Approach to the Patient with Postpartum Thyroiditis

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Postpartum thyroiditis (PPT) is the occurrence of *de novo* autoimmune thyroid disease, excluding Graves' disease, in the first year postpartum. The incidence of PPT is 5.4% in the general population, and it is increased in individuals with other autoimmune diseases such as type 1 diabetes mellitus. The classic presentation of PPT of hyperthyroidism followed by hypothyroidism is seen in 22% of cases. The majority of women with PPT experience an isolated hypothyroid phase (48%), with the remainder experiencing isolated thyrotoxicosis (30%). Up to 50% of women who are thyroid antibody positive (thyroid peroxidase antibody and/or thyroglobulin antibody) in the first trimester will develop PPT. Symptoms are more common in the hypothyroid phase of PPT and include fatigue, dry skin, and impaired memory. Despite multiple studies exploring the relationship between PPT and postpartum depression, or postpartum depression in thyroid antibody-positive euthyroid women, the data are conflicting, and no firm conclusions can be reached. Long-term follow-up of women who had an episode of PPT reveals a 20–40% incidence of permanent primary hypothyroidism. In a single study, selenium administration significantly decreased the incidence of PPT, but replication of the findings is needed before the recommendation can be made that all pregnant thyroid peroxidase antibody-positive women receive selenium. The indication for treating the hyperthyroid phase of PPT is control of symptoms, whereas treatment of the hypothyroid phase of PPT is indicated for symptomatic relief as well as in women who are either breastfeeding or attempting to conceive. **(*J Clin Endocrinol Metab* 97: 334–342, 2012)**

The Patient

A 27-yr-old woman presented to her internist 9 months after the birth of her first child. The patient had an uneventful pregnancy and delivery. She had gained 38 pounds during the pregnancy and lost almost all of the weight during the first 6 months postpartum. During the following 3 months, she noticed a 10-pound weight gain. She also complains of increasing lethargy, decreased ability to concentrate, and feeling depressed. Her past medical history is unremarkable. Family history is significant for a younger sister with systemic lupus erythematosus.

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- Describe the etiology and incidence of postpartum thyroiditis.
- Recognize the symptoms associated with both the hyperthyroid and hypothyroid phase of postpartum thyroiditis.
- Manage both the hyperthyroid and hypothyroid phase of postpartum thyroiditis.

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Abbreviations: FT3, Free T_3; FT4, free T_4; GD, Graves' disease; PPT, postpartum thyroiditis; TAb, thyroid antibody; T1DM, type 1 diabetes mellitus; TPO-Ab, thyroid peroxidase antibody; +, positive or positivity; −, negative.

Postpartum Thyroiditis (PPT) Definition

PPT is the occurrence of *de novo* autoimmune thyroid disease, excluding Graves' disease (GD), in the first year postpartum. The clinical presentation of PPT varies. In its classic form, a transient thyrotoxic phase is followed by a transient hypothyroid phase, with a return to euthyroidism by the end of the first year postpartum. Other presentations include isolated thyrotoxicosis or isolated hypothyroidism. Although all episodes of thyrotoxicosis are transitory, a percentage of women who experience a hypothyroid phase will never revert to the euthyroid state. The frequency of clinical presentations of PPT, based on data compiled from 21 studies, reveals that the majority of women have a solitary hypothyroid episode (48%) (1–21). The remainder of cases of PPT are relatively evenly split between a biphasic presentation (22%) and isolated thyrotoxicosis (30%).

Etiology

PPT is an autoimmune disorder. The data in support of PPT as an autoimmune disease are extensive. First, and probably foremost, is the association of PPT with thyroid antibody positivity [TAb+; thyroid peroxidase antibody (TPOAb) and/or thyroglobulin antibody] in the first trimester of pregnancy. TAb+ women have a 33–50% chance of developing PPT, whereas TAb-negative (TAb−) women have a very low incidence of PPT. Furthermore, not only is PPT associated with TAb+, but the higher the antibody titer, the more likely that PPT will occur. The occurrence of PPT in the postpartum, at a time of immunological rebound from the selective immunosuppression of pregnancy, provides further support for an autoimmune etiology of PPT. Histological study of fine-needle aspirates of PPT reveals a lymphocytic thyroiditis, similar to that seen in individuals with silent thyroiditis (22). Finally, PPT is associated with specific lymphocytic changes (11), a decrease in regulatory T cells (23), dynamic Ig alterations (18, 24), and specific HLA haplotypes (25–27). In essence, as stated by Muller *et al.* (28), ". . . postpartum thyroiditis is "just" an aggravation of an existing autoimmune thyroiditis after an amelioration of the inflammation during pregnancy . . . ."

