Kuijpens, Johannes Leendert Petrus.
Epidemiological studies on postpartum thyroid dysfunction and thyroid cancer in Southeastern Netherlands.
Proefschrift Erasmus Universiteit Rotterdam. - Met lit. opg. - Met samenvatting in het Nederlands.
Trefw.: postpartum schildklierfunktiestoornissen, schildklierkanker, epidemiologie, predictie, behandeling, Zuidoost Nederland

Cover design: Sebastiaan Poos
Printed by: Drukkerij Schoenmakers, Valkenswaard
ISBN 90-9011955-8
NUGI 743

Financial support for the studies came from the Dutch Praevention Fund (002822380) and the Dr de Grood Foundation.
Financial support for the publication of this thesis was provided by the Amsterdam Thyroid Club.
Material support came from the Municipal Health Service Southeast-Brabant, Valkenswaard, and the Comprehensive Cancer Centre South (IKZ), Eindhoven.

Epidemiological studies on postpartum thyroid dysfunction and thyroid cancer in Southeastern Netherlands

Epidemiologische studies van postpartum schildklierfunktiestoornissen en schildklierkanker in Zuidoost Nederland

Proefschrift

ter verkrijging van de graad van doctor

aan de Erasmus Universiteit Rotterdam

op gezag van de Rector Magnificus,

Prof.dr P.W.C. Akkermans M.A.

en volgens het besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 21 oktober 1998 om 13.45 uur

door

Johannes Leendert Petrus Kuijpens

geboren te Breda.

Promotiecommissie.

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Co-promotor:	Dr. V.J.M. Pop

Dit proefschrift is tot stand gekomen door de gezamenlijke inspanning van de afdeling Endocrinologie en metabolisme van het Academisch Medisch Centrum van de Universiteit van Amsterdam, de afdelingen Epidemiologie en biostatistiek en Immunologie van de Erasmusuniversiteit Rotterdam, de huisartsenpraktijk te Riethoven, de Klinische laboratoria van het Sint Joseph Ziekenhuis Veldhoven en de kankerregistratie van het Integraal Kankercentrum Zuid te Eindhoven. De epidemiologische studies over schildklierkanker stonden onder supervisie van dr. J.W.W. Coebergh, arts-epidemioloog.

Aan Janneke en Pieter, Juliëtte en Maarten

Contents

Chapter 1.

Introduction.
The studies described in this thesis concentrate on epidemiological and pathogenetic aspects of postpartum thyroid dysfunction (PPTD) and related topics, and on epidemiological and treatment aspects of thyroid cancer. The studies were performed in the southeastern part of the Netherlands and included prospective studies in a representative cohort of women followed during pregnancy and in the first postpartum year, and retrospective studies on thyroid cancer based on data derived from the population-based Eindhoven Cancer Registry.
In the first chapter a general introduction is given on the epidemiology of thyroid diseases in the Netherlands (Chapter 1.1), followed by a discussion on clinical aspects of PPTD and thyroid cancer (Chapters 1.2 and 1.3). Thereafter the specific aims of the present studies are formulated (Chapter 1.4).

1.1. Epidemiology of thyroid diseases in The Netherlands.
Information about the epidemiology of thyroid diseases in the Netherlands is scarce and fragmented. Data have been obtained from different sources, such as from reports of screening programmes, general practice registration projects, hospital based registries or population based registries (e.g. the Dutch Cancer Registry). To be able to put our data in perspective, an introduction to some epidemiological data concerning the most relevant thyroid disorders is presented in short.

Congenital hypothyroidism. Since 1981, 99.5% of all live births in The Netherlands are being screened for congenital hypothyroidism (CHT). The screening is performed within the first week after delivery. The results of the screening programme show that the prevalences of primary CHT and congenital thyrotropin (TSH) deficiency syndrome are 29/100,000 and 4/100,000 newborns, respectively (1). The prevalence of CHT is comparable to that in other western societies (2,3). The cause of primary CHT is thyroid ectopy in 38%, thyroid agenesis in 32% and an inborn error of thyroid hormone metabolism in 9% of the cases, respectively (1). It can be estimated that about 60 children with CHT are being born annually in the Netherlands (29+4/100,000*180,000 newborns).

