Postpartum thyroiditis: an autoimmune thyroid disorder which predicts future thyroid health

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Summary: Postpartum thyroiditis is a potentially destructive lymphocytic thyroiditis occurring in approximately 8% of the pregnant population, making it the most common endocrine disorder associated with pregnancy. This autoimmune thyroid disorder is precipitated by the postpartum immunological rebound that follows the partial immunosuppression of pregnancy, in individuals already at risk of autoimmune thyroid disease. The manifestations of postpartum thyroiditis are usually not present at the six-week postpartum visit and thus it is important that all physicians be aware of the risks, presentation and intervention required for this common disorder. Postpartum thyroiditis is a strong predictor of future thyroid health and it is essential that women with a history of postpartum thyroiditis be screened regularly, especially prior to a future pregnancy. Selenium supplementation has recently been identified as a potential means to prevent postpartum thyroiditis in women at risk but further studies are required before recommendations for its use can be made.

Keywords: postpartum, thyroiditis

INTRODUCTION

Postpartum thyroiditis is defined as the occurrence of thyrotoxicosis followed by hypothyroidism or hypothyroidism alone in the first year following pregnancy in women who did not have overt thyroid disease before pregnancy.¹ This autoimmune thyroid disorder is precipitated by the postpartum immunological rebound that follows the partial immunosuppression of pregnancy, in individuals already at risk of autoimmune thyroid disease.²

The overall prevalence of postpartum thyroiditis is approximately 8% of pregnancies. Different rates are reported globally, likely based on the length of follow-up in the postpartum period and innate differences in the populations studied, including iodine status. In Bangkok, Thailand the rate is reported to be as low as 1.1%, whereas in Brazil the reported incidence is 13.3%.³ Both of these areas report lowish iodine intake. Several high-risk groups have been identified including those with type 1 diabetes (19.1% prevalence), a positive family history (20.0%) and/or a previous history of postpartum thyroiditis (42.4% recurrence risk).⁴ The manifestations of postpartum thyroiditis are usually not present at the six-week postpartum visit and thus it is important that all physicians be aware of the risks, presentation and intervention required for this common disorder. Women who develop postpartum thyroiditis have a 25–30% risk of developing permanent

hypothyroidism within 5–10 years and should be screened at regular intervals.

PATHOGENESIS

Postpartum thyroiditis is a destructive thyroiditis associated with lymphocytic infiltration and histological features similar to that seen in Hashimoto's thyroiditis, without the same degree of fibrosis and follicular atrophy.⁵ There is strong evidence that women who develop postpartum thyroiditis have evidence of thyroid autoimmunity prior to pregnancy demonstrated by the association with the presence of anti-thyroid peroxidase antibodies (TPO-Ab). Thyroid peroxidase is a key enzyme for the synthesis of thyroid hormone through its action on iodination of tyrosyl residues and the coupling of iodotyrosyl residues to form T4 and T3.⁶ This membrane-bound glycoprotein is located on the apical surface of the thyrocyte and is a major autoantigen.⁷ TPO antibodies are seen in all forms of autoimmune thyroid disease including Hashimoto's thyroiditis, Grave's disease and postpartum thyroiditis. The level of the antibody titre reflects the severity of lymphocytic infiltration within the gland.⁶ These antibodies (unlike antithyroglobulin antibodies) are complement-fixing and thus potentially capable of inducing antibody-dependent cell-mediated cytotoxicity. However, there is a significant heterogeneity within TPO-Ab, recognizing different sites on the TPO molecule, having different degrees of complement activation and thus different potential for causing destruction.⁸ Although there is strong association of the presence of TPO-Ab with postpartum thyroiditis, it is unclear whether the TPO-Ab is directly causative or merely a marker of ongoing thyroid cell disruption.

