INVITED REVIEW

Post-partum thyroiditis – a clinical update

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Abstract

Since the late 1960s, many studies have focused on post-partum thyroiditis (PPT) and 295 papers whose titles mention PPT were recorded on MEDLINE as of August 2001. We refer briefly to some excellent reviews and some original articles in order to update our knowledge on PPT.

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Definition

Post-partum thyroiditis (PPT) is an autoimmune disorder characterized by lymphocytic infiltration of the thyroid gland and by transient thyrotoxicosis followed by hypothyroidism or by one or the other occurring in the first year after parturition. It has been the subject of several excellent reviews (1–8). Thyroid function abnormalities are not due to the presence of thyrotrophin (TSH) receptor antibodies (TRAb) either with stimulating or inhibiting thyroid activity or to a toxic adenoma.

Pathogenesis

Several findings strongly suggest that PPT is an autoimmune disease.

PPT has been reported more frequently in women with HLA-DR3, DR4 or DR5 phenotypes. These results are similar to those seen in women with Hashimoto's thyroiditis. PPT has been observed also in patients with Graves' disease and primary autoimmune hypothyroidism.

In general, PPT occurs in women with positive antithyroid peroxidase antibodies (TPOAb) in early pregnancy. During pregnancy TPOAb titres decline, whereas in the post-partum period they markedly and rapidly increase, similar to all immunoglobulin G. The fact that TPOAb in the post-partum period retain their specificity in recognizing epitopes suggests that PPT is not related to thyroid antigen specific changes but to a non-specific immune phenomenon.

TPOAb are often able to fix the complement, thus inducing the initial cell destruction. The role of complement in the development of PPT is confirmed by the observation that positive TPOAb women who

develop PPT have higher complement activation than positive TPOAb women without PPT. Lymphocytic infiltration of the thyroid is the most evident pathologic feature of PPT. However, in peripheral blood there is no variation in the ratio of T to B lymphocytes. An increased CD4⁺/CD8⁺ ratio and an increased activation of T lymphocytes has been reported in PPT women. Some authors suggested a possible role of thyroid cell specific T-cell clone with cytolytic activity. It is probable that T-cell clones reactive to thyroglobulin (Tg), TPO and TSH receptor are expanded within the thyroid during the early phase of PPT.

All these possible mechanisms, able to induce the development of PPT, are only temporary since in the vast majority of women the disease does not chronicize and normal thyroid function is resumed. Thus, the immune system has to recover normal tolerance by unknown mechanisms.

Prevalence

Prevalence of PPT is variable, ranging from 1.1% in Thailand to 16.7% of parturient women in Great Britain (Table 1) (5, 9–14). The variability of PPT prevalence may be due to different or inappropriate screening procedures or to different genetic and environment risk factors. In three different studies it has been reported that women with type I diabetes mellitus have a three times higher risk of developing PPT, and US women with type I diabetes mellitus had a 25% incidence of PPT (2). Lazarus *et al.* (15), in a prospective study, have reported that the highest risk of PPT is for those women who previously developed PPT. In that study it was shown that women with

Table 1 Prevalence of post-partum thyroid dysfunction.

Year	Author (Ref.).	Country	Prevalence (%)
1982	Amino <i>et al.</i> (5)	Japan	5.5
1982	Turney <i>et al.</i> *	USA	9.0
1984	Jansson <i>et al.</i> *	Sweden	6.5
1985	Walfish <i>et al.</i> *	Canada	7.1
1986	Freeman <i>et al.</i> *	USA	1.9
1987	Nikolai <i>et al.</i> *	USA	6.7
1987	Lervang <i>et al.</i> *	Denmark	3.9
1988	Fung <i>et al.</i> *	Great Britain	16.7
1990	Rasmussen <i>et al.</i> *	Denmark	3.3
1990	Rajatanavin <i>et al.</i> *	Thailand	1.1
1991	Roti <i>et al.</i> *	Italy	8.7
1991	Löbig <i>et al.</i> *	Germany	2.0
1992	Walfish <i>et al.</i> *	Canada	6.0
1992	Stagnaro-Green <i>et al.</i> *	USA	8.8
1992	Kannan <i>et al.</i> *	India	7.0
1996	Pizarro <i>et al.</i> *	Spain	9.3
1997	Yim <i>et al.</i> *	Korea	8.0
1999	Kent <i>et al.</i> (9)	Australia	11.5
2000	Barca <i>et al.</i> (10)	Brasil	6.7
2000	Sakaihara <i>et al.</i> (11)	Japan	5.3–21.3
2000	Furlanetto <i>et al.</i> (12)	Brasil	5.3
2000	Lucas <i>et al.</i> (13)	Spain	7.8
2001	Shahbazian <i>et al.</i> (14)	Iran	11.4

* Cited in Amino *et al.* (5)

PPT had a 69% recurrence rate of the disease at subsequent pregnancy.