Hyperthyroidism. Physician-based sentinel-studies have revealed an incidence of hyperthyroidism in the adult population of 0.5-1 per 1,000 persons per year (5,500 - 11,000 new patients per year) with a male to female ratio of about one to four (4,5,6). The incidence of hyperthyroidism in the population-based Whickham Survey in the U.K. is comparable: 0.8 per 1,000 per year in females and almost nil in males (7). The causes of hyperthyroidism in patients referred to a community hospital were Graves' disease in 47%, nodular goiter in 41%, and other causes in 12% of the cases, respectively (8).

Hypothyroidism. The reported incidence of hypothyroidism in adults is low: 0.2-0.4 per 1,000 persons per year (2,250 - 4,500 new patients per year) (4,5,6). Spontaneous hypothyroidism is in the majority of cases the result of thyroid autoimmunity; a (subtotal) thyroidectomy or treatment with radioactive iodine is the cause of most of the iatrogenic cases (5,9). In the Whickham Survey, the incidence of hypothyroidism is 4.1 per 1,000 women (3.5 per 1,000 spontaneous hypothyroidism) and 0.6 per 1,000 men per year (7).
Autoimmune lymphocytic thyroiditis is the most important cause of hypothyroidism in adults and the presence of thyroid peroxidase antibodies (TPOAb) in serum is a marker for this disease. In the Netherlands, the prevalence of TPOAb in women of 20-55 years is 10-13% (10,11) and in men of 20-70 years about 6% (12). These prevalences are similar to those in other western countries (7,11). The probability of developing overt hypothyroidism is related to the presence of TPOAb in serum and high-normal (2.0 - 4.0 mU/l) or elevated (>4.0 mU/l) TSH levels in serum: the relative risk (RR) of TPOAb alone is 5.3-8 in women and 25 in men, the RR of high-normal/elevated TSH is 8-9 in women and 44 in men and the RR of TPOAb in combination with high-normal/elevated TSH is 36-38 in women and 173 in men, respectively (7,13). Although the prevalence of TPOAb and the proportional distribution of high-normal/ elevated TSH levels in the Netherlands are similar to that in the U.K., the reported incidence of (spontaneous) hypothyroidism is different (4,6,7,13). This discrepancy is most probably due to the fact that the U.K. data are derived from a population-based screening project and the Dutch data from general practices (with unrecognized hypothyroidism cases).

Goiter/nodular thyroid disease. The prevalence of goiter has decreased dramatically since the implementation of iodine-supplementation programmes in the 30's and 40's (14-17). The daily iodine-intake in the Netherlands is sufficient, although regional differences do exist (15,17). However, the precise prevalences of goiter or nodular thyroid disease in the Dutch population are unknown.

Thyroid cancer. Thyroid cancer is a rare type of cancer in the Netherlands, accounting for <1% of all newly diagnosed cancers per year (18). The number of new patients per year remained stable in the period 1989-94: the mean number per year (excluding non-Hodgkin's lymphoma originating from the thyroid) was 80 for males and 224 for females, respectively; the annual numbers of deaths related to thyroid cancer were about 30 for males and about 70 for females, respectively (18). The incidence of thyroid cancer (calculated with the European standard population for international comparison) is 1.3 per 100,000 males and 2.6 per 100,000 females per year and the male to female ratio 0.5 (18). The incidence is similar to that in the surrounding countries; however, in the Scandinavian countries the incidence in both males and females is about twice of that in the Netherlands (19). The estimated number of patients treated for thyroid cancer since 1970 and alive in 1995 was 2,700, based on a prevalence rate or 10 per 100,000 men and 26 per 100,000 women (20).

