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Postpartum Thyroiditis and Autoimmune Thyroiditis in Women of Childbearing Age: Recent Insights and Consequences for Antenatal and Postnatal Care

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Postpartum thyroiditis is a syndrome of transient or permanent thyroid dysfunction occurring in the first year after delivery and based on an autoimmune inflammation of the thyroid. The prevalence ranges from 5–7%. We discuss the role of antibodies (especially thyroid peroxidase antibodies), complement, activated T cells, and apoptosis in the outbreak of postpartum thyroiditis. Postpartum thyroiditis is conceptualized as an acute phase of autoimmune thyroid destruction in the context of an existing and ongoing process of thyroid autosensitization. From pregnancy an enhanced state of immune tolerance ensues. A rebound reaction to this pregnancy-associated immune suppression after delivery explains the aggravation of autoimmune syndromes in the puerperal period, *e.g.*, the occurrence of clinically overt postpartum thyroiditis. Low thyroid reserve due to autoimmune thyroiditis is increasingly recognized as a serious health problem. 1) Thyroid autoimmunity increases the probability of spontaneous fetal loss. 2) Thyroid failure due to autoimmune thyroiditis—often mild and subclinical—can lead to permanent and significant impairment in neuropsychological performance of the offspring. 3) Evidence is emerging that as women age subclinical hypothyroidism—as a sequel of postpartum thyroiditis—predisposes them to cardiovascular disease. Hence, postpartum thyroiditis is no longer considered a mild and transient disorder. Screening is considered. (*Endocrine Reviews* 22: 605–630, 2001)

I. Introduction

THE MOST FREQUENT and best characterized autoimmune thyroid disease postnatally is postpartum thyroiditis. Postpartum thyroiditis is a syndrome of transient or permanent thyroid dysfunction occurring in the first year after delivery and based on an autoimmune inflammation of the thyroid. Classically, a thyrotoxic phase is followed by a hypothyroid phase (1). Several intrinsic and environmental factors have been reported to play a pathophysiological role in its development (2–6). "Postpartum" thyroiditis may also occur after loss of pregnancy at 5–20 wk gestation (7–9).

The syndrome of hypothyroidism after pregnancy was first described in 1948 by Roberton (10). Ginsberg and Walfish (11) recognized the classical thyrotoxic phase preceding this syndrome of puerperal hypothyroidism, and

Abbreviations: ADCC, Antibody-dependent cell mediated cytotoxicity; CTLA-4, cytotoxic T-lymphocyte antigen-4; hCG, human CG; IFN, interferon; IVF, *in vitro* fertilization; MHC, major histocompatibility complex; NK, natural killer; NOD, nonobese diabetic; PIBF, progesterone-induced blocking factor; TBII, TSH binding inhibitory Igs; TH1 and TH2, T helper 1 and 2; TPO, thyroid peroxidase; TSAb, thyroid stimulating antibody; TSH-R Abs, TSH-receptor antibodies.

Amino *et al.* (12) highlighted its clinical importance in the 1980s. Subsequently, the clinical awareness of this condition has become widespread.

Postpartum thyroid syndromes distinct from postpartum thyroiditis have also been identified and include postpartum disturbances in thyroid function in patients with previous or current thyroid disease (2, 3, 13) and postpartum secondary hypothyroidism (14, 15). Combinations of these postpartum thyroid syndromes, as well as combinations of preexisting Graves' disease and Hashimoto's disease with postpartum thyroiditis, have also been described (16–19).

II. Epidemiology of Postpartum Thyroiditis

The prevalence of postpartum thyroiditis varies widely, from 1.1–21.1% (12, 20–38) (Table 1). This wide variation is largely due to differences in the definition of postpartum thyroiditis (39); on the other hand, variable and sometimes inadequate ascertainment and follow-up play a role. Furthermore, in some studies thyroid scintigraphy has been omitted in some of the thyrotoxic patients, thus leading to a possible underestimation of postpartum Graves' disease. Apart from these methodological considerations, environmental and genetic factors in the population are thought to play a role in the variability of prevalence data.

Only two studies, both from Europe, obtained end-point data from more than 70% of the described source population. These studies reported similar prevalences of 6.5% and 7.2%, respectively (24, 30). Recent work from The Netherlands, with a follow-up of 65% of the original cohort, reported a prevalence of 5.2% (26). Nicolai *et al.* (29) reported a prevalence of 6.7% in a North American population with a follow-up of 65%. Hence, the prevalence of postpartum thyroiditis in iodine-sufficient areas ranges between 5–7%.

In patients with type I diabetes mellitus, higher frequencies of postpartum thyroiditis have been described. Gerstein (40) performed a prospective cohort study of 51 pregnant subjects with type I diabetes who were not taking thyroid medication. Forty patients completed follow-up. Thyroid dysfunction occurred in 10 patients: thyroiditis developed in 9 and Graves' disease in 1 patient during the first 6 months after delivery (40). Alvarez-Marfany *et al.* (41) followed 41 women with type I diabetes mellitus, 28 of whom completed follow-up at 31 months postpartum: seven subjects developed thyroiditis. Thus, the incidence of postpartum thyroiditis in type I diabetes mellitus is at least 15%.

III. Thyroid Antibodies, Autoimmune Thyroiditis, and Postpartum Thyroiditis

A. Thyroid peroxidase and thyroglobulin (Tg) antibodies

Postpartum thyroiditis is closely associated with the presence of antibodies to thyroid peroxidase (TPO) (12, 20, 21, 23, 24, 26, 27, 30, 34, 38) (Fig. 1). Indeed, if a pregnant women is positive for TPO antibodies early in pregnancy, her chances of developing postpartum thyroiditis are 30–52% (4, 42–44).

The first thyroid autoantigen discovered (1956) and shown to play a role in Hashimoto's thyroiditis was Tg (45). Later, antibodies were detected to antigens present in the cytoplasm of thyroid follicular cells (46–49). In the 1980s these "cytoplasmic" antigens were characterized as the enzyme TPO (50–53). Antibodies to TPO appeared to be much more prevalent than antibodies to Tg. When both antibodies are present, the titer of TPO antibodies tends to be higher (46, 53, 54). The exclusive presence of Tg antibodies is rare. Thus, for the routine detection of thyroid autoantibodies, it is justifiable to determine TPO antibodies only (55). In this respect it is also notable that TPO antibodies—but not Tg antibodies—can fix complement (56).

Evidence for a pathogenetic role of TPO complement-fixing antibodies is circumstantial. Activation of the complement cascade—an important mechanism for lysis of target cells in immune processes—is associated with the IgG subclasses 1, 2, and 3 (57). With regard to postpartum thyroiditis Parkes *et al.* (58) used both the complement fixation and complement C3 activation index to quantify the interaction of the complement system with thyroid antigen/antibody-complexes. They studied 152 TPO antibody-positive women and an equal number of TPO antibody-negative women. Seventy-five of the TPO antibody positive women remained euthyroid during the postpartum year, and 73 showed biochemical signs of postpartum thyroiditis. The authors provided evidence that the onset and progression of thyroid dysfunction in women with TPO antibodies was not only a function of the titer of the TPO antibodies present, but also of their ability to activate the complement system (58). Also, in another study, the same authors showed that the severity of postpartum thyroiditis, as indicated by the duration of thyroid dysfunction, is related to the ability of TPO antibodies to interact with and activate the complement system (59).

Regarding the IgG subclasses of TPO antibodies Jansson *et al.* (60) found that the relative concentration of IgG1 TPO antibodies was significantly increased in women who became hypothyroid. Hall *et al.* (61) showed significant relative elevations in IgG2- and IgG3-associated TPO antibody activity in women who developed a biphasic thyroid dysfunction. The relative IgG3 elevation coincided with the onset of thyrotoxicosis. Briones-Urbina *et al.* (62) found raised IgG1- and IgG2-associated TPO activity and low IgG3-associated TPO antibody activity in women with postpartum thyroiditis. However, Weetman *et al.* (63) found no differences in IgG subclass-associated TPO antibody distribution between women with postpartum thyroiditis and controls. Therefore, at present, there is no agreement on the significance of the subclass of TPO antibodies in postpartum thyroiditis. What seems clear, however, is that the IgG4-associated TPO antibody activity—which is non-complement-activating—remains unchanged in the postpartum period (60, 62, 63).

Although the association of TPO antibodies with postpartum thyroiditis is strong, a causative role of these antibodies in the pathogenesis of this syndrome remains unclear. In Hashimoto's thyroiditis, antibodies to TPO are thought to play only a secondary aggravating role in addition to other immune destructive mechanisms (6, 55) (Fig. 2). TPO antibodies are indeed able to bind to thyroid follicular cells and to activate the complement system and to set in motion antibody-dependent cell mediated cytotoxicity (ADCC) (see below). However, it is relevant to recall that: 1) TPO is only expressed at the apical border of thyroid follicular cells in a

TABLE 1. Epidemiological data on postpartum thyroiditis

First author (reference)	Yr	Country	No. in source population	Inclusion criteria	No. included	Time of inclusion & last fu	No. of source population included (%)/last fu (%)	Prevalence of TD (n)
Amino (12)	1982	Japan	507 consecutive F who delivered	TD, Tab+ or G	63	3 mo pp/6 mo pp	63 (12)/63 (12)	5.5% (28/507)
Jansson (24)	1984	Sweden	644 consecutive F who delivered	Informed consent	460	2 mo pp/5 mo pp	460 (71)/460 (71)	6.5% (30/460)
Freeman (20)	1986	USA	216 F at routine pp visits	Informed consent	212	4–8 wk pp/8–12 wks pp	212 (98)/44 (21)	1.9% (4/212)
Lervang (27)	1987	Denmark	694 F who delivered	Informed consent	591	3 mo pp/12 mo pp	591 (85)/23 (4)	3.9% (23/591)
Nicolai (29)	1987	USA	238 F who delivered	Informed consent	238	delivery/3 mo pp	238 (100)/154 (65)	6.7% (16/238)
Hayslip (23)	1988	USA	1,034 F who delivered	Tab+	63	2nd day pp/6 mo pp	63 (6)/51 (5)	3.3% (34/1034)
Vargas (35)	1988	USA	261 F completing 1 yr fu	Informed consent	261	delivery/12 mo pp	261 (100)/261 (100)	21.1% (55/261)
Fung (21)	1988	UK	901 F attending an antenatal clinic	Tab+ (tab-co's)	100 (132)	1st trimester/12 mo pp	220 (24)/82 (9)	16.7% (49/220)[a]
Rajatanavin (31)	1990	Thailand	812 F who delivered	Tab+	812	6 wks pp/12 mo pp	812 (100)/67 (8)	1.1% (9/812)
Rasmussen (32)	1990	Denmark	1,163 F in the 1st trimester	Tab+ (tab-co's)	36 (20)	1st trimester/12 mo pp	56 (5)/56 (5)	3.3%[a] (33% of 10% Tab)
Roti (33)	1991	Italy	372 F who delivered	Informed consent	219	1 mo pp/12 mo pp	219 (59)/42 (11)	8.7% (19/219)
Walfish (36)	1992	Canada	1376 F who delivered	Informed consent	1376	delivery/12 mo pp	1376 (100)/300 (22)	5.9% (81/1376)
Stagnaro-Green (34)	1992	USA	552 F in the 1st trimester	Tab+ (tab-co's)	38 (32)	1st trimester/6 mo pp	60 (11)/60 (11)	8.8%[a,b]
Harris (22)	1992	UK	1,248 F attending an antenatal clinic	Tab+ (tab-co's)	145 (229)	2nd trimester/8 mo pp	374 (30)/374 (30)	5.0% (62/1248)[a,c]
Pop (30)	1993	Netherlands	382 pregnant F	Informed consent	303	3rd trimester/8 mo pp	303 (79)/293 (77)	7.2% (21/293)
Kuijpens (26)	1998	Netherlands	448 pregnant F	Informed consent	310	1st trimester/9 mo pp	310 (69)/291 (65)	5.2% (15/291)
Kent (25)	1999	Australia	1,816 F who delivered	Informed consent	748	6 mo pp/6 mo pp	748 (41)/748 (41)	10.3% (76/739)
Lucas (28)	2000	Spain	757 pregnant F	Informed consent	605	delivery/12 mo pp	605 (80)/444 (59)	7.4% (45/605)
Barca (37)	2000	Brazil	830 pregnant F with no TD, no G/C/N, Tab−	Informed consent	800	1st trimester/12 mo pp	800 (96)/335 (40)	14.6% (49/335)
Sakaihara (38)	2000	Japan	4,072 pregnant F in a screening program	—	4072	1st trimester/3 mo pp	1161/4072	6.5% (76/1161)

fu, Follow-up; Tab, thyroid antibodies; TD, thyroid dysfunction; TF, thyroid function; F, females; pp, postpartum; G/C/N, goiter, cysts, or nodules.
[a] Estimated prevalence.
[b] 33% of 18% Tab+ and 3% of 82% Tab−.
[c] 43% of 12% Tab+ and 0% of 78% Tab−.