Incidence of PPT in Unselected Women

The incidence of PPT in women without another autoimmune thyroid disease varies between 1.1 and 18.2%. The wide range reflects variations in study design as well as geographical differences. The design of incidence studies varies in multiple variables, including whether screening had occurred during pregnancy, the frequency of screening postpartum, and the definition of PPT. Table 1 presents details of the 21 prospective studies performed in women without another autoimmune disease (1–21). Six of the 21 studies did not prospectively follow the entire population screened, but instead selected a cohort of women to be followed. Based on the rate of PPT in the cohort, the incidence of PPT for the entire study group was calculated. It appears that two of these six studies resulted in high rates of PPT by inadvertently including women who were TAb+ in the TAb− group. Of the 21 studies, only eight screened women during pregnancy and were therefore able to exclude women with preexisting thyroiditis. Frequency of screening varied markedly in the studies, and the percentage of patients available for follow-up at the later time points of the studies (not shown in Table 1) frequently dropped precipitously (to 20% in some cases). Finally, as demonstrated in Table 1, even the definition of PPT varied by study. All of these factors impact the reported incidence rates.

How then should we determine the average incidence rate of PPT from the literature? Given the differences in study design described above, it may be reasonably argued that calculation of an incidence rate is not feasible. On the other hand, by excluding those studies that calculated the incidence of PPT based on a limited cohort, it can be determined that the incidence of PPT is 5.4% (666 women with PPT per 12,298 women screened). This rate is in accord with the 4.9% reported by Gerstein (29) in 1990 and somewhat lower than the 8.1% incidence calculated by Nicholson *et al.* (30). Given the high dropout rate reported in many studies, García-Mayor *et al.* (31) performed a cross-sectional study of 691 women in Spain at five time points during the first year postpartum. PPT was defined as a TSH below 0.3 μU/ml or a TSH above 3.8 μU/ml. The incidence rate of PPT of 6.5% is again consistent with the 5.4% rate calculated in the present manuscript. Kent *et al.* (32) performed a point prevalence study of 748 women in Western Australia and reported a PPT prevalence rate of 11.5%. Perhaps the exact incidence of PPT is irrelevant. What is relevant is that PPT is a common disorder that impacts, at a minimum, more than one of every 20 women in the postpartum period.

Incidence of PPT in Women with Type 1 Diabetes Mellitus (T1DM) and Other Autoimmune Disorders

Based on the high rate of thyroid antibodies in women with T1DM, it would be expected that the incidence of PPT in diabetic women would exceed that seen in the general population. The first of four studies evaluating this association was published in 1991 by Bech *et al.* (33) who reported that six of 57 women (10.5%) from Copenhagen with T1DM developed PPT. This represents a 3-fold increase in incidence compared with the 3.3% rate in women

TABLE 1. Details on the 21 studies that have evaluated the incidence of PPT

First author (Ref.)	Year	Country	Total screened (n)	% TAb+ in cohort	Subgroup	Screened during pregnancy	MOPP					
							1–2	3–4	5–6	7–8	9–10	11–12
Amino (1)	1982	Japan	507		63	No		X	X			
Jansson (2)	1984	Sweden	460	9.6% (n = 44)		No	X		X			
Freeman (3)	1986	United States	212	2.80%		No	X	X (21% F/U)				
Nikolai (4)	1987	United States	238			No	X	X				
Lervang (5)	1987	Denmark	591	6.4% (n = 38)		No		X				
Fung (6)	1988	United Kingdom	901	13% (n = 117)	100 TPO-Ab+, 120 Ab−	Yes	Women seen on a regular basis until 12 MOPP					
Rajatanavin (7)	1990	Thailand	812	8.7% (n = 71)	71	No	X	X	X	X		
Feldt-Rasmussen (8) and Bech (9)	1990 and 1991	Denmark	736	10% (n = 75)	36 Ab+, 20 Ab−	Yes	X		X			X
Roti (10)	1991	Italy	219			No	X		X			
Stagnaro-Green (11)	1992	United States	552	18.7% (n = 102)	33 Ab+, 28 Ab−	Yes		X	X			
Walfish (12)	1992	Canada	1376			No						
Pop (13)	1993	The Netherlands	293	13% (38/291)		Yes	Every 6 wk until 34 wk					
Kuijpens (14)	1998	The Netherlands	291			Yes	X	X	X	X	X	
Barca (15)	2000	Brazil	368			Yes		X	X			X
Lucas (16)	2000	Spain	605			Sometimes yes/no	X	X	X		X	X
Shahbazian (17)	2001	Iran	1040			No	Every 6–8 wk	X	X		X	
Zargar (18)	2002	India	120			No	X	X	X			
Kita (19)	2002	Greece	1594	5.2% (83/1594)	74 TAb+	No	X	X	X		X	X
Filippi (20)	2008	Italy	643	9.2% (59/643)	43 TAb + and 215 TAb−	Yes			X			X
Stagnaro-Green (21)	2011	Italy	4384	6.0% (261/4384)		Yes			X			X