Both the female and male sex of the newborn have been indicated as possible risk factors.

Iodine intake has been suggested as a possible environment risk factor for PPT development. However, no conclusive result has been provided. In areas with low iodine intake, such as Thailand, a prevalence of 1.1% of the cases has been reported. In areas with mild iodine deficiency, such as Italy, the prevalence of PPT was 8.7% (16). The administration of iodine to at-risk women with adequate or mild iodine deficiency did not prevent the development of PPT (7). Furthermore, a recent effective iodine prophylaxis programme did not change consistently the prevalence of PPT in comparison with that in women residing in countries with adequate iodine intake (14). Some studies have reported that PPT is more frequent in female smokers.

At present we do not have prospective studies confirming the anecdotal association of PPT with other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome and gestational diabetes mellitus. It would also be interesting to establish whether PPT is associated with abortion.

Clinical and laboratory features of PPT

The classical course of PPT is characterized by three sequential phases: the thyrotoxic, the hypothyroid and recovery phase (Table 2). The thyrotoxic phase occurs 1–3 months after parturition and lasts for a few months, followed by hypothyroidism at 3–6 months after delivery. Finally, a normal thyroid function is achieved within a year. This classical course is seen in less than 30% of the cases. Patients have either thyrotoxicosis or hypothyroidism in approximately 35% and 40% of the cases respectively. One-third of patients develop permanent hypothyroidism.

Clinical features of thyroid function abnormalities are rarely observed. PPT may be suspected by the alert physician if risk factors have been recognized or in the case of painless enlargement of the thyroid gland or depression occurring after parturition. Therefore, thyroid function tests are necessary to establish the diagnosis of PPT. Suppressed serum TSH with elevated serum free thyroxine (FT₄) and/or free tri-iodothyronine (FT₃) concentrations suggest a condition of thyrotoxicosis. Positive TPOAb indicate the autoimmune nature of the disease. In some cases it may be necessary to differentiate PPT from Graves' recurrence in the post-partum period. Graves' disease may be diagnosed by elevated radioactive iodine uptake (RAIU). However, this test can not be performed in the nursing mother. In such a situation, positive TRAb indicate the presence of Graves' disease. In women with PPT, RAIU is invariably low during the thyrotoxicosis phase and TRAb are always absent. The hypothyroid phase is diagnosed by elevated serum TSH concentrations with low or normal serum FT₄ concentrations. In women with PPT, thyroid ultrasound study shows an increased hypoechogenicity present in 45% at 4–8 weeks to

Table 2 Thyroid abnormalities in women with PPT.

Type of thyroid dysfunction	Prevalence (%)	Onset
Transient forms		
Thyrotoxicosis followed by hypothyroidism	30	1–6 months
Thyrotoxicosis	30	1–3 months
Hypothyroidism	40	3–6 months
Thyroid hypoechogenicity	45–86	1–6 months
Permanent forms		
Hypothyroidism	25–46	>6 months
Ultrasound thyroid abnormalities	50–76	>6 months
Impaired thyroidal organization	41–64	>6 months

86% of the cases at 15–25 weeks post-partum (17). In women without PPT and negative thyroid antibody, thyroid gland hypoechogenicity was seen in only 1.5–3% of the cases. In some patients with PPT, thyroid gland hypoechogenicity occurred before thyroid function abnormalities were present.

Prediction

PPT occurs mainly in women with positive TPOAb early in pregnancy as the result of an exacerbation of a silent autoimmune process. However, also women without TPOAb may develop post-partum thyroid dysfunction. Positive TPOAb and antithyroglobulin antibodies (TgAb) during pregnancy have been suggested as possible markers for the development of PPT. Also, thyroid hypoechogenicity and elevated serum Tg concentrations 3 months post-partum have been indicated as predictive markers of PPT (3, 18, 19). More recently, Kuijpers *et al.* (20) prospectively measured TPOAb during gestation and in the post-partum period. They concluded that positive TPOAb test had a predictive value for the development of PPT of 0.38–0.80. This wide variation was related to the timing of testing during pregnancy. Considering that positive TPOAb can predict PPT in as many as 67% of the cases and that only 50% of TPOAb-positive pregnant women will develop PPT, the TPOAb test has a predictive value of 33% (20). Very recently, it has been reported that the lack of a physiological decrement in soluble CD4 molecule, a product of CD4⁺T lymphocytes, in the third trimester of pregnancy was predictive of PPT in women with a previous episode of PPT (21).

Amino *et al.* (19) have proposed a rather complex method to screen pregnant women with positive anti-microsomal antibodies (MCAB) measuring serum FT₄, FT₃, TSH, TRAb and TgAb every 4–8 weeks. Positive TPOAb pregnant women have an increased risk of developing post-partum depression (22) and of giving birth to neonates that in childhood will have a lower IQ in comparison with children of mothers without TPOAb during pregnancy (23). However, it should be considered that L-T₄ treatment will not prevent depression and probably will be beneficial only in pregnant women with low serum FT₄ concentrations.