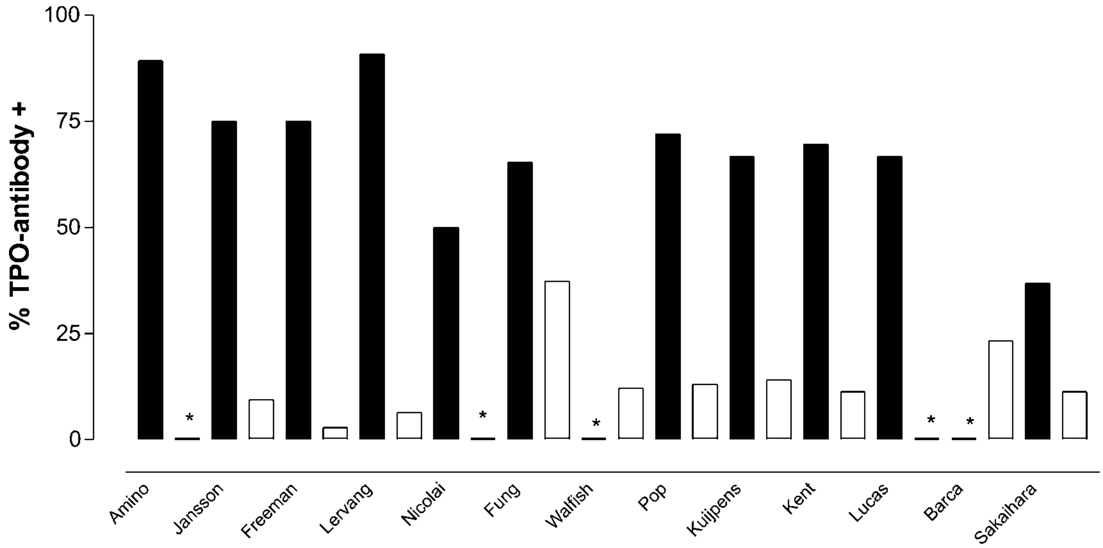

FIG. 1. ■, Prevalence of TPO antibodies in women with postpartum thyroiditis. □, Prevalence of TPO antibodies in women without postpartum thyroiditis. An *asterisk* denotes that the TPO antibody prevalence is not given or cannot be calculated from the data. See Table 1 for details of the studies.

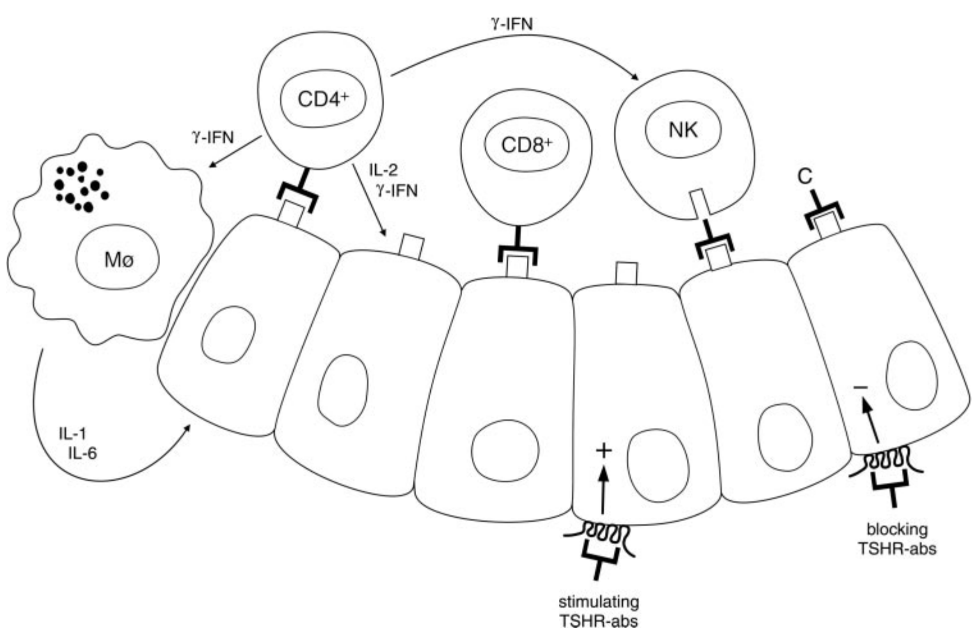

FIG. 2. The various immune mechanisms leading to alterations in thyroid metabolism and growth: 1. Thyroid-specific antibodies () *e.g.,* TPO-antibodies, recognize their target-antigens (■) on the surface of thyrocytes. These antibodies may activate complement (C) or NK cells via Fc receptors (the latter is the so-called ADCC). 2. Target antigens () can also be recognized by $CD8^+$ T cytotoxic cells or $CD4^+$ TH1 cells producing γ-IFN and IL-2. These cytokines have direct effects on thyrocyte growth and metabolism. γ-IFN is also able to activate macrophages (Mϕ) to kill thyrocytes or to produce IL-1 and IL-6 influencing thyrocyte growth and metabolism. 3. Furthermore, antibodies directed to the TSH-R either stimulate or block the receptor and coupled to the receptor various second messenger systems. This will either lead to stimulation or blockade of thyrocyte growth and metabolism.

position where it is hardly accessible to circulating antibodies if the follicles are intact (64); 2) there is only a weak association between complement-fixing thyroid cytotoxic antibodies and hypothyroidism in chronic autoimmune thyroiditis, these antibodies being found even in sera of euthyroid patients (56); 3) babies born to mothers with chronic autoimmune thyroiditis and circulating TPO antibodies have normal thyroid function (65); 4) circulating TPO antibodies are found in sera of a consistent percentage of euthyroid elderly women (66).

Bispecific antibodies with dual specificity for Tg and TPO are also associated with autoimmune thyroid disease. Initially, these antibodies were reported not to be associated with postpartum thyroiditis (67). However, in a recent multicenter study of 3,122 patients with various thyroid and nonthyroid diseases and normal subjects, the prevalence of these bispecific antibodies was 16% in subjects with postpartum thyroiditis (68). In normal control subjects (n = 220) a prevalence of only 1.4% was found. The value of 16% in postpartum thyroiditis was also significantly different from levels found in patients with Hashimoto's thyroiditis (40.5%) and Graves' disease (34.6%). Although these differences were statistically significant, the clinical relevance of these antibodies is at present unclear.

In conclusion, there is a strong association between the presence of TPO antibodies and the risk of developing postpartum thyroiditis. However, there are several good arguments against a role of TPO antibodies as the primary disruptive event in the pathogenesis of postpartum thyroiditis.

B. TSH-receptor antibodies (TSH-R Abs)

The number of studies on the role of TSH-R Abs in postpartum thyroiditis is limited. In a study from the United Kingdom TSH-R Abs were found in none of 37 women who experienced a thyrotoxic phase of postpartum thyroiditis (59). In North America and Japan, however, TSH-R Abs have been reported to occur in postpartum thyroiditis, particularly in the thyrotoxic phase. In a study of 25 Japanese postpartum women, TSH binding inhibitory Igs (TBII) were present in six, and in five of these thyroid-stimulating antibody (TSAb) activity was high. This study showed, additionally, that the hypothyroid phase was associated with an increased activity of TBII and/or a disappearance of TSAb activity (69). In another Japanese study of 71 TPO antibody-positive subjects in early pregnancy, 7 were also positive for TSH-R Abs, and all 7 developed thyroid dysfunction in the postpartum period. Five developed Graves' disease, and the remaining 2 developed transient hypothyroidism (70).

Interestingly, some case reports from North America have described postpartum thyroiditis preceding the onset of Graves' disease (71, 72). On the basis of an extensive immunological evaluation of two of these cases, Sarlis *et al.* (71) have proposed a possible pathogenic association in which TSH-R Abs play a role in the transient phases of thyrotoxicosis and hypothyroidism in the postpartum period. The authors demonstrated heterogeneity in TBII and showed the presence of stimulating TSH-R Abs activating either the cAMP or the phosphatidylinositol 4,5-bisphosphate signal cascades at the time of diagnosis of postpartum Graves' disease. It was therefore suggested that susceptible individuals might develop an immunological response that can trigger the appearance of a mixture of species of TSH-R Abs, which may lead to the sequential occurrence of painless thyroiditis and Graves' disease after pregnancy. The multiple phases of thyrotoxicosis and hypothyroidism that can occur in these patients may then reflect the existence and changing spectrum of the various TSH-R Abs in their sera (71). In our area—The Netherlands—however, the prevalence of TSH-R Abs is very low (0.3%), and until now—as in the United Kingdom—cases of TBII-positive postpartum thyroiditis have not been reported. We are thus of the opinion that in Western Europe TSH-R Abs in the postpartum period should be taken as reflecting *de novo* or relapsing Graves' disease (and not of postpartum destructive thyroiditis in the sense we discuss it here).

Interestingly, several studies have found that the first postpartum year not only constitutes an important risk factor for the development of autoimmune destructive thyroiditis, but also of Graves' disease (73–76). With regard to persistent thyrotoxicosis after pregnancy, Hayslip *et al.* (77) tested serum for the presence of TSH-R Abs in three such cases, all of which were positive for both TBII and TSAb. The authors also tested 21 women with classical postpartum thyroiditis for TSH-R Abs. Only one woman with hypothyroidism had high levels of TSH-R Abs when she was hypothyroid and 1 month after initiation of T_4 therapy.

In conclusion, exacerbation of existing Graves' disease or *de novo* Graves' disease does occur after pregnancy. However, studies differ in prevalence between North America and Japan *vs.* Europe. It would be of interest to study the onset of Graves' disease in relation to the puerperal period in larger prospective studies.

IV. Cell-Mediated Immunity, Autoimmune Thyroiditis, and Postpartum Thyroiditis

T lymphocytes are crucial in the pathogenesis of autoimmune thyroiditis (6, 78–83). This has been clearly shown in T lymphocyte transfer studies in animal models of spontaneously developing autoimmune thyroiditis (84), such as the biobreeding-diabetes prone (BB-DP) rat (85), the obese strain (OS) chicken, and the nonobese diabetic (NOD) mouse (86–89).

First, autoreactive T lymphocytes must be involved in the autoimmune process because the autoreactive B lymphocytes need the help of T-helper 2 (TH2) lymphocytes to produce the TPO and Tg antibodies of the IgG isotype (90). TH2 lymphocytes bear the marker CD4 and produce the B cell-stimulatory cytokines IL-4 and IL-5 (91). Another TH2 type cytokine is IL-10, which has immunosuppressive capabilities, particularly for cell-mediated immune destructive mechanisms (92, 93). Hence TH2 lymphocytes are presently considered as relatively harmless for target cells in endocrine autoimmune diseases, also because the antibodies play only a secondary role.

Apart from TH2 lymphocytes, there is a subset of T cells that is also CD4+, the so-called T-helper 1 (TH1) lymphocytes. These cells are—unlike TH2 cells—well equipped to stimulate the cytotoxic and cytolytic arm of the cell-mediated immune system, *e.g.*, to activate macrophages and natural killer (NK) cells via cytokines such as γ-interferon (γIFN) to kill target cells (94) (Fig. 2).

In addition to CD4+ TH1 cells, T lymphocytes of CD8+ phenotype are also generally involved in the destruction of target cells (Fig. 2) (6). These cytotoxic cells recognize autoantigens directly on target cells when in the context of major histocompatibility complex (MHC) class I molecules. Target cells are killed by CD8+ T lymphocytes via perforin and other cytotoxic molecules.

The balance between life and death of target cells is also regulated by proapoptotic and antiapoptotic factors operative in the target cells when under immune attack. Proapoptotic signal generation by the death receptor CD95—also known as Fas—requires recruitment and activation of downstream initiator and effector caspases (a family of cysteine proteases that catalyze the enzymatic and catabolic reactions that lead to cell death), which can be antagonized by antiapoptotic molecules such as members of the bcl-2 family and cFLIP (95, 96).

The interaction between CD95 and its ligand CD95L has recently been proposed as a major mechanism for autoimmune thyrocyte destruction in Hashimoto's thyroiditis (97, 98). CD95L is constitutively expressed on thyrocytes (99). After autoimmune T and B cell inflammation, thyrocytes also start to express CD95 in Hashimoto's thyroiditis. The thyrocytes are therefore likely to die through "suicide" or "fratricide" (100). Although CD8+ T cells do occur in high numbers in Hashimoto's thyroiditis, a direct cytotoxic effect of CD8+ infiltrating T lymphocytes is, however, less likely as a major contributor to thyrocyte destruction: CD8+ T cells that approach thyrocytes are CD95 positive and are thereby themselves vulnerable to apoptosis via the CD95L expression by thyrocytes (99). It is probably the secretion of TH1 cytokines by CD4+ and CD8+ T cells in Hashimoto's thyroiditis that is important: IFN γ activates infiltrating macrophages to become cytolytic/cytotoxic, while the cytokine also promotes the caspase up-regulation and CD95-induced apoptosis in thyrocytes of Hashimoto's glands (6, 101). There are indications that in Graves' disease T cell infiltrates work differently—although up-regulating CD95 on thyrocytes, the T cells now also up-regulate antiapoptotic mechanisms (cFLIP and Bcl-xl) in the thyrocytes due to their TH2 type character. The final outcome is then nondestructive (102).