MOPP, Months postpartum; Def. of PPT Hyper, definition used in the study to diagnose the hyperthyroid phase of PPT; Def. of PPT Hypo, definition used in the study to diagnose the hypothyroid phase of PPT; F/U, follow-up; FT4I, free T_4 index; FT3I, free T_3 index; N/A, data not available; TT4, total thyroxine; Ab+, thyroid antibody positive; Ab−, thyroid antibody negative.

in Denmark who were not diabetic (8, 9). Gerstein (34) in 1993 screened 40 Canadian women with T1DM for thyroid dysfunction 1 wk after delivery and at 3 and 6 months postpartum. PPT occurred in 25.0% (10 of 40) of the women, representing a 4-fold increase when compared with the 6% incidence in unselected Canadian women reported by Walfish *et al.* (12). In 1994, Alvarez-Marfany *et al.* (35) followed 28 women with T1DM from the New York metropolitan area throughout pregnancy and the first year postpartum. Twenty-five percent (seven of 28) of the women developed PPT, as contrasted with an 8.8% incidence in unselected women from the same geographic region (11). Alvarez-Marfany *et al.* (35) noted that the presence of thyroid antibodies during pregnancy in women with T1DM was not predictive of PPT. Gallas *et al.* (36) in 2002 evaluated 82 women with T1DM from The Netherlands. The PPT incidence of 15.9% in women with T1DM was three times higher than the 5.2% found in unselected women from The Netherlands (14).

The incidence of PPT is also increased in women with other autoimmune thyroid disorders. Tagami *et al.* (37) investigated 39 pregnancies in 34 women with GD. Treatment for GD during pregnancy was required in 23 of the pregnancies, whereas GD was in remission in the other 16 pregnancies. The incidence of PPT was 44% (17 of 39 of the pregnancies), which exceeded the recurrence rate for GD (26% or 10 of 39). The mean time of occurrence of PPT was 4.5 months, and women with PPT had a lower free T_3 (FT3)/free T_4 (FT4) ratio than women with a postpartum exacerbation of GD. Caixàs *et al.* (38) demonstrated that even women with preexisting hypothyroidism on adequate replacement doses of levothyroxine can develop PPT. Specifically, PPT can develop if women with Hashimoto's disease have remaining thyroid tissue that is viable.

The link between PPT and other autoimmune disorders is striking. Stagnaro-Green *et al.* (39) reported that 14% of 43 pregnant women with systemic lupus erythematosus developed PPT. Similarly, Elefsiniotis *et al.* (40) found that 25% (four of 16) of women with chronic viral hepatitis developed PPT. Evaluating the link between PPT and other autoimmune disorders from a different perspective, Manetti *et al.* (41) identified antipituitary antibodies in 27% (eight of 30) of women who previously had an episode of PPT. Similarly, Gudbjörnsson *et al.* (42) studied 40 women with a history of PPT and found a significant increase in clinical and laboratory features of Sjogren's syndrome.