1.2. Postpartum thyroid dysfunction.

In 1948 Roberton was the first to describe women with symptoms of hypothyroidism in the postpartum period whose complaints were treated succesfully with thyroid extract (21). The syndrome of postpartum thyroid dysfunction (PPTD) remained unrecognised until the seventies when Amino et al. and Ginsberg and Walfish described small series of patients with periods of

transient hypothyroidism and transient hyperthyroidism in the months following delivery (22,23,24). Soon it was suggested that PPTD was part of the spectrum of autoimmune thyroid diseases because of its strong association with microsomal antibodies (MsAb) in serum, the presence of lymphocytic thyroiditis at fine needle biopsy, a familial predisposition and the association with other endocrine autoimmune diseases such as type-I diabetes mellitus (25,26). In the 80's several research groups in Japan, the United Kingdom (Wales), Sweden and Canada investigated the etiology, pathogenesis and epidemiology of PPTD.
Within the scope of this thesis, we have defined PPTD as any form of clinical thyroid dysfunction (an abnormal TSH and an abnormal fT4 at the same time) occurring in the first postpartum year.

Clinical evaluation.
During the course of PPTD different patterns of thyroid dysfunction occur: persistent or transient hyperthyroidism, persistent or transient hypothyroidism, or the most typical ("classic") biphasic course with a transient thyrotoxic phase 1-3 months after delivery, a hypothyroid phase 3-6 months after delivery, followed by recovery (27,28). Most cases are due to postpartum thyroiditis (PPT), a self-limiting destructive thyroiditis of autoimmune origin. Persistent thyrotoxicosis is rare and is caused by an exacerbation of Graves` disease (27,29).
The dominating complaint in women with PPTD is tiredness and lack of initiative, both in the thyrotoxic and hypothyroid phases (24,28,30,31,32). Lazarus et al. concluded that the hyperthyroid symptoms nervousness, weight loss, sweating, shaking hands, palpitations and heat intolerance, were not discriminative for identifying women with thyrotoxicosis; on the other hand, the hypothyroid symptoms lack of energy, aches and pains, memory disturbance, dry skin and cold intolerance, were significantly more frequent in PPTD cases, and the severity of symptomatology was related to the presence of TPOAb rather than to the actual thyroid (dys-)function (33). Depression in the postpartum may also be a sign of PPTD (34,35). However, the occurrence of depression seems to be associated with the presence of TPOAb independent of thyroid dysfunction, although women with PPTD did have more severe depressive symptomatology (10,33,36).
A diffuse, painless goiter is present in the majority of cases (24,25,30,31,37). However, in many cases PPTD is a disorder with mild complaints and most of the symptoms may remain unrecognized or may be attributed to the postpartum state itself (28,34).
Laboratory testing. To confirm the diagnosis of PPTD thyroid function tests should be performed, i.e. serum TSH and serum fT4. In addition, TPOAb testing should also be performed. The measurement of other antithyroid antibodies, such as antithyroglobulin antibodies, is of limited value. To distinguish between Graves' disease and the thyrotoxic phase of PPT a thyroid radioactive iodine uptake (RAIU) test with ^{123}I or ^{99m}Tc-pertechnetate scan is the test of choice (28,34,37). The RAIU is very low in the destructive thyrotoxic phase of PPT and high in Graves' disease high; in the late recovery phase of PPT the RAIU may be normal or low (27,28,34).
Treatment. Most authors agree that treatment is not required in most cases, unless symptoms are severe (27,28). In case of thyrotoxic symptoms such as palpitations or tachycardia, a short course of propranolol can be prescribed. When hypothyroid symptoms and/or depression occur L-thyroxine should be considered (28,38).

Prognosis and follow-up.