There are many studies on immune cell abnormalities in postpartum thyroiditis. These will be reviewed below. Collectively, these studies support the notion that such mechanisms play a role and that indeed the syndrome should—at least in part—be regarded as belonging to the spectrum of autoimmune thyroid diseases.

A. Histology of postpartum thyroiditis

The histological features of postpartum thyroiditis are entirely consistent with an autoimmune etiology. Two types of thyroidal lymphoid cell infiltrates are normally observed in classical Hashimoto's thyroiditis:

1. *Destructive infiltrates (103).* These infiltrates do not show a recognizable pattern of topological organization and consist of mixtures of CD4+ and CD8+ T lymphocytes, macrophages, NK cells, and some B lymphocytes. The infiltrating cells are found in areas of destroyed thyrocytes, which are CD95 and CD95L positive. The milieu of the infiltrates is presumably of TH1 character, promoting its cytolytic potential (91).

2. *Focal accumulations of lymphoid cells with a high degree of histological organization (104).* These infiltrates are not destructive and may be found side-by-side intact thyrocytes in mild forms of Hashimoto's autoimmune thyroiditis (focal thyroiditis). They can also be seen in Graves' disease (105–107). The infiltrates represent intrathyroidally developed lymphoid tissue of an architecture similar to that of mucosa-associated lymphoid tissue. Such thyroid-associated lymphoid tissue is composed of T cell zones, B cell follicles, and plasma cells in the periphery of the focal infiltrate. Sometimes the plasma cells extend in cord-like structures radiating from the lymphoid tissue between the thyroid follicles. We presume that this lymphoid tissue is involved in the generation of the actual thyroid autoimmune reaction, including the production of autoantibodies (108). The T cell zones of the intrathyroidal lymphoid tissue consist of CD4+ and CD8+ lymphocytes in a ratio of about 2–3:1. The function of the T lymphocytes in these focal accumulations is thought to be the regulation of the autoimmune response. In Graves' disease, such infiltrates presumably have a TH2 pattern of cytokine production that might confer a defense against apoptotic destruction.

With regard to postpartum thyroiditis, Mizukami *et al.* (109) described histological and immunohistochemical findings of thyroid tissue in a series of 15 patients with this disease. Histology revealed both the focal organized and the diffuse destructive type of lymphocytic thyroiditis with folliculolysis and disruption. Intact follicles showed mild epithelial hyperplasia. There was no difference between the hypothyroid and early recovery phase. Three specimens from the late recovery phase showed only histological features of focal thyroiditis without follicular destruction. Unfortunately, there are no histological data on patients with permanent hypothyroidism after an episode of postpartum thyroiditis. The immunohistochemical examination by Mizukami *et al.* (Ref. 109, but see Ref. 110) as well also showed a significantly increased expression of MHC class II antigen on thyroid follicular cells. Since inflammatory T cell cytokines, such as γIFN, up-regulate MHC class II expression on thyrocytes, such expression probably indicates a local production of such cytokines by infiltrating T cells (111, 112). The importance of MHC class II expression on thyroid epithelial cells is no longer viewed as a sign of the thyrocytes' capability to present antigen to T cells. Although capable of stimulating T cells, other professional antigen-presenting cells in their vicinity, such as the dendritic cells, are better in such function. The MHC class II expression of the thyrocytes is therefore just a sign of the TH1 pattern of cytokine production in their vicinity, which will actually contribute to their destruction.

B. T lymphocytes

Chan and Walfish (113) studied the expression of MHC class II as a marker of T lymphocyte activation. Of 28 postpartum patients, 4 were studied in the thyrotoxic phase and 11 in the hypothyroid phase, and the remaining 13 were euthyroid after a previously documented hypothyroid or thyrotoxic phase. Patients in the thyrotoxic phase had a significantly increased proportion of circulating activated T lymphocytes. Similar data were not provided for patients in the hypo- and euthyroid phases. When CD4 and CD8 subsets were quantified, patients in the hypo- and euthyroid states had significantly higher percentages of the CD4+ subset and significantly lower percentages of the CD8+ subset, leading to higher CD4/CD8 ratios compared with thyrotoxic patients.

Stagnaro-Green *et al.* prospectively followed 33 thyroid autoantibody-positive and 28 antibody-negative women during pregnancy and 6 months postpartum. Evidence of T cell activation (*i.e.*, raised numbers of MHC-class II+ cells) was found in the postpartum period, and a higher CD4/CD8 ratio occurred in women developing postpartum thyroiditis compared with normal postpartum TPO antibody-negative controls (34).

In a prospective study of 291 women, 15 of whom developed postpartum thyroiditis, Kuijpens *et al.* studied various cell-mediated immune parameters including the number of circulating MHC-II+ T lymphocytes in pregnant women from 12 wk of gestation until 9 months postpartum. They too detected T cell activation in TPO-positive women subsequently developing postpartum thyroiditis: percentages of MHC-II+ T cells were significantly higher at all time points studied (12 and 32 wk of gestation and 4 wk postpartum) in TPO-positive women developing postpartum thyroiditis compared with TPO-positive women not developing the disease (26) (Fig. 3).

Collectively, the data from these studies are suggestive of an activation of circulating T cells in postpartum thyroiditis.

Jansson *et al.* (114) investigated circulating, as well as intrathyroidal, lymphocyte subsets in different stages of postpartum thyroiditis. The authors were unable to find differences in circulating lymphocyte subsets between 9 thyrotoxic and 18 hypothyroid patients *vs.* normal controls. Intrathyroidal lymphocyte subsets obtained by fine-needle aspiration were comparable in the 10 hypothyroid and the 3 thyrotoxic patients with adequate aspirates (in normal subjects, intrathyroidal lymphocytes are absent). The authors found differences between subset distribution in the thyroid and the circulation. There was a relative accumulation of B cells within the thyroid of hypothyroid patients compared with peripheral blood. Also, a relative decrease in intrathyroidal CD8+ T cells resulted in higher CD4+/CD8+ ratios in the thyroid aspirates than in the blood of hypothyroid patients with postpartum thyroiditis. According to the authors, these data are compatible with the local synthesis of thyroid-directed autoantibodies in postpartum thyroiditis (114). However, in our opinion these data just highlight the different migration and homing patterns of the various subsets of immune cells to sites of chronic inflammation.

C. Natural killer (NK) cells

Apart from the CD3+ T cells and the CD19+ CD20+ B cells, there is yet another subset of lymphocytes important in cell-mediated immunity. These are the NK cells or large granular lymphocytes. NK cells are lymphocytes with distinct morphological and functional properties. Their cell surface classically expresses CD16 and CD56 antigens. NK cells are able to kill tumor cells without the need for prior sensitization. NK cells are activated by IL-2, IFNα, and -β and particularly by IL-12. The cells have two main mechanisms of target cell killing.

The first mechanism is ADCC. Fc receptor-bearing cells, such as the NK cells and macrophages, are capable of binding to the thyrocyte via a linking of their Fc receptors with antibodies bound to the surface of thyrocytes. Once activated, the NK cells lyse target cells via the release of perforin and lymphotoxin (6, 115, 116).

The second mechanism makes use of cell-cell contact in which special, yet ill defined, lectin-like NK-receptors, known as NKR-P1 receptors, recognize glycosylated surface molecules on target cells. Once activated, the NK cells lyse target cells again via the release of perphorin and lymphotoxin. NK cells are also able to secrete cytokines such as γIFN,

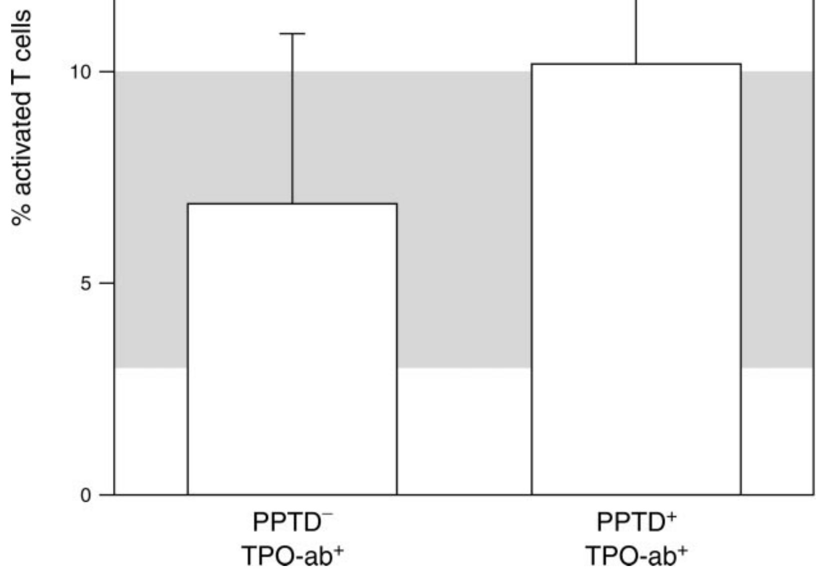

FIG. 3. The percentage of circulating activated T cells in TPO-antibody positive (TPO-Ab$^+$) pregnant women. The percentage of circulating T cells was calculated for each pregnant woman as the mean of three values measured at gestational weeks 12 and 36 and 4 wk postpartum. As can be seen, TPO-Ab$^+$ women who develop postpartum thyroiditis (PPTD$^+$, n = 10) have significantly higher values of circulating activated T cells than TPO-Ab$^+$ women who do not develop PPTD (n = 16). The difference is statistically significant (*t* test, $P < 0.05$, Instat program). The *hatched area* represents values found in nonpregnant, TPO-Ab$^-$, healthy controls. [Reproduced with permission from J. L. Kuijpens *et al.: J Clin Endocrinol Metab* 83:1959–1966, 1998 (26). © The Endocrine Society.].

which further promotes the cellular immune response and recruits T cells. Interestingly, NK cells (but also the CD8+ cytotoxic T lymphocytes) possess, in addition to the above described receptors that activate the killing machinery in the cell, special inhibitory receptors. These so-called killer cell inhibitory receptors (KIRs) are able to recognize MHC class I molecules. Hence, when target cells abundantly express MHC-class I molecules, NK cells will not be able to kill these cells (116).

Neither Hayslip *et al.* (77) nor Hidaka *et al.* (117) observed a difference in functional NK activity of peripheral blood lymphocytes in patients with postpartum thyroiditis compared with normal postpartum women. However, when Hidaka *et al.* (117) analyzed serial changes of NK cell activity in individual patients they found a significant increase in NK activity during the postpartum phase of thyrotoxicosis caused by either destructive thyroiditis or Graves thyrotoxicosis (around 2–4 months postpartum). This might suggest that thyrotoxicosis *per se* stimulates NK cell activity. Indeed, IL-12—a NK activating cytokine—is raised in the thyrotoxic state (118).

We, ourselves, should also realize that NK cells are not only involved in target cell lysis, but also act in the regulation of the B and T cell growth and activation (119). Changes in NK cell numbers and activities may therefore not only serve defense mechanisms directly, but may also reflect altered setpoints in the immune system. This latter notion may explain observations by Kuijpens *et al.* (26). These investigators found that NK cell levels were not associated with postpartum thyroiditis itself, but with TPO antibody positivity: TPO antibody-positive pregnant women had low percentages of circulating NK cells. There was no difference between those developing postpartum thyroiditis and those who did not. Interestingly, NK cell numbers are also low in states of psychological depression and may therefore reflect altered setpoints in the hypothalamo-pituitary-adrenal axis, which occurs in severely depressed patients.

In conclusion, changes in NK cell numbers and activities have been found in postpartum thyroiditis, but the role of NK cells in the development of postpartum thyroiditis remains uncertain. Clearly, further research is needed.

When the above described data on TPO antibodies, complement, activated T cells, apoptosis, and the histology of postpartum thyroiditis are combined, a picture is emerging that at least part of the postpartum thyroiditis cases must be regarded as aggravations of an ongoing process of thyroid autosensitization, leading to an enhanced violation of thyrocyte integrity. When their cases of postpartum thyroiditis are studied in detail, it is relevant to note that Kuijpens *et al.* (26) came to the conclusion that two forms of postpartum thyroiditis might exist, an autoimmune and a nonautoimmune form. The autoimmune form, 10 of their relatively low number of 15 cases, was immunologically characterized by the presence of TPO antibodies and various cell-mediated immune disturbances. The nonautoimmune form, 5 cases, lacked any sign of immune involvement. These latter cases were also different in their symptomatology in that they experienced only a mild transient phase of thyrotoxicosis. Further research on larger series of postpartum thyroiditis cases is necessary to confirm or refute the existence of two such forms and their associated clinical implications.