As previously noted, most women who develop PPT are euthyroid by the end of the first postpartum year. Lazarus

TABLE 1. Continued

Def. of PPT Hyper	Def. of PPT Hypo	% PPT	% Hyper phase only	% Hypo phase only	% Biphasic
$T_4 > 11.0$ μg/dl, $T_3 > 200$ ng/dl, FT4 > 2.1 ng/dl	$T_4 < 4.6$ μg/dl, FT4 < 1.0 ng/dl, TSH > 10 mU/liter	5.5% (n = 28)	46% (13/28)	29% (8/28)	25% (7/28)
FT4 > 25.7 pmol/liter and FT41 > 145	TSH > 4 mU/liter	6.5 (n = 30)	6.7% (2/30)	73% (22/30)	20% (6/30)
N/A	N/A	1.9% (n = 4)	50% (2/4)	None	50% (2/4)
N/A	TSH > 7.5 mU/liter	6.7% (n = 16)	44% (7/16)	38% (6/16)	19% (3/16)
FT4 > 27 pmol/liter and FT4 1.140 and/or FT31 > 2.5	TSH > 5 mU/liter	3.9% (n = 23)	30% (7/23)	30% (7/23)	39% (9/23)
FT4 and TSH > 2 SD outside the normal range	FT4 and TSH > 2 SD outside the normal range	16.7% calculated	43% (n = 21)	35% (n = 17)	18% (n = 9)
N/A	N/A	1.1% (n = 9) calculated	33% (3/9)	33% (n = 3)	11% (n = 1)
FT4I > 129 and/or FT3I > 2.8 with TSH < 0.3 or TSH < 0.12	FT41 < 56 and/or FT31 < 1.6 and TSH > 5 or TSH 0.8	3.3% calculated			
$T_4 > 12$ μg/dl and/or $T_3 > 180$ ng/dl, with TSH < 0.4	TSH > 3.8	8.7% (n = 19)	21% (4/19)	73% (n = 15)	0%
TSH < 0.2 mU/liter	TSH > 5.0 mU/liter	8.8% calculated	42% (5/12)	8.3% (1/12)	50% (6/12)
FT4 > 23.4 pmol/liter and/or TSH < 1.0	FT4 < 7.8 pmol/liter and/or TSH > 6.0	6.0 (82/1376)	27% (22/82)	21% (17/82)	48% (39/82)
TSH < 0.3 and ↑ FT4 or ↑ FT3	TSH > 3.7 and ↓ FT4 or ↑ FT3	7.2% (21/293)	52% (11/21)	19% (4/21)	30% (6/21)
TSH < 0.15 mU/liter and FT4 > 19.6 pmol/liter	TSH > 2.0 mU/liter and FT4 < 8.7 pmol/liter	5.2% (15/291)	60% (9/15)	33% (5/15)	7% (1/15)
N/A	N/A	13.3% (49/368)	12% (6/49)	84% (41/49)	4% (2/49)
TSH < 0.1 mU/liter	TSH > 4.0 mU/liter	7.8% (n = 45)	22.2% (10/45)	42.3% (19/45)	35.5% (16/45)
$T_4 >$ μg/dl and/or $T_3 > 220$ ng/dl and TSH < 0.3 mU/liter	TT4 < 4.5 μg/dl and TSH > 10.0 mU/liter	11.4% (n = 119)	35% (42/119)	57% (68/119)	8% (9/119)
TSH < 0.185 mU/liter	TSH > 10.0 mU/liter	7.0% (n = 8)	63% (5/8)	0%	37% (3/8)
Not given	Not given	2.4% (calculated)	18% (7/38)	40% (15/38)	42% (16/38)
TSH < 0.4 mU/liter	TSH > 4.0 mU/liter	18.2 (calculated)	49% (28/57)	25% (14/57)	26% (15/57)
TSH < 0.27 mU/liter	TSH > 4.2 mU/liter	3.9% (169/4384)	68% (115/169)	14% (23/169)	26% (15/57)

et al. (43) reported on the clinical course of subsequent pregnancies in 54 women who had an initial episode of PPT. None of 17 women who were TPO-Ab-negative (TPO-Ab−) and PPT− in the initial pregnancy developed PPT in their next pregnancy. On the other hand, the majority of 13 women (69%) who were PPT+ and TPO-Ab+ during the first pregnancy had a recurrence of PPT in their second pregnancy. Not surprisingly, 25% of women who were PPT− and TPO-Ab+ in the first pregnancy, developed PPT+ in a subsequent pregnancy.