Women who have suffered from PPT are at risk for recurrent PPTD after a following pregnancy. They are also at risk for developing permanent hypothyroidism in future life (31,39,40,41). The recurrence-rate of PPTD after a following delivery is about 40% (39). The risk of developing permanent hypothyroidism after PPTD is estimated as 20-30% in a 5 year period and is associated with relatively high TPOAb titers, more severe hypothyroidism and lack of a thyrotoxic phase (28,40,41). It can be envisaged that in these women a more severe and prolonged autoimmune process already exists, which has resulted in a reduced functional capacity of the thyroid. In the general population, the risk of developing permanent hypothyroidism correlates also strongly with the presence of high TPOAb titers, especially in combination with high normal or increased serum TSH concentrations (7,13).

It should be advised that women who have recovered from PPTD and are positive for TPOAb should have checked their TSH annually to discover (subclinical) hypothyroidism in time (28).

Epidemiology.

Incidence. The incidence of PPTD varies in different ethnic groups and geographic regions, possibly due to differences in genetical predisposition might have been missed in studies with wide intervals between assessment points or short-term follow-up after delivery. The reported incidences range from 0-2% in Middle and Southeast Asian countries and in U.S. blacks, to 4-10% in the causasian population in the U.S., Canada, Northwestern Europe and Japan (10,30,37,39,42-48). Based on studies that meet strict and uniform methodological criteria it is likely that the most accurate estimate of the incidence of PPTD is 4-8% (10,49).

Risk factors. Several risk factors for the development of PPTD have been identified. Of these, the presence of TPOAb (identical to microsomal antibodies (MsAb)) in serum is the most prominent. The prevalence of TPOAb in fertile women is about 10%; however, in women with PPTD the prevalence is 80% (10,49). Women positive for TPOAb in gestation or in the early postpartum period have a RR of 20-80 for developing PPTD (10,49). However, the positive predictive value of TPOAb testing in pregnancy and/or postpartum is 40-70% (10,37,44,49,50,51,52).

The associations with the presence of HLA-DR3, -DR4 and -DR5 (40,50,51,53,54), a positive family history for autoimmune endocrine (thyroid) diseases (25,37,39,44,55) and the increased risk in women with type-I diabetes mellitus (26,56,57,58) refer to a genetically defined predisposition.

The influence of lifestyle-habits (such as smoking and diet) on the risk of developing PPTD remains controversial. Fung et al. found smoking associated with an increased risk, in contrast to Jansson et al. and Lazarus et al.who did not find smoking related to PPTD (33,42,44). With regard to dietary factors, the severity of PPTD has been correlated to both insufficient and excessive iodine intake (50,59).

Histopathology of PPT.

Mizukami et al. described the histology and immunopathology of PPTD due to PPT based on fifteen cases (60). The specimens for examination were obtained by performing percutaneous needle biopsy during the hypothyroid phase or the (euthyroid) recovery phase. In the hypothyroid and early recovery phases focal or diffuse lymphocytic infiltration was present

in all specimens. A mild to moderate destruction next to hyperplastic changes in the follicles was shown in all cases. None of the specimens showed fibrosis (as a sign of irreversible changes as in end-stage Hashimoto's thyroiditis (61)). In the late euthyroid phase a focal thyroiditis with mild to moderate lymphocytic infiltration and a restored architecture of the follicles was found. Some follicles were mildly hyperplastic, but the majority had normal sizes (60). The same histopathological patterns have also been found by other authors who had performed percutaneous needle biopsies, and it was noted that the results of the histopathological examinations were identical to those found in spontaneous silent thyroiditis (62,63). An example of lymphocytic thyroiditis is shown the Figure.
Immunohistology of the lymphocytic infiltration of the thyroid revealed predominantly T lymphocytes with an increased CD4 to CD8 ratio. The follicular cells showed an intense expression of HLA-DR antigen on their surface (60,64).