In postpartum thyroiditis the rapid destruction of thyroid follicles is most frequently followed by a recovery of thyroid function. At present, it is largely unclear how the immune system generally regains equilibrium after activation; and this is also the case for the recovery phase after postpartum thyroiditis. A few mechanisms have been discussed in this respect (74). First, apoptosis of T cells can be induced by exposure to large amounts of antigen. The transience in postpartum thyroiditis might thus be due to the induction of clonal apoptosis of thyroid-specific T cells that may follow the release of thyroid antigens in the circulation when many thyrocytes lose their integrity. Second, it is now known that cells traffic between fetus and mother during normal human pregnancy (120), and particularly the delivery is a time for major entry of fetal cells into the mother's circulation (121). It has therefore been hypothesized that if tolerance to these microchimeric cells develops, immuno-tolerogenic mechanisms similar to those observed during pregnancy are involved, and that this may lead to an attenuation of the thyroid autosensitization (74, 122). Indeed, in a mouse model it has recently been shown that in 60% of pregnant animals with experimentally induced thyroiditis fetal cells were present within the maternal thyroid, as compared with no fetal cells in the thyroids of the control mice (123, 124). Also the induction of PRL secretion as a result of breast-feeding is a factor that could play a role in the transient character of postpartum thyroiditis. PRL is able to influence immune function (125). Human T and B lymphocytes contain PRL receptors, the immuno-incompetent state in hypophysectomized mice is restored by PRL administration, and antibodies to PRL can inhibit lymphocyte proliferation (126–128). The effects of hyperprolactinemia on human immune function have, however, not been clearly elucidated. With respect to breast-feeding and the occurrence of postpartum thyroiditis, it should be noted that in a prospective study no relation between breast-feeding and postpartum thyroiditis was noted (21).

V. The Pathogenesis of Autoimmune Thyroiditis: A Polygenic, Multifactorial Disease. Are Multiple Factors Also Involved in the Outbreak of Postpartum Thyroiditis?

Since the above reviewed data are highly suggestive that the puerperal period is a precipitating factor for an aggravation of autoimmune thyroiditis, it becomes relevant to address the question on the pathogenesis of autoimmune thyroiditis in general. The natural course of autoimmune thyroiditis is thought to encompass a long subclinical prodromal phase. Therefore, researchers have turned to the earlier mentioned inbred animal models of spontaneously occurring variants of autoimmune thyroiditis to study the pathogenesis and the early phases of the disease. The studies performed in animal models have led to the conclusion that organ-specific autoimmune syndromes, such as autoimmune thyroiditis, should be regarded as polygenic diseases, with a penetrance that is strongly influenced by environmental factors (Fig. 4) (6, 87). The interaction of various permissive environmental factors with an immune system that fails to distinguish adequately between self and nonself leads to the activation of a plethora of pathogenic immune mechanisms. In the animal models an afferent stage of enhanced autoantigen presentation, a central stage with excessive expansion and maturation of autoreactive T and B lymphocytes, and an efferent stage of the pathogenic effects of autoreactive T lymphocytes and B lymphocytes on their targets can be discerned (Fig. 4). In each stage, endogenous and/or exogenous factors are able to elicit the abnormalities characteristic of that stage (Fig. 4). Only combinations of genetic susceptibilities, gender, and environmental factors, such as infectious agents, dietary factors, and toxins, lead to clinically overt autoimmune disease.

Also in humans there is evidence that the clinically overt stage of autoimmune thyroiditis is preceded by a phase of TPO antibody-positive subclinical thyroiditis of variable duration (Fig. 5). Genetic factors are not the only determinants in the development and progression of the disease. This is elegantly illustrated by studies of chronic autoimmune hypothyroidism in twins (129). Genetic susceptibility is implicated in autoimmune thyroid disorders by concordance rates that are higher in monozygotic pairs than in dizygotic pairs. However, the fact that the concordance rate among monozygotic twins is always below 1 strongly suggests that environmental factors also are of etiological importance.

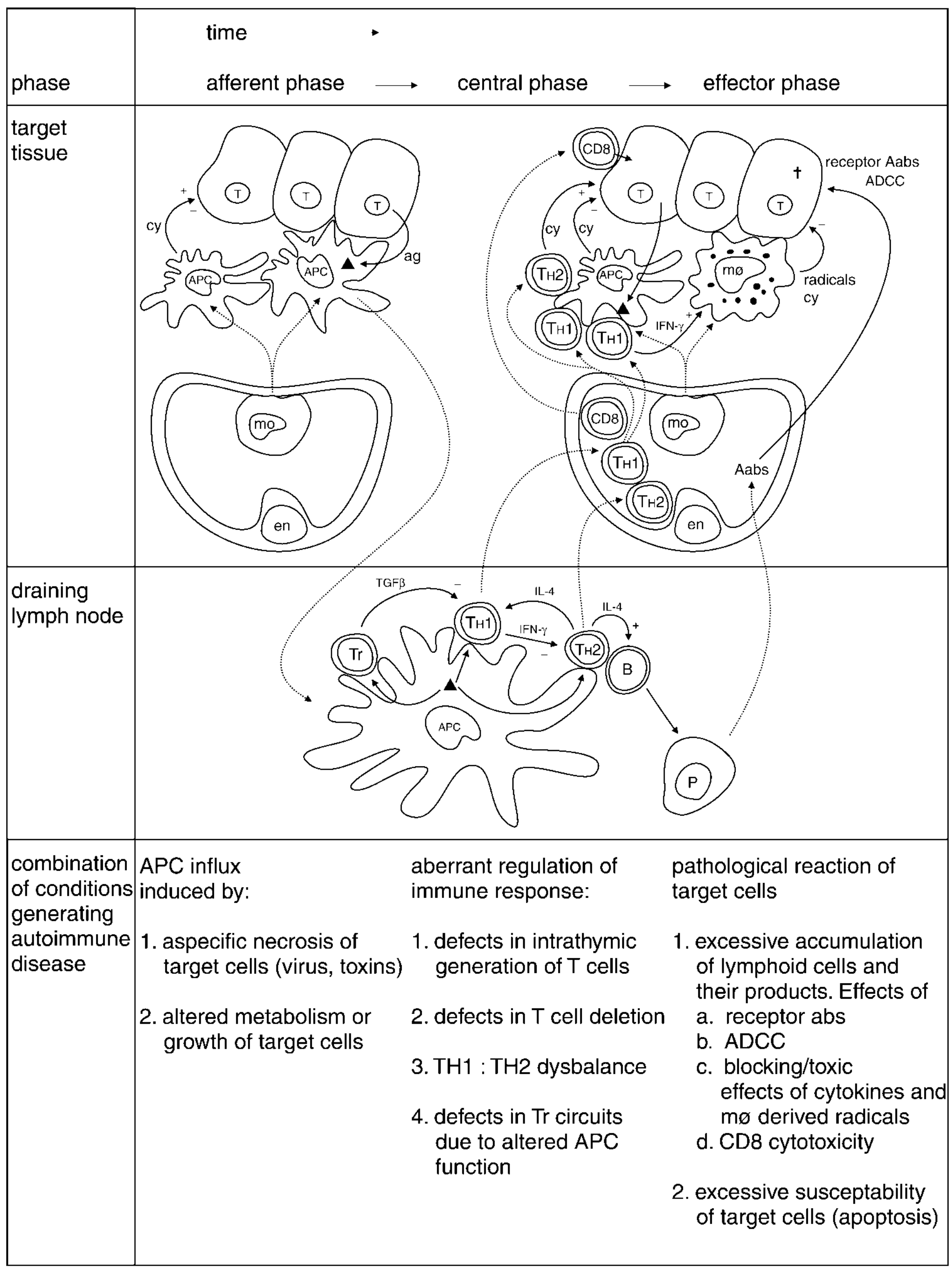

FIG. 4. In a bird's eye view, the following developmental stages can be distinguished in the thyroid autosensitization process, leading to spontaneously developing thyroid autoimmune disease in animal models: 1. An initial, *afferent phase* of an accumulation of antigen presenting cells (APC), particularly of dendritic cells and subclasses of macrophages (Mϕ) in the thyrocyte (T). Such APC influx can be induced, for instance, by an aspecific necrosis of thyrocytes due to iodine intoxication. 2. A later, *central phase* of an apparently uncontrolled production of autoreactive CD4$^+$ T lymphocytes, CD8$^+$ T lymphocytes, and of autoantibodies of the IgG class. Initially, this production of immune effectors takes place in the draining lymph nodes due to the traffic of APC from the thyroid to the draining lymph nodes. Later, immune effectors are also produced in areas of lymphoid tissue locally developed in the thyroid. The uncontrolled production of immune effectors is due to an inborn aberrant regulation of the immune response. Many defects leading to such aberrant regulation exist in the various animal models. Some are listed in the figure. 3. A last, *efferent phase* in which the thyrocytes become susceptible for the autoimmune attack exerted by the generated autoreactive T lymphocytes, the macrophages and the autoantibodies (see also Fig. 2). This commonly results in the destruction of the tissue, or in a blockade of its function or growth, as is the case in autoimmune hypothyroidism. Occasionally, it may also result in stimulation of the thyrocyte, as is the case in Graves' disease (see also Fig. 2). Aabs, Autoantibodies; Cy, cytokines; en, endothelial cell; mo, monocyte; P, plasma cell; Tr, T regulator cell.

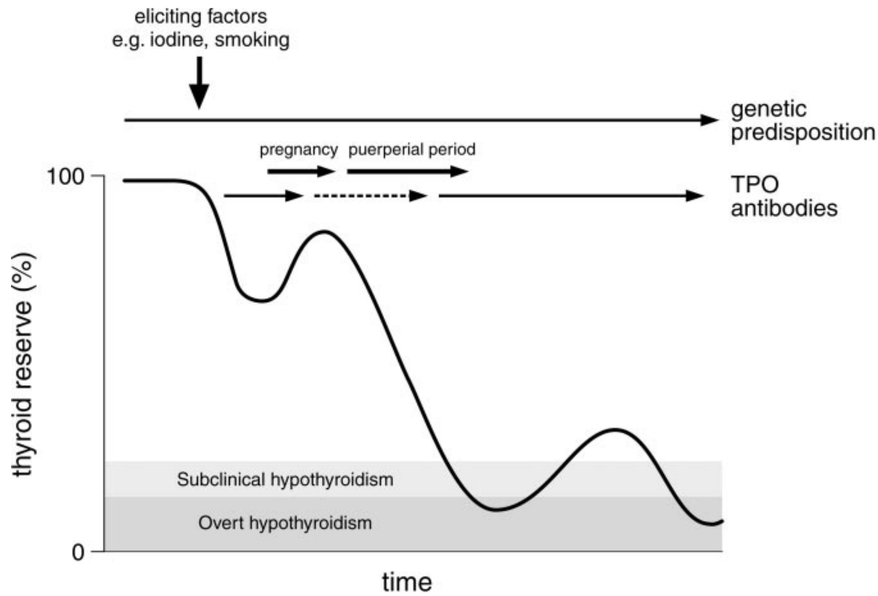

FIG. 5. A scheme depicting the gradual loss of thyroid reserve over time (often years) due to thyroid autoimmune mechanisms. On the basis of a genetic predisposition for endocrine and thyroid autoreactivity, an insult on the level of the thyroid [leading to the attraction of antigen-presenting cells (APC)], and various other eliciting factors (*e.g.*, smoking) (see Fig. 4) a thyroid autoimmune reaction is initiated. TPO antibodies are markers of the ongoing thyroid autosensitization process. Pregnancy ameliorates the process, while the puerperal period aggravates thyroid autoimmunity. If thyroid reserve was already considerably compromised before pregnancy, or if the transient autoimmune attack in the puerperal period is severe enough, subclinical hypothyroidism and even overt hypothyroidism will develop (PPTD).

A. Genetic influences

Multiple genes determine the aberrant immune response toward self in organ-specific autoimmunity. Most important are the genes of the major histocompatibility region (MHC) region located on the short arm of chromosome 6. MHC molecules are the antigen-presenting molecules located on the cell membrane of antigen-presenting cells (130). These molecules determine the T cell response to specific peptide structures (Fig. 6) (87). There is a strong association between the genetic inheritance of the MHC molecules HLA-DR3, -DR-4, and -DR-5 and the occurrence of thyroid-specific autoimmune diseases (131). It is thought that these MHC molecules and the associated DQ molecules represent structures with an enhanced capability to present the major thyroid antigens TPO and Tg to T cells (57).

Genes other than the MHC genes are also involved in the aberrant immune response toward self. One of these genes, the cytotoxic T-lymphocyte antigen-4 (CTLA-4) gene on chromosome 2q33, is a general regulator of the immune reaction (132). CTLA-4 is a costimulatory molecule with an important negative effect on T cell activation (Fig. 6) (133). The CTLA-4 locus has recently been linked to and associated with the occurrence of Graves' disease and thyroid-associated orbitopathy as well as with the occurrence of type I diabetes (134–137).