Symptoms Associated with PPT

In 1948, Robertson (44) published the first large case series of PPT based on 219 unselected women who had 483 pregnancies. Robertson reported that 26% of women had symptoms of mild hypothyroidism, whereas severe symptoms were present in 10% of the cohort. Symptoms experienced by the women are included in the title of Robertson's manuscript ("Lassitude, Coldness and Hair Changes Following Pregnancy, and their Response to Treatment with Thyroid Extract"). Eight papers assessing symptoms associated with PPT have been published since 1948 and are presented in Table 2. Only half of the eight studies evaluated whether the symptoms seen in women who experience PPT were significantly higher than symptoms seen in controls. Furthermore, the majority of studies did not indicate the frequency of the various symptoms. Nevertheless, despite study limitations, the data demonstrate that symptoms experienced more frequently in the hyperthyroid phase of PPT (when compared with controls) are fatigue, palpitations, and nervousness. During the hypothyroid phase of PPT, tiredness and impaired memory occur more commonly than in euthyroid postpartum controls. Interestingly, Kuijpens *et al.* (45) report that fatigue, cold intolerance, hoarseness, dry hair, and paresthesia were more common in TPO-Ab+ women with PPT when contrasted to TPO-Ab− women with PPT.

PPT and depression (Table 3)

Much attention has been given to a possible link between PPT and postpartum depression. In 1982, Amino *et al.* (1) recommended further study of psychiatric disease and PPT after describing three PPT patients admitted for psychiatric symptoms whose symptoms abated when thyroid function returned to normal. Stewart *et al.* (46) evaluated thyroid function and TAb status in 30 women with psychosis within 1 yr of delivery. Hor-

TABLE 2. Hyperthyroid and hypothyroid symptoms of PPT as described in eight studies

Author	Year	Country	Hyperthyroid symptoms	Hypothyroid symptoms
Amino (1)[a]	1982	Japan	Fatigue (55%), palpitations (20%)	Not reported
Jansson (2)	1984	Sweden	Fatigue	Not reported
Nikolai (4)[b]	1987	United States	Fatigue, tachycardia, nervousness, weight loss, tremor, muscle and joint aches and stiffness, malaise	Fatigue, tachycardia, nervousness, weight loss, tremor, muscle and joint aches and stiffness, malaise
Lervang (5)	1987	Denmark	Tiredness, palpitations, nervousness, increase sweating	Tiredness (43%)
Walfish (12)[a]	1992	Canada	Palpitations, heat intolerance, nervousness (29%)	Hypothyroid phase more symptomatic than the hyperthyroid phase
Kent (32)	1999	Australia	Weight loss (9%)	Constipation (14%)
Lazarus (52)[a]	1999	United Kingdom	Lack of energy, irritability	Lack of energy, aches and pains, poor memory, dry skin, cold intolerance
Hayslip (47)[a]	1988	United States	No increase in symptoms	Impairment of memory (71%), carelessness (71%)

[a] Differences were statistically greater than control.

[b] Manuscript does not state whether symptoms were in the hyperthyroid or hypothyroid phase.

monal status in all 30 women was within normal limits, and the prevalence of thyroid antibodies was similar to that seen in 30 age-matched controls. It is well established that PPT is not associated with psychotic depression in the postpartum. On the other hand, as will be shown in the following paragraphs, much uncertainty remains regarding the relationship between PPT and nonpsychotic depression, and nonpsychotic depression in TAb+ euthyroid women.

Studies evaluating the hypothyroid phase of PPT and nonpsychotic depression have yielded mixed results. Hayslip *et al.* (47) reported that 53% of 17 women in the hypothyroid phase of PPT (3–5 months postpartum) were depressed, as contrasted with 0% in 18 euthyroid women ($P < 0.01$). Harris *et al.* (48) in 1989 found an increased prevalence of depression in one of three depression scales in women with PPT when compared with controls ($P < 0.05$). Likewise, Pop *et al.* (49) in 1991 reported an increase in postpartum depression in women with postpartum thyroid dysfunction (38 *vs.* 10%; $P < 0.02$). On the other hand, Walfish *et al.* (12) found no increase in postpartum depression in women with PPT when compared with controls. Kent *et al.* (32) also found no relationship between PPT and depression. Finally, Lucas *et al.* (50) did not find an increase in postpartum depression in women with PPT. In summary, only 43% (three of seven) of the studies have demonstrated a relationship between PPT and depression in the postpartum period.