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Approximately 12–26% of women will have evidence of TPO-Ab, with the prevalence increasing with age.⁶ For those women who are TPO-Ab positive in the first trimester, 33–50% will go on to develop postpartum thyroiditis compared with 0–5% in those who are TPO-Ab negative.⁶ TPO-Ab titre naturally decreases during pregnancy secondary to the immunosuppressed state. For those who remain TPO-Ab positive in the third trimester, 80% will develop postpartum thyroiditis.⁶

The fact that only 50% with first trimester TPO-Ab go on to develop postpartum thyroiditis may be related to different epitopes. Other factors such as maternal immune modulators or environmental factors may play a role in determining the risk of postpartum thyroiditis. Women who develop postpartum thyroiditis have a higher CD4/CD8 ratio and a greater number of activated T-cells. TPO-Ab-positive women who develop postpartum thyroiditis have been shown to have lower plasma cortisol levels and higher gamma interferon at 36 weeks of pregnancy compared with a TPO-Ab-positive euthyroid group. This suggests that a subset of TPO-Ab-positive women, who are less immunosuppressed during pregnancy, are at greater risk of developing postpartum thyroiditis.⁹

Fetal microchimerism refers to the appearance of fetal cells carrying paternal and maternal antigens in the maternal circulation. This begins by 4–5 weeks postconception and is a universal finding.¹⁰ Several studies have demonstrated the presence of fetal cells within the thyroid glands of women with autoimmune and nodular thyroid disorders; however, there are no studies in postpartum thyroiditis specifically.^{10–12} Once fetal cells migrate to the thyroid gland, they survive due to the relative immunosuppression of pregnancy. One attractive theory for the development of postpartum thyroiditis is that these fetal intrathyroidal cells become targets for maternal immune activity when the immune system rebounds postpartum.¹⁰ However, several studies have failed to show any epidemiological association between parity and other autoimmune thyroid disorders.¹³ The importance of the presence of intrathyroidal fetal cells and the role of paternal antigens as a precipitant of enhanced immune response in the maternal thyroid gland postpartum remains uncertain.

Several environmental factors have been studied as potential precipitants of postpartum thyroiditis as they have been linked to other autoimmune thyroid disorders. Smoking has multiple effects on the immune system including activation of B- and T-cells, increased cytokine production and possibly increased antigen presentation by damaging cells.¹⁴ Although clearly associated with increased risk of Grave's disease, especially the ophthalmological manifestations, there are limited data for association of smoking and postpartum thyroiditis. One meta-analysis, which included four studies of women with postpartum thyroiditis, reported a positive association between smoking and postpartum thyroiditis (odds ratio [OR] 1.97; 95% confidence interval [CI] 1.23–3.17).¹⁵ Galanti *et al.*¹⁶ reported on 35 women with postpartum thyroiditis and found a 40% prevalence of smoking in women with postpartum thyroiditis compared to 22% in women who did not develop postpartum thyroiditis.

Iodine is required for iodine hormone synthesis but iodine repletion may also play a role in thyroid autoimmunity.¹⁷ Potential mechanisms for inducing thyroid autoimmunity include increased iodination and thus immunoreactivity of thyroglobulin, direct toxic effect on thyrocytes or through immunomodulation.¹⁷ Although iodine prophylaxis has been

associated with an increased incidence of thyroid autoantibodies, iodine supplementation given during pregnancy and/or in the postpartum period does not appear to influence the rate of postpartum thyroiditis in women with TPO-Ab.^{18,19}

Selenium is an essential trace element, which as a component of selenoproteins has important biological activity including impact on malignancies,²⁰ cardiovascular disease,²¹ viral infections, in particular HIV,²² and inflammatory conditions.^{23,24} Selenium deficiency is associated with increased incidence of thyroid autoimmunity changes in ultrasound appearance including increased thyroid volume and hypoechogenicity, a marker of lymphocytic infiltration.²⁵ There are two major selenoproteins in thyroid tissue: glutathione peroxidase and iodothyronine deiodinases.²⁶ Glutathione peroxidase catalyses the reduction of hydrogen peroxide, protecting against oxidative damage generated from thyroid hormone production.²⁷ Selenium enters the food chain through plants which take it up from the soil.²³ The primary dietary sources in the USA include wheat (bread and pasta), beef, poultry and fish.²⁷ However, there is a large geographical variation primarily due to selenium levels in the soil, with very low levels in volcanic regions.²³ In Europe selenium levels appear to be falling.²⁸ The recommended daily intake is 60 µg/day during pregnancy and 70 µg/day during lactation, based on levels required for optimal activity of the antioxidant selenoenzyme glutathione peroxidase.²⁹ In Canada, one of the two commonly used maternal vitamins, Pregvit[®], does not contain selenium and the other, Materna[®], contains 30 µg.