With regard to postpartum thyroiditis, several authors have reported an association between the syndrome and HLA-DR3 (34, 138–140), HLA-DR 4 (5, 141, 142), and HLA-DR5 (35, 61, 139, 143) (Table 2). Jansson *et al.* (5) found that all three women who developed permanent hypothyroidism were HLA-DR5 positive, suggesting that this phenotype might be related to the development of permanent hypothyroidism. In a population-based case-control study in the United Kingdom including 122 women (of whom 58 had TPO and/or Tg antibodies and 64 had postpartum thyroiditis) and 161 thyroid autoantibody-negative controls, no significant association was found between the CTLA-4 polymorphism and postpartum thyroiditis (144).

In conclusion, there are clear associations of certain MHC genes with postpartum thyroiditis.

B. Female gender, pregnancy, and thyroid autoimmune predisposition

Thyroid autoimmune diseases have a predilection for the female gender (145, 146). The female-male ratio for most thyroid diseases is 4:1 (147, 148). Likewise, in the NOD mouse model, females are more prone to autoimmune diseases. Castration of young males increases the prevalence rates of type I diabetes mellitus at a later age, indicating a protective role of T. Indeed, when the male castrated NOD mice are treated with T, autoantibody levels and autoimmune inflammation decrease again (149, 150). However, castration of young female NOD mice does not lead to a significant lowering of autoimmune insulitis; neither does treatment with supraphysiological doses of E of NOD mice lead to an acceleration of autoimmunity (150). In other animal models of autoimmune disease (systemic lupus erythematosus models) E administration does have some accelerating effects (151). This might indicate that the role of female hormones is limited in endocrine autoimmune diseases. In human male-to-female transsexuals castration followed by treatment with female hormones did not induce higher levels of TPO antibodies compared with the normal female population (152). This illustrates the complexity of the phenomenon of T-induced immunosuppression and highlights the danger of extrapolating from animal data to the human situation.

During pregnancy many patients with autoimmune disorders experience a remission (148, 153–156). The explanation for this phenomenon is based on a heightened state of immune tolerance induced by the pregnant state (157, 158). Adaptation of the maternal immune system is essential for immune tolerance of the fetus, since the fetus expresses paternal MHC molecules (157, 158).

The placental immune system plays a central role in the

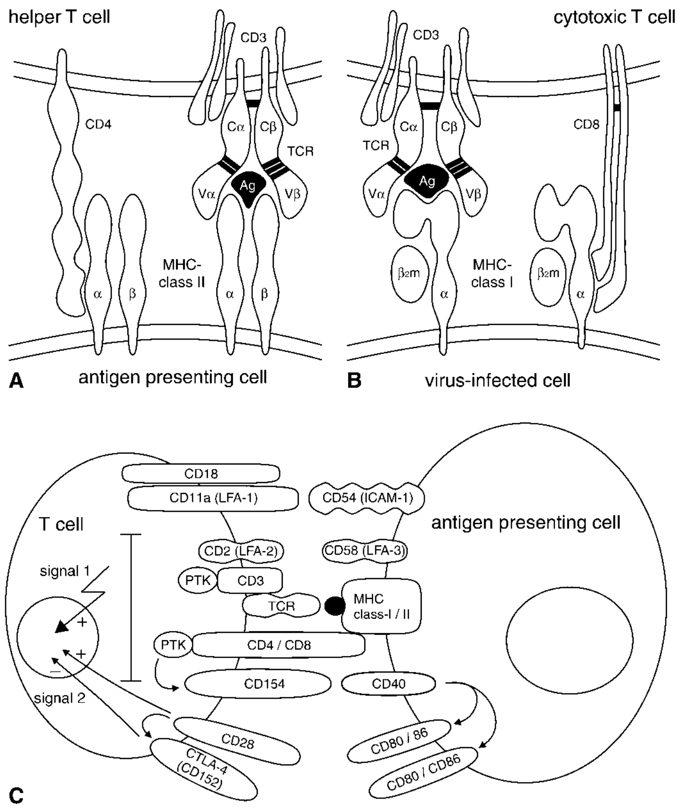

FIG. 6. The interactions between antigen presenting cells (APC, including virus-infected cells) and T cells at the level of antigen-specific interactions, adhesion molecules, and costimulatory molecules. Panels A and B represent interactions between MHC molecules, the T cell receptor (TCR), and CD4/CD8 molecules. Panel C depicts interactions between MHC and the TCR and between various adhesion molecules (ICAM-1/LFA1, LFA-3/LFA-2) providing signal 1 for T cell stimulation. Further interactions of the costimulatory molecules (CD80/CD86 and CD28), provide a second signal essential for full T cell activation. In such full T cell activation (signal 1 plus signal 2) CTLA-4 is up-regulated on the T cell. The interaction of CTLA-4 with CD80/CD86 on the antigen-presenting cells (APC) provides negative signals for the activated T cell to down-regulate the initiated response. Interestingly, patients with endocrine autoimmunity have a polymorphism of the CTLA-4 molecule. [Adapted with permission from A. Hoek *et al.: Endocr Rev* 18:107–134, 1997 (87). © The Endocrine Society.].

acceptance of the fetus (159–161). In early and successful pregnancies nonclassical NK cells (with a distinctive phenotype: CD56+ CD16− CD3−) and macrophages accumulate in the decidua at the feto-maternal interface. These cells exert only a low cytolytic activity on the fetal trophoblastic cells and play a primary role in placental morphogenic processes and down-regulate the local immune response (162). The functions of these local immune cells are governed by various mechanisms, such as the expression on the trophoblastic cells of a special paternally imprinted MHC-class I molecule, *i.e.*, HLA-G, and also by the local production of various pregnancy-associated proteins and hormones (93, 121, 163). These proteins and hormones include the enzyme indolamine 2,3 dioxygenase involved in tryptophan metabolism (164, 165), a pregnancy-specific glycoprotein encoded by the gene PSG11 and the hormones progesterone, E2, and human CG (hCG). These later hormones have, in addition to their local placental effects, systemic effects (163, 166). Particularly progesterone is an important contributor to pregnancy-associated immunomodulation (167). Immunological effects of progesterone are partly mediated by a protein fraction of 34 kDa: the so-called progesterone-induced blocking factor (PIBF) (168, 169). This factor is produced by progesterone-exposed activated T cells and affects both placental NK cells and macrophages, but also the circulating cells (168–170). PIBF is endowed with immunomodulatory properties such as a strong regulating activity on perforin expression by NK cells (158, 169, 171). It also affects the TH1/TH2 balance via an increased production of IL-3, IL-4, and IL-10 and a decreased production of IL-12 from lymphocytes and macrophages (158). Treatment with anti-PIBF induces a shift toward a TH1 response (decreased IL-10 and increased γIFN production) and leads to increased rates of pregnancy resorption (172).

E2 has a similar effect on the TH1/TH2 balance (163). In neuroantigen-specific T cell clones, E2 showed a dose-dependent enhancement of antigen-stimulated IL-10 secretion. The secretion of γIFN was also enhanced but the maximum enhancement occurred at lower E2 concentrations and at lower magnitudes than observed for IL-10 (173).

Interestingly, progesterone induces hCG release from the trophoblast through its stimulation of TH2-type cytokines (158, 166, 170). hCG subsequently stimulates progesterone production from the corpus luteum (166), thus creating a positive feedback loop.

In conclusion, various factors, but particularly hormonal factors, down-regulate TH1-mediated effector arms of the immune system during pregnancy.

A rebound reaction to the above described pregnancy-associated immunomodulations is thought to induce the aggravation of thyroid autoimmune syndromes in the puerperal period. If, indeed, autoimmune thyroid failure is induced by TH1 mechanisms while TPO antibodies are secondary to thyroid destruction, a TH2 to TH1 "return shift" in the puerperium might explain the outbreak of postpartum thyroiditis. However, considering the shift from TH1 to TH2 immune response during pregnancy, the amelioration of Graves' disease frequently observed during pregnancy remains puzzling, since this disease is considered to be a typical TH2-type disease. Apparently, immunomodulating mechanisms other than TH1/TH2 shifts also play a role in pregnancy.

Interestingly, and from a clinical point of view, important, the fall in TPO antibodies during pregnancy is not associated with an improvement of thyroid function. In a prospective study of 87 thyroid antibody-positive women with normal thyroid function at the time of initial screening, Glinoer *et al.* (174) found that despite the expected decrease in the titers of thyroid antibodies during gestation, thyroid function showed a gradual deterioration toward subclinical hypothyroidism. This is due to the fact that pregnancy in itself, in addition to the above described immunological phenomena, affects thyroid function directly since there is an increased demand for thyroid hormones. Three independent factors concur to exert stimulatory effects on the thyroid machinery to fulfill this increased demand. The first factor is the thyroidal response in the first trimester to adjust to the marked

TABLE 2. Association between HLA class II expression and postpartum thyroiditis

First author (reference)	Yr	Ethnic origin		Association
		Postpartum thyroiditis (n)	Controls (n)	
Farid (139)	1983	Caucasian (25)	Caucasian (17)	DR3, DR5
Lervang (141)	1984	Caucasian (13)	Caucasian (704)	DR4
Jansson (5)	1985	Caucasian (50)	Caucasian (243)	DR4
Thompson (142)	1985	DNS (32)	DNS (100)	DR4
Tachi (140)	1988	Japanese (44)	Japanese[a]	DR3
Vargas (35)	1988	Caucasian (38)	Caucasian (98)	DR5
Kologlu (138)	1990	Caucasian (221)	Caucasian (600)	DR3
Stagnaro-Green (34)	1992	Caucasian (11)	Caucasian/Hispanic (42)	DR3
Parkes (143)	1996	Caucasian (86)	Caucasian (1010)	DR5

DNS, Data not shown.
[a] Historical controls.

increase in the circulating levels of T_4 binding globulin, the latter due to increased E production from the placenta. The second factor is related to the thyrotropic action of hCG, also occurring in the first trimester. The third factor, operative later in gestation, is related to modifications in the peripheral metabolism of thyroid hormones, particularly at the placental level (175, 176).

C. Environmental factors, iodine intake

Both iodine excess and iodine deficiency are capable of disturbing an existing tolerance for thyroid autoantigens. Most important in this respect is an iodine excess in autoimmune-prone individuals (177–179). After the introduction of iodine supplementation to a population, a rise in thyroid autoantibodies and a higher incidence of lymphocytic thyroiditis has been observed (180–184). In goitrous NOD mice, OS-chickens, or BB-DP rats, a high iodine intake induces a rise in the titer of thyroid autoantibodies and an outburst or acceleration of lymphocytic thyroiditis in these animals (185–187).

Proposed pathogenic mechanisms of this iodine-induced thyroid autoimmunity are: 1) an iodine-induced thyrocyte necrosis with an increased release of autoantigens resulting in an enhanced attraction of antigen-presenting cells (188, 189); 2) a higher antigenicity of Tg due to a higher iodination grade (190–192); and 3) a direct stimulation of B lymphocytes, T lymphocytes, dendritic cells and macrophages by iodine or iodinated substances.

The prevalence of postpartum thyroiditis does not seem to be related to the iodine intake status of a population (Table 1). Interestingly, in this respect, in a case-control study, Othman *et al.* (193) did not observe a difference in iodine excretion in the immediate postpartum period between 73 women who developed postpartum thyroiditis and those 135 women who did not. With regard to the effect of changes in iodine intake on the occurrence of postpartum thyroiditis, the data are conflicting. On the one hand, there are data indicating that increased iodine intake can influence the severity of thyroid dysfunction in postpartum thyroiditis. In Sweden, an iodine-sufficient area, Kämpe *et al.* treated 20 women who were TPO positive in early pregnancy with iodine (0.15 mg/d) for 40 wk postpartum. In those women who developed thyroid dysfunction, TSH levels were higher and T_4 levels were lower compared with the group who received no medication (194). On the other hand, Nøhr *et al.* (195) in Denmark, in an area with mild to moderate iodine insufficiency, performed a placebo-controlled, randomized, double-blind trial on the impact of iodine supplementation (0.15 mg/d) during pregnancy and the postpartum period in 72 TPO antibody-positive women. In this study, iodine supplementation did not induce or worsen postpartum thyroiditis (184).

D. Environmental factors, toxins, and cigarette smoking

Chemical toxins constitute another source of potential pathogenic factors in the development of thyroid autoimmunity (196). Exposure to methylcholanthrene enhances the thyroid autoimmune response in Buffalo rats (177).

In humans, thiocyanate from tobacco smoke is probably the most important environmental toxic factor in the development of Graves' disease. Thiocyanate is actively metabolized by the thyroid and is able to inhibit iodine transport. It is also a competitive substrate for TPO (197–202). It is therefore not surprising that it has been hypothesized that the toxic effects of thiocyanate explain why smoking leads to thyrocyte necrosis and/or thyroid metabolic abnormalities, processes that are driving forces behind a thyroid-specific autoimmunization (203).