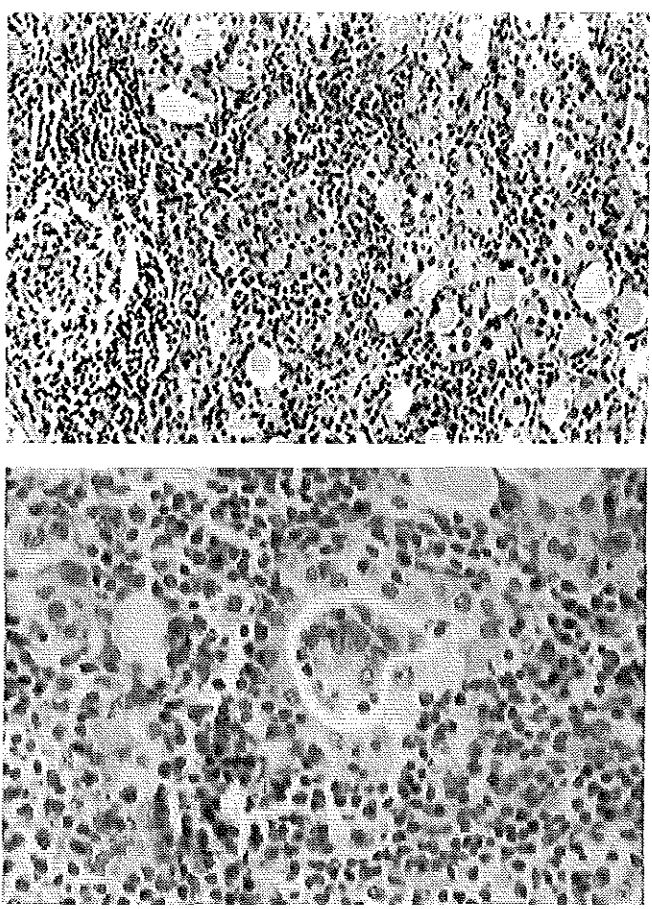

Figure. Autoimmune thyroiditis with lymphocytic infiltration, a lymphoid follicle, and collapse and destruction of thyroid follicles. A: magnitude X100; B: X200. (courtesy P.J.J.M. Klinkhamer, pathologist, Regional Institute for Pathology PAMM, Eindhoven)

The pathogenesis of autoimmune thyroid disease.

The primary function of the immune system is to discriminate between "self" and "non-self" and to protect the body by eliminating infectious agents and to minimize the damage they cause (65,66). In healthy individuals a certain reactivity towards "self" is considered to be a normal event that is, however, controlled by several downregulating mechanisms. Disturbances or imbalances of these downregulating mechanisms may result in an excessive immune reactivity towards "self", causing damage ("autoimmune disease").

The pathogenic mechanisms of autoimmune thyroid disease (AITD) resulting in hypothyroidism have primarily been studied in animal models for spontaneous and induced autoimmune hypothyroidism. Putative animal models for Graves' disease are yet to be validated. In patients, tissues, cells and sera are difficult to obtain, especially from the early asymptomatic stages of the disease. However, the results of the animal studies may be extrapolated with some caution to human autoimmune hypothyroidism.

The animal models indicate that the pathogenesis of autoimmune lymphocytic thyroiditis is predominantly immune cell-mediated and a multistep process, requiring several abnormalities before full blown disease develops (66,67). The following five phases can be discerned (67):

1. A phase of predisposition. There appears to be a genetically linked predisposition to autoimmune reactivity to thyroid antigens. In animal models a specific make up of the MHC-molecule contributes to excessive autoimmune reactivity towards particular autoantigens. In humans PPT is positively associated with the presence of HLA-DR3, -DR4 and -DR5 and negatively with HLA-DR2 (40,51,53,54,66). It is thought that some thyroidal antigens combine better with certain MHC haplotypes. It is also possible that the association with these haplotypes simply points in the direction of a genetic make up prone to a high autoimmune reactivity in general.