At present, it seems that we do not have an effective programme to screen all women for the occurrence of PPT. Only pregnant women with type I diabetes mellitus and those with a previous episode of PPT should be screened for the occurrence of thyroid dysfunction.

Prevention of PPT

In order to prevent the occurrence of PPT, L-T₄, 100 µg daily, or 150 µg iodide have been administered for the first 40 weeks of post-partum to women who had positive TPOAb in early pregnancy and therefore at risk to develop PPT (24). Women receiving L-T₄ did not show the expected increment of serum TSH concentrations during the hypothyroid phase, whereas some women receiving iodide showed an aggravation of thyroid dysfunction.

However, both treatments were ineffective in preventing the post-partum increment of antithyroid antibodies. In another study, autoimmune hypothyroid pregnant women administered with replacement doses of L-T₄ throughout pregnancy showed discordant changes in L-T₄ requirement in the first year after delivery in the 56.1% of the cases in comparison to the 9.7% of post-surgical hypothyroid cases (25). The need to adjust L-T₄ requirements in an elevated proportion of autoimmune hypothyroid women in the first year post-partum indicates that in these women PPT occurred despite L-T₄ treatment.

Treatment of PPT

In general, symptoms and signs of thyroid dysfunction are not helpful in the treatment decision of PPT patients. Thyrotoxicosis is transient and rarely clinically suspected. If a biochemical diagnosis of thyrotoxicosis (Table 3) has been made, β blocker drugs can be administered for the duration of the thyrotoxic phase. In contrast, antithyroid drugs are not indicated since the excess of circulating thyroid hormones is due to increased release of thyroid hormones from the gland and not to their overproduction. Steroid treatment, as well, is not recommended since their therapeutic effect was not consistent. Also, without any

Table 3 Treatment of thyroid dysfunction in PPT women.

Dysfunction	Treatment	Duration	Goals
Transient thyrotoxicosis	β blocker drugs or no therapy	Until thyroid function test normalization	Reduce symptoms and signs of thyrotoxicosis, if any
Transient hypothyroidism	Replacement doses of L-T ₄	12–18 months; then discontinue L-T ₄ and measure serum TSH; if elevated resume L-T ₄ indefinitely	Normalize serum TSH concentrations
Permanent hypothyroidism	Replacement doses of L-T ₄	Indefinitely	Normalize serum TSH concentrations

pharmacological treatment, women with PPT gain the euthyroid state. During the hypothyroid phase, L-T₄ at replacement doses is recommended. A recent study suggests that the women who achieve biochemical euthyroidism without any treatment showed at 18 months after parturition a median serum TSH concentration at the upper normal range and significantly higher than control group (26). This finding probably suggests that women with PPT who had a hypothyroid phase should be treated indefinitely. This conclusion is supported also by the study of Premawardhana *et al.* (27), who showed that in the long-term follow-up women who had hypothyroidism and positive TPOAb in the post-partum had permanent biochemical hypothyroidism and ultrasound thyroid abnormalities in 46% and 76% of cases respectively. Also, the observation that women who had a past history of PPT continue to have a positive perchlorate–iodine discharge test, suggestive of an impaired thyroidal iodine organification, supports the need of permanent L-T₄ replacement treatment (28).

Doses of L-T₄ will be adjusted measuring serum TSH concentrations that should be in the normal range limits. We do not advocate serum FT₄ measurement to monitor L-T₄ therapy.

Long-term follow-up

Women who had suffered PPT will develop permanent hypothyroidism in 25–30% of cases. We have previously stated that after an episode of PPT subtle defects of thyroid hormonogenesis will be permanent. However, this condition is not considered a clear situation of even subtle hypothyroidism. Therefore, it is not mandatory to treat all the women with replacement doses of L-T₄. Rather, it will be important to recognize those women who will develop permanent hypothyroidism. It has been reported that permanent hypothyroidism occurs more frequently in women with elevated titre of antimicrosomal antibodies (AMAb) during pregnancy and in those who experienced hypothyroidism alone, especially in the most severe form. However, the rate of progression from PPT to permanent hypothyroidism over 5 years is 3.6% per year, a value similar to that observed in the general female population with positive TPOAb (19).

Recently, it has been observed that highest risk of developing permanent hypothyroidism is for women with high TPOAb titres, with the hypothyroid phase of PPT and with thyroid hypoechogenicity (27). These women had a relative risk of 32 to develop permanent hypothyroidism. Because of this, a long-term follow-up of PPT women with these thyroid abnormalities seems necessary. At present, we do not have indications of how frequently to evaluate these women. In the general population it has been suggested that screening for hypothyroidism should be conducted every 5 years

(29). We have no doubt that TSH measurement will be the most sensitive test to detect the occurrence of hypothyroidism.

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