Alternatively, smoking might have direct effects on the immune system. Smoking leads to clear alterations in the function of pulmonary monocyte-derived cells and to an altered production of proinflammatory cytokines in the lung. Whether this is reflected in functional aberrations of systemic or intrathyroidal monocytes and other antigen-presenting cells needs to be investigated.

In the United Kingdom, almost two-thirds of patients with Graves' ophthalmopathy smoke cigarettes in contrast to 10–20% of the normal healthy population (204, 205). In a recent population-based twin case-control study, clinically overt autoimmune thyroid disease was significantly associated with smoking. Most importantly, this association remained significant in disease-discordant monozygotic twin pairs, eliminating the effect of genetic factors in the development of thyroid disease (206).

With regard to postpartum thyroiditis, a case-control study in the United Kingdom showed that smoking more than 20 cigarettes/d was significantly related to the development of the syndrome (21) but not with the development of permanent autoimmune hypothyroidism (207). In a prospective study of 291 women, of whom 15 developed postpartum thyroiditis, Kuijpens *et al.* (208) found by multivariate analysis that "ever smoked" was an independent risk factor for postpartum thyroiditis with a relative risk of 3.1, compared with "never smoked."

In conclusion, evidence is growing that smoking is a clear precipitating factor for autoimmune thyroid disease, including the outbreak of postpartum thyroiditis.

VI. Postpartum Thyroiditis Viewed as a Transient Exacerbation of a Preexisting and Ongoing Process of Autoimmune Thyroiditis

The natural course of thyroid autoimmune diseases often encompasses a long subclinical prodromal phase, and the process of thyroid autosensitization and subsequent destruction of thyrocytes may fluctuate over several years. The ultimate failure of the gland in many cases is the consequence of a process that started years earlier (Fig. 5). From this perspective, postpartum thyroiditis is "just" an aggravation of an existing autoimmune thyroiditis after an amelioration of the inflammation during pregnancy (see above). The fluctuations in intensity are driven by the hormonal changes associated with pregnancy and the subsequent puerperal period, and eliciting environmental factors. This is clearly illustrated by the pattern of the TPO antibody titer during pregnancy and the postpartum period (Fig. 5).

Figure 1 summarizes the reports on the TPO antibody status in women with postpartum thyroiditis. Collectively, these reports show that 30–60% of women positive for TPO antibodies in pregnancy develop postpartum thyroiditis. After a first episode of postpartum thyroiditis, the chance of recurrence after a subsequent pregnancy is 70% in women who are TPO antibody positive. The chance of postpartum thyroiditis is 25% in TPO antibody-positive women without a history of previous thyroid dysfunction in the puerperal period (209).

VII. The Clinical Course of a Postpartum Exacerbation of Autoimmune Thyroiditis

Postpartum thyroiditis classically runs a biphasic course: a thyrotoxic phase is followed by a hypothyroid phase (1, 11, 34, 210). The disease can also present as either transient thyrotoxicosis or hypothyroidism. Hypothyroidism tends to occur earlier when preceded by thyrotoxicosis than when occurring alone (21). The onset of thyrotoxicosis is variable, ranging from the first to the sixth month postpartum and lasting 1 to 2 months (12, 20, 21, 23, 24, 27, 29, 30, 33, 36). Five authors have systematically investigated the symptoms of postpartum thyroiditis compared with euthyroid postpartum women (Table 3) (12, 23, 25, 36, 211). During the thyrotoxic phase the physical symptoms are usually mild compared with Graves' thyrotoxicosis, and fatigue, palpitations, weight loss, heat intolerance, and irritability were more prevalent in women with postpartum thyroiditis than in euthyroid postpartum women. Other reported symptoms are psychological disturbances (12, 22–24, 27, 30, 209, 212), tremor, and nervousness (12, 20, 24, 27, 29, 209, 213). The thyrotoxic phase of postpartum thyroiditis is due to leakage of thyroid hormones from destroyed thyrocytes and is therefore self-limiting.

The hypothyroid phase, developing approximately 4–8 months postpartum and usually lasting 4–6 months, is clinically more important (see below). The hypothyroid phase of postpartum thyroiditis is due to loss of thyrocytes by immune destructive mechanisms. Prevalent symptoms are muscle and joint aches and stiffness (23, 27, 29). In systematic studies, these symptoms were not discriminatory in contrast to fatigue, loss of concentration, and constipation (Table 3).

It is generally believed that mental depression is the most prominent discriminatory symptom of the hypothyroid phase of postpartum thyroiditis, often ascribed to the changes consequent upon delivery and the lack of night rest (12, 21, 23, 24, 27, 29, 32, 33, 36). Several studies have specifically, and solely, investigated the association between postpartum thyroiditis and postpartum depression. A critical appraisal of the literature revealed that postpartum depression is significantly associated with postpartum thyroid dysfunction regardless of the thyrotoxic or hypothyroid phase (22, 212). Consequently, in terms of clinical management and appropriate treatment, it is pivotal to recognize the origin of the depressive symptoms.

Harris *et al.* (214) examined the rates at which depression occurred at 6–8 wk postpartum in 65 thyroid antibody (Tg and TPO)-positive and 82 antibody-negative women. Women with postpartum thyroiditis had a small but signif-

TABLE 3. Systematic studies on the symptomatology of postpartum thyroiditis

First author (reference)	Yr	Country	No. included/no. analysis of symptoms	Time of inclusion/time of last assessment	Hypothyroidism			Thyrotoxicosis				
					Depression	Fatigue/concentration loss	Constipation	Fatigue	Palpitations	Weight loss	Heat intolerance	Irritability
Amino (12)	1982	Japan	63/63[a]	3 mo pp/6 mo pp				–	–			
Hayslip (23)	1988	USA	63/63	2nd day pp/6 mo pp	–[c]	–						
Walfish (36)	1992	Canada	1,376/208	Delivery/12 mo pp					–		–	
Lazarus (211)	1996	UK	152[b]/152	1 mo pp/9 mo pp				–				–
Kent (25)	1999	Australia	748/130	6 mo pp/6 mo pp			–			–		

[a] Only thyrotoxic patients.

[b] Source population consisted of 1,996 women attending an antenatal clinic; inclusion thyroid antibody+; 235 were thyroid antibody+ of these 152 were included.

[c] A *dash* denotes that the symptom is significantly more prevalent in women with postpartum thyroiditis than in normal euthyroid postpartum women.

icant excess of DSM III defined major depression (Table 4). Pop *et al.* (212) studied 293 women from 32 wk of gestation until 34 wk postpartum and also found an association of major and minor depression (according to Research Diagnostic Criteria) with postpartum thyroiditis. Kent *et al.* (25) also found that postpartum thyroiditis carries a slightly increased risk for the occurrence of depression. However, in a recent study from Spain in which 605 women were followed Lucas *et al.* (28) found no association of depression with postpartum thyroiditis. A different sociological background in Spain compared with the countries in which the other studies were performed might explain this negative result. The presence of TPO antibodies *per se* is not associated with postpartum depression (22, 25, 30).

After critically reviewing the present data, we conclude that there is an association between postpartum thyroid dysfunction and depression. Considering the mechanism behind this association, it is noteworthy that hypothyroidism influences neurotransmitters important in affective disorders; hypothyroidism, for instance, reduces central 5-hydroxytryptamine neurotransmission (215). This reduction reverses with T_4 replacement (216). Alternatively, it has been speculated that cytokines released during a thyroid autoimmune reaction, *e.g.*, IL-1 and IL-6, interact with central neurotransmission, initiating depression (4).

Whether goiter is a symptom of postpartum thyroiditis is still questionable. In most clinical studies of postpartum thyroiditis, a high prevalence of goiter was observed (12, 23, 27, 29, 31, 33). However, this was not a universal finding (20, 21), and iodine intake probably plays a role here. In iodine-replete areas the thyroid as measured by ultrasonography does not increase in size during pregnancy (217), while it does in iodine-deficient areas. This increase is most likely due to an adaptation to the low environmental iodine, leading to a more vigorous response of the thyroid to growth stimuli (218) and exacerbated by the pregnant state (see above). Apart from this adaptation mechanism, the development of a goiter in postpartum thyroiditis could be a symptom of the autoimmune thyroiditis process itself, representing a glandular enlargement due to the lymphocellular infiltration. A palpable goiter at term was found to be predictive for postpartum thyroiditis in areas of mild iodine deficiency (33, 219). This was not the case in iodine-sufficient areas (21). A palpable goiter, however, can be interpreted as a symptom of preexisting autoimmune thyroiditis. In women with type I diabetes, Gerstein (40) found that the presence of a goiter at term was a risk factor for the development of postpartum thyroiditis. In conclusion, the presence of a goiter most likely is a symptom of postpartum thyroiditis especially in iodine-sufficient areas.

Adams *et al.* (220) studied the ultrasonographic appearance of women at risk of postpartum thyroiditis. Between 4 and 8 wk postpartum, hypoechogenicity was present only in 45% of thyroid antibody-positive women who subsequently developed postpartum thyroiditis, compared with 17% in thyroid antibody- positive women in whom thyroid function remained normal ($P < 0.05$). Hypoechogenicity was present in only 1.5% of thyroid antibody-negative women ($P < 0.001$). These observations have recently been extended by the investigators who found that persistent hypoechogenicity on thyroid ultrasound after the puerperal period indicated an ongoing process of destructive thyroiditis that was related to the development of permanent hypothyroidism (221). However, at present, the use of thyroid ultrasound in the follow up of postpartum thyroiditis is not well documented. From these studies we conclude that the ultrasound appearance of postpartum thyroiditis is hypoechogenicity. It should be noted, however, that 14% of women with TPO antibodies and postpartum thyroiditis had no ultrasound hypoechogenicity. Conversely, only 3% of TPO antibody-negative women without postpartum thyroiditis had ultrasound hypoechogenicity, but 39% of women with TPO antibodies but not postpartum thyroiditis did have ultrasound hypoechogenicity (220). The clinical value of thyroid ultrasound in the diagnosis and follow-up of postpartum thyroiditis seems therefore limited.

TABLE 4. Association of thyroid antibodies and postpartum thyroiditis with depression

First author (reference)	Yr	Country	Inclusion criteria	No. Included/no. with psychiatric assessment	Time of inclusion and last psychiatric assessment	Incidence of depression	RR of depression[a]	*P* value
Association with postpartum thyroiditis (*i.e.*, thyroid dysfunction)								
Harris (214)	1989	UK	Tab+ (tab-co's)	147 (147)/147 (147)	6–8 wk pp/6–8 wk pp	5% (8/147)[b]	5.2	<0.01
Pop (212)	1991	Netherlands	Informed consent	303/293	3rd trimester/8 mo pp	21% (61/293)[c]	1.6	0.02
Kent (25)	1999	Australia	Informed consent	748/69	6 mo pp/6 mo pp	11% (8/69)[b]	1.4	N.S.
Lucas (28)	2000	Spain	Informed consent	605/605–444 (1–12 mo pp)	Delivery/12 mo pp	9% (4/45)	0.7	N.S.
Association with thyroid antibodies (normal thyroid function)								
Pop (30)	1993	Netherlands	Informed consent	303/293	3rd trimester/8 mo pp	21% (61/293)[c]	1.73	N.S.
Harris (22)	1992	UK	Tab+ (tab-co's)	145 (229)/110 (132)	2nd trimester/7 mo pp	39% (94/242)[c]	1.47	N.S.
Kent (25)	1999	Australia	Informed consent	748/45	6 mo pp/6 mo pp	11% (5/45)[b]	1.19	N.S.

Tab, Thyroid antibodies; N.S., not significant.
[a] Thyroid dysfunction *vs.* euthyroid, or Tab+ *vs.* Tab−.
[b] According to DSM III/DSM III R.
[c] According to Research Diagnostic Criteria.

VIII. The Diagnosis, Follow-Up, and Treatment of a Postpartum Exacerbation of Autoimmune Thyroiditis

The diagnosis of postpartum thyroiditis must, first, be based upon a high index of clinical suspicion. Women presenting with nonspecific physical and/or psychological complaints in the first postpartum year should undergo testing of thyroid function. This should be done by measuring the serum TSH concentration followed, if abnormal, by determining the free T_4 (fT_4) concentration in the same sample.

