.79 ($p<0.01$ highly significant).

Table 6c: T3 values of Abnormal Cases

Serial Number	1st Observation	2nd Observation
1	211.56	157.1
2	213.03	133.01
3	173.76	122.3
4	191.15	147.03
5	177.05	119.93
6	179.00	113.32
7	70.22	99.31

The mean T3 for the hyperthyroid patients was 3.87 ± 0.3 nmol/L. The seventh case was hypothyroid with T3 level 0.97 nmol/L.

On comparing the 1st and 2nd observation t = 4.10 ($p<0.01$ highly significant).

Table 7: The frequency of thyroid symptoms in patients with abnormal TSH

Symptom	No. of pts. Out of 7
Goitre	1
Palpitation	3
Fatigue & weakness	7
Resting pulse rate per minute	96 ± 12 (6 hyper), 74 (1 hypo)
Increased appetite	1
Increased sweating	4
Weight loss	2

Fatigue and weakness were the commonest symptoms. Palpitations were experienced by 3 women, and the resting pulse rate was 96 ± 12 beats per minute in cases with hyperthyroidism. The woman with hypothyroidism had a resting heart rate of 74 beats per minute. Sweating and weight loss associated with change in appetite were also reported.

Notably, thyroid microsomal antibody titres were negative in all cases with postpartum thyroid dysfunction.

Discussion

Postpartum thyroid dysfunction is specified as a pregnancy related disorder in the International Classification of Disease 10 (ICD-10-CM 2020), which became effective on October 1, 2019. PPTD is assigned the diagnosis code O90.5, and is detailed as follows: Postpartum thyroiditis

- O90.5 is applicable to maternity patients aged 12 - 55 years inclusive.

The following code(s) above O90.5 contain annotation back-references that may be applicable to O90.5:

- O00-O9A - Pregnancy, childbirth and the puerperium
- O85-O92 - Complications predominantly related to the puerperium

Approximate Synonyms

- Postpartum thyroiditis (thyroid inflammation after childbirth)

Clinical Information

- Transient autoimmune thyroiditis occurring in the postpartum period. It is characterized by the presence of high titers of autoantibodies against thyroid peroxidase and thyroglobulin. Clinical signs include the triphasic thyroid hormone pattern: beginning with thyrotoxicosis, followed with hypothyroidism, then return to euthyroid state by 1 year postpartum.

Pregnancy related thyroid disorders have been described in literature for almost a century, where Gardiner referred to it as pregnancy complicating simple goitre and Grave's disease.[19] Robertson associated symptoms suggestive of thyroid disease after pregnancy and alluded to their response to treatment with thyroid extract.[20] In the mid 1970's to 1980's several authors described hypo or hyperthyroidism after pregnancy and discussed

the differential diagnoses for the same, ranging from Grave's disease to autoimmune thyroiditis.[18,21-24]. This period also saw a rise in the detection of thyroid autoantibodies and authors described their significance in relation to symptoms of thyroid disease during and after pregnancy.[25,26]

Postpartum thyroid dysfunction was by now an established entity, and we set out in the early 1990's to estimate its prevalence in the population in our catchment area. Our study was a pilot or dipstick to broadly understand this target patient population, and the pathophysiology and management of post partum thyroid dysfunction. The tools available to us for assays and antibody titres were expensive and limited in their availability, and our study methodology was simple as allowed by the then existing state of the art in our academic milieu. However, our data shown above provided interesting observations, which are consistent with other studies conducted before and after this period by other investigators.

The sample of 100 postpartum subjects yielded 7 cases with abnormal TSH levels, which was in agreement with the 5-9% occurrence of PPTD reported in contemporary literature.[27,28] There was no correlation between maternal age and PPTD in our study but women with abnormal TSH were in their fourth decade of life. The number of children or parity of a woman did not have a direct correlation with PPTD all women with deranged TSH levels in our study were multiparous. There were no primiparous women with abnormal TSH level. Maybe the last two observations add up to advanced maternal age associated with maternal parity. These data are shown in tables 1, 2, 5a&b. It may be worth exploring if primiparity in advanced age is associated with TSH disturbances, or if multiparty in younger age has less TSH perturbations, however that was beyond the scope of our study at that time.

Table 3 shows the normal range of T3, T4 and TSH in different age groups. These reference ranges have remained the same in present times, however the cut-off level for TSH as being normal during pregnancy has been revised. This is done to allow for early detection and treatment of subclinical hypothyroidism to ensure optimal foetal development.

Tables 4a&b show the TSH levels at 3 and 6 months postpartum while 6a,b&c look at individual cases which had abnormal TSH levels at 3 months. The 7 abnormal cases at 3 months observation return to normal by the end of 6 months. This suggests resolution of the thyroid dysfunction during our observation period, and as these cases were not treated with any medication, spontaneous recovery appears to be the natural course of PPTD. This again falls in line with the current definition of PPTD as being a disorder within 12 months postpartum.[27]

The frequency of symptoms of thyroid disease postpartum, shown in table 7 and observed in clinical practice, occasionally poses a diagnostic and therapeutic dilemma. They overlap with symptoms and signs of a normal pregnancy, puerperium and postpartum period. Maternal fatigue, weight and appetite alterations, and psychological changes are commonly seen in women after delivery. Goitres maybe small or barely discernable and do not correlate with laboratory findings to trigger further investigations or treatment. Our laboratory data also did not reveal antithyroid antibodies in any of the patients with abnormal TSH, even though they have been studies extensively and described in literature to the extent of being positive in three fourths of women after childbirth. This may be due to a small sample size in our study, or a less sensitive method for assessing antibody titres.

The American Thyroid Association published its revised detailed guidelines for management of thyroid disorders in pregnancy.[27] These were updated from their 2011 guidelines keeping in view the advancements in diagnostic and therapeutic tools, and a better understanding of the aetiopathogenesis of thyroid dysfunction during and after pregnancy. When we consider the salient recommendations from these guidelines and correlate them with our data and outcomes, we

find a congruence in the incidence, clinical and laboratory findings, disease resolution and monitoring of patients with PPTD. This suggests that while science and clinical medicine have evolved in the assessment of postpartum women for thyroid disorders, the natural course of the disease and its management have remained largely unchanged.

Conclusion

Routine screening for thyroid dysfunction must be conducted during the antenatal and postpartum visits, along with clinical appraisal of signs and symptoms of thyroid disease in the mother. These include fatigue, hair fall, skin changes, lethargy, palpitations and general malaise. Mulitparity, TPO anti-body titer, maternal age, and a history of infertility treatment or miscarriage may increase the risk of developing PPTD.

If the TSH is abnormal an estimation of free T3 and T4 is needed to indicate the level of glandular activity. Most cases of PPTD resolve spontaneously however, TSH levels should be monitored every two months upto I year postpartum, and treated appropriately with thyroid hormone supplementation or anti-thyroid medication if the patient is symptomatic.

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