2. An initial phase. The first leucocytes entering the thyroid during the onset of disease are monocyte-derived cells, such as macrophages and dendritic cells. Particularly dendritic cells have been identified as the first immune cells invading endocrine organs such as the thyroid and the pancreas in the process of thyroiditis and insulitis (68,69). These dendritic cells are the antigen-presenting cells par excellence, and they abundantly express both MHC class-I and class-II molecules on their surface (70). The mechanism by which dendritic cells start to accumulate in the thyroid in the absence of antigenic stimulation is still unknown, but it is likely that various mechanisms may play a role. Firstly, local tissue damage caused by factors such as viral infections or environmental factors (e.g. drugs, diet, iodine-intake) may trigger this process (71,72). Secondly, locally released factors from hyperactive thyrocytes may also play a role. These factors may activate the endothelium to express high levels of adhesion molecules, which make them more adhesive for passing leucocytes (72). Extravasation of leucocytes is promoted by an activated endothelium. In this phase of the disease, the thyroid follicle cells do not express MHC class-II molecules.

3. A phase of an excessive production of autoreactive T cells and autoantibodies. The dendritic cells descended from the thyroid transport thyroid autoantigens via the lymph to the draining regional lymph nodes. In the lymph node the dendritic cells contact T lymphocytes and will present the autoantigens to these cells. The autoimmune reaction is started, the lymph nodes become swollen, the T cell areas activated, the IgM-IgG isotype switch occurs, and thereafter plasma cells (producing auto-antibodies) can easily be detected (67). In the animal models, the basis for this aberrant excessive immune reactivity is formed by various defects, e.g. those

occurring in suppressor circuits (loss of or defects in T suppressor cells), those that make T cells resistant to apoptosis, and defects in dendritic cells and macrophages. In human patients, both numerical and functional deficits of the T suppressor cell system have been reported, as well as defects in dendritic cells and macrophages (67).

4. An effector phase. Whether full-blown autoimmune hypothyroidism will develop depends also on a genetically determined susceptibility of the thyroid follicle cell. It has been supposed that the follicle cell has an intrinsically programmed enhanced trait for aberrant MHC class-II expression leading to more susceptibility for the immune attack or for a damaging cytokine action. Bottazzo et al. showed that HLA-DR was abberantly expressed by thyroid follicle cells in pateints with Graves' disease and Hashimoto's thyroiditis, whereas normal thyroid cells do not express HLA-DR (73). Mizukami et al. found a more frequent and intense expression of HLA-DR antigen on thyrocytes in the active phase of PPT compared to chronic thyroiditis (60).

5. A phase of perpetuation of the autoimmune reaction. In the later, more chronic phases of the thyroid autoimmune reaction there is sometimes a development of intrathyroidal lymphoid tissue (thyroid-associated lymphoid tissue (TALT); comparable to the mucosa-associated lymphoid tissue (MALT) located in the mucosal surfaces of the gastrointestinal, respiratory and genitourinary tracts, and consists of aggregates of non-encapsulated lymphoid tissue (65)). The hallmark of TALT is the presence of a special post-capillary venule: the "high endothelial venule" (HEV). HEVs are normally present in lymph nodes and MALT, and may develop at sites of chronic inflammatory (e.g. autoimmune) processes (65). The HEV endothelial cells interact with the circulating lymphocytes and facilitate a large influx of lymphocytes (65,72). This eases a local perpetuation of the (chronic) autoimmune process in the thyroid. In this phase the thyroid follicle cells close to the TALT express MHC class-II molecules on their surface, probably induced by the locally produced cytokines as IFN-γ.

The activation of the immune system in the post partum period leading to PPT is thought to be due to a "rebound" immunoactivation after delivery following the general immunosuppression during pregnancy (27,66).

Depression and its relation with PPTD.