The differential diagnosis of the thyrotoxicosis comprises primarily Graves' disease. Because management and follow-up of postpartum destructive thyrotoxicosis and Graves' disease differ, it is important to establish a causal diagnosis. Clinical features have been discussed in the previous section; here it is important to note that symptoms and the presence of a goiter are not helpful in differentiating postpartum destructive thyrotoxicosis from Graves' disease. The presence of ophthalmopathy, however, points to a diagnosis of Graves' disease (222). Diagnosis is further based on the presence of TSH-R Abs and thyroid scintigraphy (222). The presence of TSH-R Abs represents Graves' disease, which was either unrecognized before pregnancy and relapsed after delivery, or developed *de novo* after delivery (39, 210). It is important to be aware that thyrotoxicosis in patients with a previous history of Graves' disease does not necessarily represent relapse: postpartum thyroiditis can be superimposed on Graves' disease (18). Momotani *et al.* systematically followed 96 episodes of postpartum hyperthyroidism in the first year after delivery in women with a history of Graves' disease: in 26 cases radioiodine uptake was low ($<10\%$) during the thyrotoxic phase, indicating destructive postpartum thyroiditis (19). Indeed, the diagnosis of postpartum destructive thyrotoxicosis (*i.e.*, postpartum thyroiditis) is best established by the presence of a low radioiodine uptake. Thyroid scintigraphy should therefore be part of the diagnostic workup. During breast-feeding, however, the administration of iodine-131 is contraindicated. When iodine-123 is used, breast-feeding should be stopped for 3 d (223, 224). By using technetium (^{99m}Tc) pertechnetate, interruption of breast-feeding for only 24 h is required (223, 225).

Serum Tg has been considered as an early indicator of postpartum thyroiditis (226). But as serum Tg concentrations are also elevated in nearly all patients with Graves' disease (227), the determination of the serum Tg concentration is not helpful in differentiating postpartum destructive thyrotoxicosis from Graves' disease. In women with postpartum thyroiditis, thyroid ultrasound hypoechogenicity correlates well with thyroid dysfunction (228). Similar abnormalities, however, have also been described in Graves' disease (220). Increased IL-6 levels have been found in Graves' disease and several thyroid-destructive processes (229, 230). In postpartum thyroiditis, however, IL-6 levels are not different compared with women without postpartum thyroiditis (231). Therefore, IL-6 measurement could be potentially useful in the differential diagnosis of postpartum thyrotoxicosis. However, the routine measurement of IL-6 is currently not always available.

With regard to the follow-up, permanent hypothyroidism is the most important sequel of postpartum thyroiditis. Nicolai *et al.* (29) found a prevalence of hypothyroidism of 12% after 3 yr . Tachi *et al.* (140) followed 44 Japanese women with a history of postpartum thyroiditis for a mean interval from delivery of 8.7 yr (range 5–16 yr) and found 29% of them to be permanently hypothyroid. In the study by Jansson *et al.* (24), the prevalence of hypothyroidism was 30% at the end of 5 yr. Othman *et al.* (207) followed 43 patients with postpartum thyroiditis (90% TPO antibody positive) during a period of 2–4 yr. Twenty-three percent of the women developed permanent hypothyroidism compared with none of 171 controls. Very recently, Premawardhana *et al.* (221) reported a follow-up on 98 TPO-positive women, of whom 48 developed postpartum thyroiditis. During a follow-up period of 66–140 months, 24.5% developed (sub)clinical hypothyroidism, whereas only 1.4% of a group of 70 TPO antibody-negative controls developed thyroid dysfunction. Lucas *et al.* (28) followed 42 patients during a mean period of 40 months. Five of these 42 women became permanently hypothyroid. In this study there was no significant difference in percentage of TPO positivity between women with postpartum thyroiditis who subsequently became hypothyroid and those who did not. TPO antibody levels, however, were higher in those women who developed permanent hypothyroidism. Barca *et al.* (37) followed 49 women with postpartum thyroiditis during the second postpartum year and found 30 of these women to have developed hypothyroidism at 24 months.

So we can conclude from these studies that permanent hypothyroidism occurs in 12–61%, a wide variation thus far unexplained. Differences in definition and variable ascertainment of follow-up may explain this wide variability.

Considering the occurrence of permanent hypothyroidism, studies performed by Roti *et al.* (232) and Creagh *et al.* (233) are of interest. They performed iodide perchlorate discharge tests in women with previous postpartum thyroiditis and found organification defects in 41% and 64%, respectively. Follow-up in these two studies was 3 to 7 yr. Collectively, the above data show the persistent character of the underlying thyroid disorder in postpartum thyroiditis and emphasize the need for a prolonged follow-up, particularly in TPO-positive women.

Special consideration should be given to women with hypothyroidism antedating pregnancy. An increased need for T_4 during pregnancy is well documented in these women (175, 232, 234) and after delivery the T_4 requirement is presumed to return to its pregestational level (235). However, it should be stressed here that in analogy to what has been described for Graves' disease, postpartum thyroiditis can occur in patients with a known previous diagnosis of primary hypothyroidism, leading to a further decline in thyroid function. In a recent study, Caixàs *et al.* (17) observed discordance between pregestational and postpartum T_4 requirements suggestive of postpartum thyroiditis in 12 of 18 patients diagnosed with autoimmune thyroiditis before pregnancy.

Do patients with postpartum thyroiditis need treatment? With respect to thyrotoxicosis, we have already pointed out the importance of an accurate diagnosis. In symptomatic cases a short course of β-blockade may be beneficial, *e.g.*, 40–120 mg propranolol or 25–50 mg atenolol daily until serum fT_4 concentrations are normal. Antithyroid drug therapy should obviously not be given because there is no increased thyroid hormone synthesis.

Hypothyroidism should always be treated with T_4 replacement therapy. Spontaneous recovery of thyroid function should not be anticipated (236). Instead, it is reasonable to stop T_4 after 2–6 months to determine whether remission has occurred (4). If so, we advise discontinuation of treatment followed by yearly assessment of thyroid function. Others suggested a pragmatic approach: to maintain the T_4 replacement therapy and postpone the cessation of therapy until the family is complete (237). In discussing T_4 replacement therapy with the patient, it is important to realize that T_4 administration does not always improve the psychological disturbances if present.

IX. Adverse Consequences of Autoimmune Thyroiditis During Pregnancy and Postpartum

We have discussed postpartum thyroiditis as an acute stage of autoimmune thyroid destruction—with subsequent repair—in the context of an existing and ongoing process of thyroid autosensitization. This process frequently leads to a gradual development of permanent thyroid failure. The recognition of the very nature of this process, combined with recently described detrimental effects of a low thyroid reserve due to autoimmune thyroiditis, has important repercussions on clinical practice especially in women of childbearing age.

A. Effects of autoimmune thyroiditis on conception and pregnancy

The relationship between existing thyroid autoimmunity and the probability of spontaneous abortion has been the subject of a number of studies. Stagnaro-Green *et al.* (238) found that the presence of TPO and/or Tg antibodies in the first trimester of pregnancy is a risk factor for spontaneous fetal loss. The authors studied 552 consecutive women in the first trimester of pregnancy and found that the spontaneous abortion rate in thyroid antibody-positive women was significantly higher than in antibody-negative women (17% *vs.* 8.4%). These results were confirmed by Glinoer *et al.* (239) who found a higher rate of spontaneous abortion in 45 women with thyroid autoantibodies compared with 603 controls: 13.3% *vs.* 3.3%.

In a prospective study of 54 women who conceived after *in vitro* fertilization (IVF) we were unable to find a significant association between the spontaneous abortion rate and the presence of TPO antibodies before pregnancy. Although miscarriages occurred in 33% of TPO antibody-positive women and in only 19% of the TPO-negative women, the difference was not statistically significant (240). Surprisingly, we found a nearly significant ($P = 0.05$) higher pregnancy rate in the TPO-positive women compared with the TPO-negative women. Our results thus contradict those of the two studies mentioned above, and several biases can be proposed to explain this discrepancy (241). First, the number of women with thyroid autoimmunity was low in our study, and the severity of the thyroid autoimmune process was mild (defined by the presence and cutoff value, respectively, of TPO antibodies). Second, we determined TPO antibodies before pregnancy—as opposed to during pregnancy—in women without a history of habitual abortion. In view of the discussed immunological changes occurring during pregnancy, these differences in study design have probably led to an inclusion of women with less severe forms of thyroid autoimmunity which might, at least in part, explain the discrepancy.

It has also been postulated that thyroid autoimmunity and its consequences influence the timing of miscarriage. Singh *et al.* studied 487 women who conceived with assisted reproductive techniques and found that the presence of thyroid autoantibodies, measured 14 d after embryo transfer, identified women at risk of later miscarriage. Later miscarriage was defined as a miscarriage occurring after clinical recognition of the pregnancy, *i.e.*, after visualization of the gestational sac by ultrasonography. TPO antibody positivity had no effect on early, hCG-detected, miscarriage rates (242).

In women with a history of habitual abortion the presence of non-organ-specific autoantibodies, notably of antiphospholipid and anticardiolipin antibodies, has been associated with fetal loss (243). Data on the relationship between thyroid autoantibodies and habitual abortion are conflicting. Several studies found an association between TPO antibodies and recurrent first-trimester fetal loss (244–248). However, others could not confirm this observation (249, 250). Interestingly, Vaquero *et al.* (251) have recently investigated the role of mild thyroid abnormalities in women with thyroid antibodies and recurrent first-trimester abortions. A total of 42 women with TPO and/or Tg antibodies and recurrent first-trimester abortions were studied. In this study, treatment with intravenous Igs was compared with thyroid hormone treatment. The authors showed that treatment with thyroid hormone was more effective than treatment with intravenous Igs since 55% of women with thyroid antibodies treated with intravenous Igs resulted in live births as compared with 81% live births in women with thyroid antibodies treated with thyroid hormone. The authors and editors explained these data suggesting that mild degrees of thyroid insufficiency, perhaps at the level of the female genital tract, not detectable by routine thyroid testing, and not thyroid autoimmunity *per se*, is causal in the earlier mentioned association between the presence of thyroid antibodies and recurrent abortion (251, 252).

In conclusion, at present there are sufficient data showing an association of thyroid autoimmunity in early pregnancy and subsequent miscarriage. However, when taking into account the conflicting data on the presence of thyroid antibodies and recurrent abortion, the cause of this association, *e.g.*, a defective immune system failing to become tolerant to the fetus or mild thyroid insufficiency, remains uncertain. Taking into consideration the data of Vaquero *et al.* (251), we are of the opinion that in women with recurrent miscarriage and thyroid antibodies, treatment with L-T_4 is an option, although further controlled studies are essential.

B. Consequences of autoimmune thyroiditis for the offspring

It has become increasingly clear that maternal hypothyroxinemia in areas of severe iodine deficiency causes not only the birth of neurological cretins (253) but is also responsible for less severe mental deficits (254–257). Notably, the motor and cognitive impairments of the offspring were associated with the maternal T_4 levels and not with maternal T_3 or TSH levels (258). Moreover, because of their relatively normal T_3 levels, these women were not clinically hypothyroid (258). The association of maternal hypothyroxinemia and neurodevelopmental outcome of the offspring has recently been extended to populations living in iodine-sufficient areas.

In a recent study by Pop *et al.* (259), a significant association between maternal TPO antibody levels at 32 wk gestation and an IQ loss of 10 points at the age of 4.5 yr in the offspring was demonstrated. In a follow-up study the authors formulated a hypothesis for this association. The neurodevelopment of 220 children aged 10 months was assessed. Children born to women with maternal serum fT_4 levels below the tenth percentile at 12 wk gestation (irrespective of elevation of TSH and/or TPO antibodies) had significantly lower neurodevelopmental scores compared with children of mothers with higher fT_4 values. Women with low fT_4 levels at 12 wk gestation were largely affected by autoimmune thyroiditis, which can explain the previously found association between elevated TPO antibody levels at 32 wk gestation and impaired child development at 4.5 yr of age (260). However, there was no correlation between neurodevelopmental scores of the infants and maternal fT_4 at 32 wk gestation, which is a puzzling finding in view of the expected deterioration in thyroid function during pregnancy in women with autoimmune thyroiditis (176, 260). Whatever the explanation for this unexpected finding, the fact remains that after appropriate statistical analysis fT_4 levels below the tenth percentile at 12 wk gestation represented a significant risk factor for impaired psychomotor development.

Findings by Pop *et al.* have been extended by Haddow *et al.* (261). These investigators provided evidence that children born to mothers with hypothyroidism during the second trimester of pregnancy, as determined by an elevated TSH, have lower IQ scores and more educational difficulties at age 7–9 yr than children born to mothers with normal TSH levels during pregnancy. In their study 25,216 serum samples were prospectively collected, and 47 women with TSH levels at or above the 99th percentile of the values for all pregnant women were identified. Additionally, 15 women with TSH values between the 98^{th} and 99.6^{th} percentiles, and low T_4 levels were also included, as were 124 matched controls. The children of the 62 women with elevated TSH levels during pregnancy performed less well on all 15 neuropsychological tests carried out (in 2 of these the difference was significant), and children had more school difficulties and learning problems ($P = 0.06$). In this study 77% of the women with hypothyroidism had high titers of TPO antibodies (261). These data further underline the notion that chronic autoimmune thyroiditis is the most frequent cause of low normal fT_4 levels and raised TSH levels in these women. Taken together, the studies by Pop *et al.* and Haddow *et al.* provide evidence that not only overt but also relatively mild and hitherto unrecognized states of thyroid failure are associated with persistent and significant impairment in neuropsychological performance of the offspring.