CLINICAL COURSE

The clinical course of postpartum thyroiditis is variable and may include only hyperthyroidism with spontaneous resolution (32%), only hypothyroidism usually followed by spontaneous resolution (43%) or hyperthyroidism followed by hypothyroidism which usually has a spontaneous resolution (25%).³⁰ Approximately 30% of women affected will remain hypothyroid one year postpartum.

The transient hyperthyroidism presents between one and six months postpartum (median 14 weeks) and lasts 1–2 months.¹ The clinical manifestations of hyperthyroidism are usually mild and may be unnoticeable to the woman, or attributed to normal postpartum changes. The hypothyroid phase occurs between three and nine months (median 19 weeks) and usually lasts 4–6 months. Many women will present in the hypothyroid phase, but on careful questioning have symptoms suggestive of hyperthyroidism preceding the diagnosis. It is important to note, that postpartum thyroiditis often begins after the usual six-week postpartum appointment. Thus the woman would need to initiate a consultation with her physician, which she may be reluctant to do if the symptoms seem likely to be compatible with normal changes postpregnancy.

The primary differential diagnosis during the hyperthyroid phase is Grave's disease, which not uncommonly exacerbates with the resurgence of the immune system following pregnancy. However, postpartum thyroiditis is 20 times more common than previously undiagnosed Grave's disease.³ The main differentiating characteristics are listed in Table 1. Thyroid-stimulating hormone (TSH) receptors antibodies (thyroid-stimulating immunoglobulins) may be present in up to 25% of women with postpartum thyroiditis and thus do not confirm the diagnosis of Grave's disease. Differentiation

Table 1 Clues to differentiate the cause of hyperthyroidism in the postpartum period

	Postpartum thyroiditis	Grave's disease
Prevalence	Approx. 6% of pregnancies	0.2%
Timing following delivery	2–6 months	4–12 months
Previous history	None prior to pregnancy (unless previous postpartum thyroiditis)	Previous history of hyperthyroidism
Severity of symptoms	Generally mild	May be severe
Duration of symptoms	4–8 weeks	Continue until treatment
Thyroid enlargement	No or small diffuse goitre, no bruit	Small to large diffuse goitre, may have a bruit
Exophthalmos	None	10–25%
TSH receptor antibody	Present in up to 25%	Occurs in 90%
Nuclear imaging	Decreased uptake	Increased uptake

Adapted from Stagnaro-Green, *J Clin Endocrinol Metabol* 2002;**87**:4042

may be possible on clinical grounds or by the absence of thyroid-stimulating immunoglobulins in the hyperthyroid phase. Alternatively, observation for 4–6 weeks will detect spontaneous recovery from the hyperthyroidism or progression to hypothyroidism. Nuclear imaging will clearly differentiate the two conditions; however, in our experience most new mothers, especially if breastfeeding, will decline the nuclear imaging given the necessary requirement to interrupt breastfeeding for up to 72 hours. Given the mild, transient nature of the symptoms, most women do not require beta-blockade during the hyperthyroid phase. Thionamides (propylthiouracil and methimazole) are not useful in postpartum thyroiditis.

The hypothyroid phase may be asymptomatic or may be associated with marked hypothyroid symptoms including fatigue, constipation, loss of concentration and poor memory. The evidence for the association of postpartum thyroiditis

and postpartum depression is conflicting.¹ Both thyroid hormone levels and autoantibodies, independent of thyroid function, have been studied for association with postpartum depression. Kent *et al.* screened 748 Australian women at 4.5–5.5 months postpartum with thyroid hormone levels, TPO-Ab and General Health Questionnaire for depression and anxiety. There was an 11.5% prevalence of anxiety and 9.4% prevalence of depression, but no relationship to thyroid hormone levels or antibodies.³¹ If a woman is diagnosed with depression, thyroid function tests (TFTs) should be done, but there is not a strong enough association to use the risk of postpartum depression as a reason to screen without symptoms. If the woman is symptomatic from hypothyroidism, if the TSH is >10 mU/mL or if the woman is planning another pregnancy in the near future, treatment should be initiated.³ There should be an attempt to withdraw the thyroid hormone replacement therapy either within a year or once pregnancy is no longer desired, to determine whether there is permanent hypothyroidism and need for lifelong replacement.