A body of literature has also developed evaluating the association between depression and TAb+ in women who remain euthyroid postpartum. The first study to evaluate this potential connection was conducted by Harris *et al.* (48) in 1989. No difference in the rate of postpartum depression was found in TAb+ women when compared with TAb− women. In a follow-up study, however, Harris *et al.* (51) in 1992 reported an association between TAb+ and PPT ($P < 0.005$). In the following year, Pop *et al.* (13) found no increase in postpartum depression in euthyroid TPO-Ab+ women. Kent *et al.* (32) also evaluated TPO-Ab+ and depression in euthyroid women and reported no

TABLE 3. Results of 11 studies that evaluated the association between PPT and postpartum depression and between TAb+ and postpartum depression in euthyroid women

First author (Ref.)	Year	Country	PPT and depression	TAb+ and depression
Stewart (46)	1988	Canada	NS	Not evaluated
Hayslip (47)	1988	United States	53 *vs.* 0%, $P < 0.01$	Not evaluated
Harris (48)	1989	United Kingdom	One of three scales positive; 62 *vs.* 14%; $P < 0.05$	NS
Pop (49)	1991	The Netherlands	38 *vs.* 10%; $P = 0.02$	Not evaluated
Harris (51)	1992	United Kingdom	Not evaluated	43 *vs.* 28%; $P < 0.005$
Walfish (12)	1992	Canada	NS	Not evaluated
Pop (13)	1993	The Netherlands	Not evaluated	NS
Kent (32)	1999	Australia	NS	NS
Lazarus (52)	1999	United Kingdom	NS	$P < 0.0056$
Kuijpens (45)	2001	The Netherlands	Not evaluated	59 *vs.* 38%; $P = 0.03$
Lucas (50)	2001	Spain	NS	Not evaluated

NS, Not significant.

association. Finally, in the two most recent studies on this topic both Kuijpens *et al.* (45) and Lazarus (52) reported a significant increase in postpartum depression in postpartum euthyroid TAb+ women. In summary, studies evaluating the relationship between TAb+ and postpartum depression in euthyroid women have been mixed, with 50% (three of six) of the studies demonstrating a significant association. Cytokine release has been postulated as a potential mechanism linking depression with TAb+ (53). Harris *et al.* (54) in 2002, in prospective placebo-controlled, double-blind study, reported no difference in postpartum depression in TPO-Ab+ women treated with levothyroxine compared with postpartum depression in TPO-Ab+ women given placebo. The study did report an overall rate of major depression of 18.5% and of depression in general of 38%, providing further evidence linking PPT and TPO-Ab+.

Incidence of Permanent Hypothyroidism at Long-Term Follow-Up

The incidence of persistent hypothyroidism at the end of the first postpartum year has been evaluated in seven studies and varies between 4 and 54% (1, 21). The reason for the discrepancy between the various studies is unclear, although it should be noted that a 1-yr incidence of hypothyroidism of 54% is unusually high. Long-term follow-up of thyroid status in women who had an episode of PPT yields more consistent data (55–59). The majority of the studies revealed that 20–40% of women develop permanent hypothyroidism over the ensuing 3–12 yr. Women at increased risk for developing permanent hypothyroidism had higher titers of thyroid antibodies and higher TSH levels during the initial hypothyroid phase; they were older, multiparous, and had a greater degree of thyroid hypoechogenicity on ultrasound.

Prevention of PPT

The benefits of preventing PPT would be avoidance of symptoms of thyroid dysfunction in the postpartum and preventing or delaying permanent hypothyroidism. The initial prevention study, performed by Kämpe *et al.* (60) in 1990, evaluated the impact of treating TPO-Ab+ women with either levothyroxine or iodine, as contrasted with no intervention. The incidence of hypothyroidism in the three groups was similar. Women treated with levothyroxine had a decrease in the hypothyroid symptoms of PPT, whereas iodine supplementation increased the degree of thyroid dysfunction. In 2000, Nøhr *et al.* (61) evaluated the impact of iodine given to TPO-Ab+ women during pregnancy and the postpartum *vs.* iodine administration solely during pregnancy, as contrasted with a placebo control. Iodine supplementation had no impact on either the incidence or severity of PPT. The most recent PPT prevention study, performed by Negro *et al.* (62) in 2007, evaluated the impact of selenium treatment in TPO-Ab+ women. Selenium decreased the incidence of PPT as well as permanent hypothyroidism when compared with a placebo control group. Women given selenium also had a significant decrease in the titer of TPO-Ab in the postpartum period. A recent review of selenium concluded that selenium administration is effective in decreasing TPO-Ab titer and decreasing hypoechogenicity in individuals with autoimmune thyroid disease. Nevertheless, treatment of TPO-Ab+ women with selenium to prevent PPT remains premature, pending study replication.