In a recent publication, Morreale de Escobar *et al.* (258) have summarized and discussed present epidemiological and experimental evidence and argue convincingly that conditions resulting in first-trimester hypothyroxinemia (defined as a low for gestational age circulating maternal free T_4, whether or not TSH is increased) pose an increased risk for poor neuropsychological development of the fetus. Although we will discuss the issue of screening in *Section X* of this review, it is relevant at this point to stress that the effects of screening and treatment with T_4 on the progeny, and the mothers, needs to be assessed prospectively (and from a strict scientific point of view placebo-controlled, double-blind) for efficacy and safety.

We recently observed a decrease in maternal serum fT_4 after ovarian hyperstimulation for IVF (262). Considering the possible importance of fT_4 levels for the neuropsychological development of the offspring, our findings could potentially have serious implications, and we urge prospective neuropsychological studies to be carried out in children born after IVF. Particularly the offspring of women whose fT_4 levels are already in the low normal range before the start of ovarian hyperstimulation should be followed, especially in areas of iodine deficiency and the documented relative hypothyroxinemia during pregnancy (175, 263).

C. Consequences of autoimmune thyroiditis for older women

Maternal states of mild thyroid failure due to autoimmune thyroiditis may lead to serious long-term consequences not only for the offspring, but also for the women themselves. First, the risk of permanent clinical thyroid failure is high: odds ratios as high as 38 have been found (see above) (264). Second, and probably more importantly, subclinical hypothyroidism may predispose to myocardial infarction and arterial atherosclerosis. Hak *et al.* (265) recently showed in a population-based cross-sectional study of 1,149 women in Rotterdam, that the population attributable risk of subclinical hypothyroidism for atherosclerosis and myocardial infarction is comparable to other known major cardiovascular risk factors . An association between TPO antibody positivity *per se* and atherosclerosis and myocardial infarction was not found; however, the associations between atherosclerosis and myocardial infarction and subclinical hypothyroidism were stronger if thyroid failure was accompanied by the presence of TPO antibodies (265). These data are at variance with the 20-yr follow-up of the Whickham survey cohort, which did not find an association between evidence of autoimmune thyroiditis (defined as treated hypothyroidism, presence of thyroid antibodies, or raised TSH) documented at the first survey with mortality or development of ischemic heart disease (266). These discrepant findings are most likely due to differences in study groups (different ages) and definitions of autoimmune thyroiditis and hypothyroidism as well as the initiation of T_4 replacement therapy in cases of hypothyroidism in the Whickham survey (266).

All in all, evidence is accumulating that the early phases of thyroid autoimmunity, which may not immediately lead to clinically overt thyroid failure, have adverse consequences for the well-being of affected individuals and their offspring. A mild, but nevertheless relevant, decrement of the thyroid reserve often accompanies the early phases of thyroid autoimmunity. This "hidden thyroid failure" becomes more important when the thyroid needs to perform optimally, such as during pregnancy and in states when there is an otherwise heightened risk for atherosclerosis. The occurrence of postpartum thyroiditis is a clear sign that the thyroid reserve is under serious autoimmune threat and already considerably compromised.

The above listed studies provide an incentive to consider screening for autoimmune thyroiditis to prevent the potentially harmful sequels described above.

X. Screening, What and When?

Screening programs can detect subjects with unsuspected hypothyroidism or those at risk of developing thyroid disease or postpartum thyroiditis, but the costs, risks, and benefits of screening for thyroid disorders before and after pregnancy must be considered (267). To establish a case for screening, several criteria must be met. Clear answers to the following questions are required:

1. Is the prevalence of autoimmune thyroiditis high enough to justify screening?
2. Is there enough morbidity?
3. Is there an effective way to prevent this morbidity?
4. Are there effective screening tools and when should these be applied?
5. Is screening cost effective?

Ad. 1) The first question has been dealt with extensively in *Section II* of this review. In comparison to other diseases for which screening is recommended, the prevalence rate of around 5–7% for thyroid autoimmunity in young women and a prevalence of elevated TSH levels in pregnant women as high as 2–3% seems high enough to justify screening in women of childbearing age (175, 268).

Ad. 2) Considering the morbidity of autoimmune thyroiditis in women of childbearing age we have discussed that there is:

a. an increased risk of miscarriage;

b. a significant risk of developing hypothyroidism during gestation;

c. a potential risk for the neuropsychological development of the offspring;

d. a clearly increased risk of developing postpartum thyroiditis; and finally

e. that there is an increased risk for developing permanent clinically overt hypothyroidism in later life.

In conclusion, the morbidity associated with autoimmune thyroiditis is considerable.

Ad. 3)

a. Miscarriage. There are now data to suggest that recurrent miscarriage in women with thyroid antibodies can be prevented by T_4 administration (251).

b. Hypothyroidism during gestation. Transition from mild, subclinical hypothyroidism to overt hypothyroidism in pregnancy can be effectively and safely treated with T_4.

c. Neuropsychological development of the offspring. It is at present unknown whether T_4 replacement therapy will effectively prevent detrimental effects on the offspring in these cases. Clearly, double-blind randomized trails are needed to clarify this issue (269).

d. Postpartum thyroiditis. There is only one study on the prevention of postpartum thyroiditis with L-T_4 administration. In this study postpartum treatment of 18 women who were TPO positive in early pregnancy with L-T_4 (0.1 mg daily from 4–38 wk and 0.05 mg from 39–42 wk postpartum) did not result in a change in the incidence or time course of postpartum thyroiditis. However, as expected, the degree of hypothyroidism was significantly reduced compared with 20 untreated antibody-positive women (maximum TSH 23 *vs.* 6.9 mU/liter, $P < 0.05$) (194). With regard to other treatment options, administration of corticosteroids has been described in a woman with recurring episodes of postpartum thyroiditis. Both the hyper- and hypothyroid phases were prevented (270). However, in general, the effect is small (1), and we certainly do not recommend this approach as there are no controlled data and steroids can have serious adverse effects.

e. Permanent hypothyroidism. In women at risk for overt hypothyroidism L-T_4 is an effective and safe preventive treatment.

Thus, at present, only screening to identify subjects at risk for hypothyroidism seems indicated. Clearly, a case can be made for screening of maternal hypothyroxinemia in the first trimester of pregnancy, but we, and others, are of the opinion that controlled screening trials should be required before screening of all pregnant women can be recommended (269).

Ad. 4) What screening tools could be used if the development of a (pilot)-screening program is considered and when should these tools be applied?

a. Miscarriage. Because relevant studies have shown an association of thyroid autoimmunity in early pregnancy and subsequent miscarriage, measurement of TPO antibodies could be considered as soon as pregnancy is established.

b and c. Hypothyroidism during pregnancy and neuropsychological development of the offspring. After publication of the study by Haddow *et al.* (261), The Endocrine Society recommended the development of a cost-effective strategy for screening pregnant women for hypothyroidism before or early during pregnancy (*www.endo-society.org/pubrelations/pressReleases/archives/1999/hypothyroid.cfm*, assessed 23-01-01). It should be realized that in the studies by Pop *et al.* and Haddow *et al.* neuropsychological development of the infants was associated with fT_4 and TSH, respectively. Therefore, fT_4 and TSH are both candidates as screening tools when developing such a screening program. In view of the arguments presented by Morreale de Escobar *et al.* (258) fT_4 seems to be the most rational choice (267). Another point to consider is that whatever screening tool is chosen, cut-off values need to be established taking into account the different gestational ages (217, 267). This is especially prudent for TSH as hCG has clear thyrotrophic actions.

What would be the best time for screening? Assuming that the (mild) hypothyroxinemia itself is responsible for impaired neuropsychological development, one would ideally start to screen fertile women antenatally. However, it seems unrealistic to expect that we will be able to organize a prepregnancy screening program. Women cannot, and probably should not, be expected to consult their physician before becoming pregnant (176). Screening in early pregnancy is probably the best that we can accomplish, and screening algorithms for autoimmune thyroiditis and subclinical and overt hypothyroidism have already been proposed (176, 271). Interestingly, a screening program in Japan, a country where the frequency of thyroid disease among pregnant women may be lower than elsewhere, was initiated in 1986 and by 1997, 70,632 early-pregnant women had been screened. Screening consisted of TSH, fT_4, and Tg antibodies. Abnormal results were obtained in 2%. The overall incidence of hyperthyroidism and hypothyroidism was 1 in 413 and 1 in 692 women, respectively. Two-thirds of women with hypothyroidism had evidence of chronic autoimmune thyroiditis (272). These data show that a screening program in early pregnancy is feasible.

d. Postpartum thyroiditis. We have already discussed that the presence of TPO antibodies in early pregnancy is associated with a 30–52% risk of developing subsequent postpartum thyroiditis (4, 42–44). TPO antibodies in early pregnancy could thus be an appropriate screening tool for development of postpartum thyroiditis.

e. Permanent hypothyroidism. To detect subclinical hypothyroidism it is mandatory to determine TSH and, if elevated, fT_4 (preferably from the same blood sample). TPO antibodies are a powerful risk factor for the transition from subclinical (elevated TSH and normal fT_4) to overt hypothyroidism; therefore, the measurement of TPO antibodies, in our opinion, is also indicated in the case of an elevated TSH with normal fT_4 (264). When considering screening for thyroid dysfunction, it should be noted that the American Thyroid Association recommends screening with a sensitive serum TSH assay in adults beginning at age 35 yr and every 5 yr thereafter (273). The American College of Physicians is more conservative: they advise case finding in women older than 50 yr of age who are seen by primary care physicians for non-thyroid-related reasons (274, 275).

We stated previously that, considering treatment options, at present, screening to detect subclinical hypothyroidism and the transition to overt hypothyroidism seems indicated. We support, therefore, the recommendations by the American Thyroid Association, but suggest that screening should be performed earlier in pregnant women.

Ad. 5) We are unaware of long-term prospective studies addressing the issue of cost-effectiveness for any of the indications discussed here.

If screening programs are set up, the results should be scientifically evaluated. Before these screening programs are instituted, case finding is justified, *i.e.*, the identification of women at risk of autoimmune thyroid disease and its consequences during pregnancy and later in life. Thus, in our view, TSH determinations should be carried out in young women with a goiter, type I diabetes, previous postpartum "depression/blues," a "thyroid history," a family history of thyroid disease, and a personal history of smoking as well as in women with an induced low fT_4 level, *i.e.,* during ovarian hyperstimulation. If the TSH level is abnormal, the fT_4 should be determined, and in the case of subclinical hypothyroidism TPO should be determined additionally.

XI. Conclusion

Postpartum thyroiditis is defined as a syndrome of transient or permanent thyroid dysfunction occurring in the first year after delivery and based on an autoimmune inflammation of the thyroid. Classically, a thyrotoxic phase is followed by a hypothyroid phase. The prevalence of postpartum thyroiditis ranges from 5–7%.

In this review, postpartum thyroiditis is conceptualized as an acute phase of autoimmune thyroid destruction in the context of an existing and ongoing process of thyroid autosensitization. The following arguments support this view: 1) the relationship between the occurrence of postpartum thyroiditis and the presence of TPO antibodies; 2) the histology of postpartum thyroiditis (both focal organized and diffuse destructive lymphocytic thyroiditis with folliculolysis and disruption); 3) the presence of circulating activated T cells in postpartum thyroiditis patients; 4) the associations between the genetic inheritance of MHC molecules and the occurrence of postpartum thyroiditis; and 5) the fact that postpartum thyroiditis frequently leads to permanent autoimmune thyroid failure.

It is the combination of genetic susceptibility and environmental factors that lead to thyroid autoimmunity in general and also to postpartum thyroiditis. From pregnancy, an enhanced state of immune tolerance ensues, leading to an amelioration of existing thyroid autoimmunity. A rebound reaction to this pregnancy-associated immune suppression after delivery explains the aggravation of autoimmune syndromes in the puerperal period, *e.g.*, the occurrence of clinically overt postpartum thyroiditis.

Low thyroid reserve due to autoimmune thyroiditis is increasingly recognized as a serious health problem, particularly during pregnancy and postpartum. Existing thyroid autoimmunity increases the probability of spontaneous fetal loss. Moreover, there are indications that thyroid failure due to autoimmune thyroiditis, often mild and subclinical, leads to permanent and significant impairment in neuropsychological performance of the offspring. Finally, there is now emerging evidence that, as women age, subclinical hypothyroidism, as a sequel of postpartum thyroiditis, predisposes them to cardiovascular disease. Hence, the concept of postpartum thyroiditis being a mild and transient disorder is now changing. The recognition of the true nature of postpartum thyroiditis, *i.e.*, an acute phase in an ongoing and chronic thyroid autoimmune process, and the negative consequences such a chronic process can have for offspring of affected mothers and for the mothers themselves, in the long run, are reasons to consider screening.

Designing and performing adequate studies to delineate screening tools and cost-effectiveness will be the challenge for the future. Meanwhile, case finding is mandatory. We think that, at present, there is a good case for treating subclinical hypothyroidism especially in women of childbearing age.

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This article is dedicated to the memory of Eline M. Berghout.

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