PERMANENT HYPOTHYROIDISM AND POSTPARTUM THYROIDITIS

The postpartum period is a window of opportunity for estimating the risk of permanent hypothyroidism (Figure 1). Premawardhan *et al.*³² compared TPO-Ab-positive women who developed postpartum thyroiditis ($n = 48$), TPO-Ab-positive women who did not develop postpartum thyroiditis ($n = 50$) and TPO-Ab-negative women ($n = 70$) at 77–81 months postpartum and found thyroid dysfunction in 46%, 4% and 1.4%, respectively ($P < 0.001$). The 4% risk in women who did not develop postpartum thyroiditis is similar to the 2%/year risk of progression to hypothyroidism seen in TPO-Ab-positive individuals without an intervening pregnancy. The strongest predictors of long-term thyroid dysfunction were higher TPO-Ab titres, TSH >20 mIU/L and hypo-echogenicity on a thyroid ultrasound in the postpartum period.

Figure 1 Estimates of risk for developing postpartum thyroiditis and permanent hypothyroidism

SCREENING AND PREVENTION STRATEGIES FOR POSTPARTUM THYROIDITIS

Since we can identify women at high risk of developing postpartum thyroiditis and there is an association with a significant risk of future lifelong hypothyroidism, some have recommended that all women be screened for TPO-Ab's in pregnancy. However, given the lack of evidence that early treatment ameliorates symptoms, universal screening is not recommended.¹ It is important to recognize that a woman may become pregnant within the first year postpartum when her thyroid function is fluctuating, which could have significant impact on her next pregnancy. Thus, women at high risk e.g. those who are known to be TPO-Ab positive, those with other autoimmune disorder especially type 1 diabetes and those with previous postpartum thyroiditis should have a TSH level done at three and six months postpartum.¹ If TPO-Ab's are not detected in the first trimester, no further screening is required.

Given the ability to identify women at high risk, the next question is, can it be prevented? Iodine supplementation has not been shown to be helpful or harmful.^{18,19} However, there is increasing evidence of promise for selenium repletion both through animal and human studies.^{2,33,34} Negro screened 2227 Caucasian women to find 169 euthyroid TPO-Ab-positive women who were randomly assigned to 200 µg/day of selenomethionine or placebo, starting after 12 weeks gestation and continued postpartum. The results were compared with 85 TPO-Ab negative, euthyroid, age-matched controls. Both TPO-Ab-positive groups showed a significant decline in TPO-Ab titre during pregnancy, with the selenium group having a much lower rebound in titre postpartum. Those women who received selenium did not show any progression of inflammation (based on ultrasound echogenicity) during the one year follow-up, whereas the pattern significantly worsened in those who did not receive selenium. In all, 27.3% of the selenium-supplemented group versus 44.6% in the no selenium group had evidence of moderate or advanced thyroiditis on ultrasound at 12 months postpartum. The rate of postpartum thyroiditis was significantly reduced in the group that received selenium, 28.6% compared with 48.6% (relative risk [RR] 0.59; 95% CI 0.38–0.90), as was the rate of permanent hypothyroidism, 11.7 versus 20.3% (RR 0.58; 95% CI 0.27–1.24). In the TPO-Ab-negative control group, 3.7% had postpartum thyroid dysfunction. Although there were no adverse events related to selenium supplementation in this study, caution must be used, since selenium supplementation in iodine-deficient areas may exacerbate hypothyroidism significantly.³⁵ Although the results are encouraging, a recent Cochrane review highlights the importance of further large-scale randomized controlled trials to confirm safety and efficacy.³³

CONCLUSION

Postpartum thyroiditis is a common endocrinological condition that is part of the autoimmune thyroid disorder spectrum. It is an important condition to recognize in order to provide appropriate management and reassurance, to ensure optimum thyroid hormone levels prior to a subsequent pregnancy and to identify women at high risk of permanent hypothyroidism. The recently recognized potential for selenium supplementation to prevent postpartum thyroiditis and its long-term risks is an area in need of further research.

Declarations: None.

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