Prediction of PPT

Identifying women at risk for developing PPT could result in focused screening in the postpartum. TPO-Ab measured in the first trimester is the optimal screening tool (11, 14). Between 33 and 50% of TPO-Ab+ women will develop PPT. As previously noted, not only is the presence of TPO-Ab+ predictive, but so is the titer, with women with higher titers having a greater likelihood of developing PPT. Screenings for TPO-Ab+ at the second postpartum day (63) as well as serum soluble CD4 (64) have both been proposed as alternative screening strategies. However, screening at the time of delivery will miss women whose titers of TPO-Ab decreased during pregnancy and became undetectable at birth, and soluble CD4 is not widely available and has not been extensively evaluated. Increased thyroid hypoechogenicity is predictive of PPT, often predating thyroid function test abnormalities, but it has limited universal clinical applicability based on cost (65, 66). However, it is possible that future studies will demonstrate that ultrasonography of TPO-Ab+ women could enhance the ability to predict PPT compared with TPO-Ab testing alone.

Premawardhana *et al.* (67) evaluated multiple variables with the goal of identifying women at increased risk for developing permanent primary hypothyroidism after resolution of an episode of PPT. Ninety-eight TPO-Ab+ women, 48 of whom had developed PPT, and 70 TPO-Ab− controls were evaluated. The hypothyroid form of PPT, the severity of the hypothyroidism, the titer of TPO-Ab+, and the degree of thyroid ultrasound echogenicity identified women at high risk for developing permanent primary hypothyroidism.

Screening

Screening for PPT and for that matter thyroid disease in pregnancy in general has generated much debate. A decision on screening should take into account all thyroid dis-

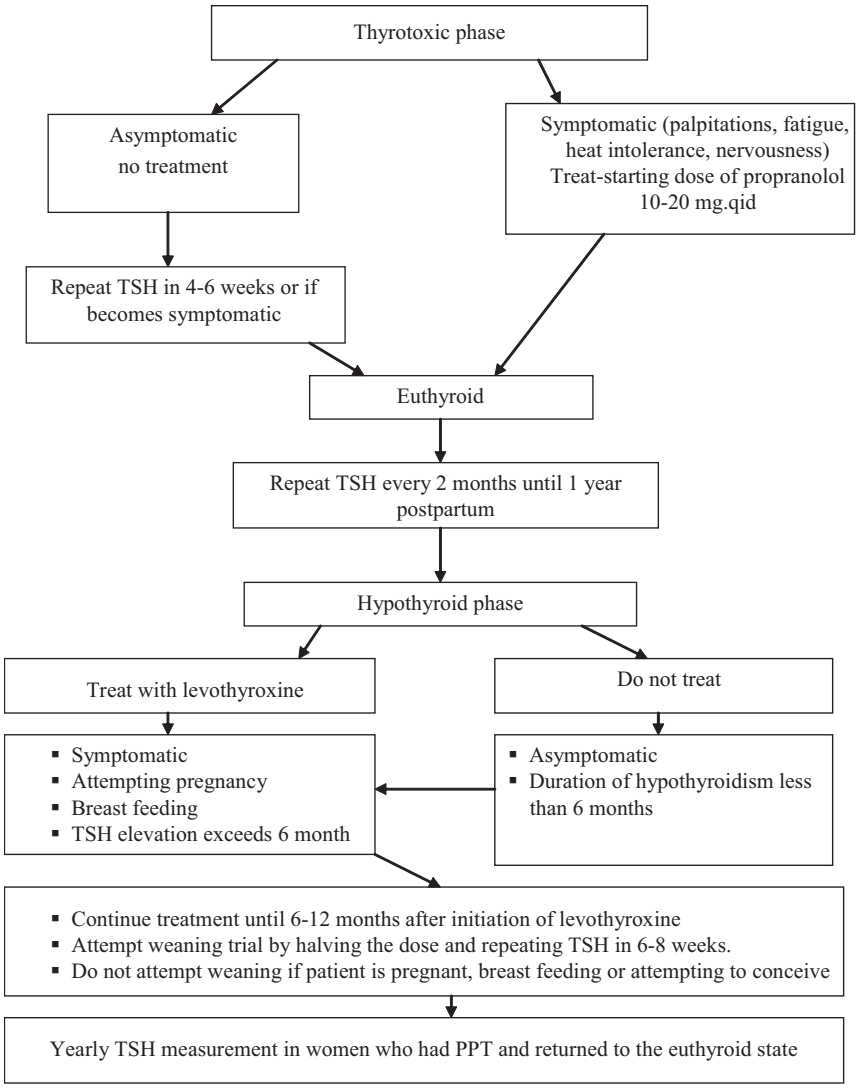

FIG. 1. Algorithm for the treatment and follow-up of women who are diagnosed with PPT. [Reprinted from A. Stagnaro-Green *et al.*: Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 21:1081–1125, 2011 (68), with permission. © American Thyroid Association.]

orders that can occur during and after pregnancy, and not solely the risk of PPT. The American Thyroid Association recently published guidelines for diagnosing and managing thyroid disease during pregnancy and postpartum (68). First-trimester screening, consisting of a TSH and reflex FT4 for an abnormal TSH, was recommended for women identified as high risk for thyroid disorders. The guidelines also state that women with postpartum depression should have a TSH, FT4, and TPO-Ab performed. The present author also recommends that women who have had a prior history of PPT, who have another autoimmune disease, or are known to be TPO-Ab+ be screened at 3 months for PPT with a TSH and reflex FT4. If they are euthyroid and TPO-Ab−, no further screening is indicated. However, if they are TPO-Ab+ and euthyroid, TSH levels should be obtained at 6 and 9 months after delivery.

Treatment

Treatment of PPT (Fig. 1) is based on clinical experience because there have been no trials comparing therapeutic alternatives. Treatment of the hyperthyroid phase is based on achieving symptomatic relief because the thyrotoxic phase of PPT is always transitory, and typically mild. Antithyroid drugs are ineffective because the thyrotoxic phase of PPT is a destructive thyroiditis. Consequently, intervention consists of propranolol titrated to a dose that provides symptomatic relief. Treatment is typically for a couple of months and is weaned based on resolution of symptoms. Levothyroxine administration for hypothyroidism is initiated if the woman is symptomatic, attempting pregnancy, or breastfeeding, or if the TSH elevation exceeds 6 months. Weaning from levothyroxine should be attempted 6 to 12 months after the initiation of therapy unless the woman is pregnant, attempting pregnancy, or breastfeeding. In women who are successfully weaned, annual TSH levels should be performed given the high rate of primary hypothyroidism developing over time.

Returning to the Patient

Given the symptoms of depression experienced by the patient, thyroid tests were obtained. This is consistent with Recommendation 63 of the American Thyroid Association guidelines which state that "women with postpartum depression should have TSH, FT4, and TPO-Ab tests performed" (68). The patient had a high titer of TPO-Ab with an elevated TSH and decreased FT4. Levothyroxine was initiated, and euthyroidism was achieved within a couple of months with a daily dose of 50 μg of levothyroxine. Shortly thereafter, the patient became pregnant. Her second pregnancy was uneventful except for the need to increase the dose of levothyroxine to 75 μg daily to maintain a TSH below 2.5 mIU/liter. At the time of delivery, the patient had a tubal ligation performed because she had completed her family. Six weeks postpartum, her TSH was suppressed and the dose of levothyroxine was decreased to the prepregnancy level. Six months postpartum, the TSH was again elevated, necessitating an increase in the dose of

levothyroxine to 100 μg daily. The changes in levothyroxine needed postpartum where attributed to PPT occurring in the remaining viable thyroid tissue. She stopped breastfeeding at 9 months postpartum. At 18 months postpartum, the levothyroxine dose was decreased in half to determine whether thyroid hormone replacement was still required. Six weeks later, the patient returned noting symptoms of hypothyroidism. Laboratory tests revealed an increased TSH and decreased FT4. The levothyroxine dose was increased to achieve euthyroidism, and the patient was informed that she had developed permanent primary hypothyroidism.

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