Depression is a syndromal illness with both psychological and biologic components. According to the DSM criteria, the syndrome consists of a series of diverse complaints and signs. Depressed mood and loss of pleasure or interest are the key symptoms, other symptoms and signs are feelings of sadness, desperation, feelings of worthlessness, anorexia or hyperphagia, loss of concentration, slowness and insomnia or hypersomnia (74,75,76). This syndrome must last for at least two weeks and must be incapacitating. A "minor" depression is considered to be present when a relatively sustained depressive mood exists in combination with 3 or 4 of the above mentioned symptoms or signs. When the depression is alternating with manic episodes, the disorder is called "bipolar disorder".

There are two important classification systems for psychiatric diseases: the Research Diagnostic Criteria (RDC) defined by Spitzer et al. (77) and the Diagnostic and Statistical Manual of Mental Disorders (DSM, fourth edition) (78). According to the RDC criteria major and minor depression can be distinguished (77). The DSM criteria represent a multi-axial classification system with inclusion and exclusion criteria and was based on the RDC (78).

Depression is a multifactorial disorder and is caused by interactions between predisposing

genetically determined factors (such as minor disturbances of the neuro-endocrine system), biologic factors (such as physical disease), psychosocial factors (such as educational level), and external stressors (such as major life events (e.g. bereavement)) (74,75,79).
Depression is a major health problem in view of its high prevalence: the one-year prevalence in women 25-44 years is about 10% in The Netherlands (80). Depression is also frequently present in pregnancy and after delivery: Pop and O'Hara found 7-8% of pregnant women depressed in the second half of pregnancy, and in the postpartum period 10-14% of the women were depressed at different time points (81,82). Harris et al. found very high cumulative incidences of depression in postpartum women: 43% of women negative for antithyroid antibodies and 63% of the women positive for antithyroid antibodies were depressed at 1 to 4 time points in the first postpartum year (36).
The association between depression and thyroid diseases, in particular lymphocytic thyroiditis, is wellknown and has been described in many case reports and clinical studies. Patients with either hyper- or hypothyroidism may present with depression as the most prominent symptom; vice versa, depressed patients may show an increased prevalence of thyroid dysfunction (9,10,12,83,84). In general, depression is more pronounced in hypothyroid than in hyperthyroid patients.
The results of recent studies indicated that depression is not merely the result of the thyroid dysfunction, but seems to be related to the presence of TPOAb (10,11,12,36). This association between the presence of TPOAb (as sign of an early form of lymphocytic thyroiditis) and depression may be rooted in an interaction between the central nervous system (and its reaction on stressful life events) and the immune system, and/or vice versa (85,86). Probably patients at risk for AITD are more sensitive for external stressors acting via the nervous system; alternatively, the correlation between autoimmune lymphocytic thyroiditis and depression indicates a genetically linked predisposition for both disorders.

1.3. Thyroid cancer.

Epidemiology.
Incidence. Thyroid cancer is a rare malignancy: in the Netherlands it represents about 0.5% of all new cancers diagnosed in 1994 (18). The incidence in the Netherlands is similar to that in the surrounding countries, but lower than in the Scandinavian countries (see Table 1) (19). The highest incidences are found in Iceland, in Filipinos in the U.S., and in French Polynesia (see Table 1).
The incidence rates for papillary and follicular thyroid cancer have been increasing in the period 1950-85 and decreasing slightly thereafter (87-90). The increasing incidence of the papillary type is thought to be due to the wide use of radiation treatment for benign head and neck disorders between 1930 and 1960 and/or changes in dietary habits (90).
Risk factors. The only well recognized risk factor for thyroid cancer (in particular the papillary type) is the exposure to external irradiation for repeated diagnostic and therapeutical reasons and accidental exposure at a young age (e.g. exposure to high doses of ^{131}I after the Chernobyl accident in 1986) (90-93). The excess risk appeared to be related to age (children <5 yrs. had the highest risk) and dose (a higher dose revealed a higher risk); adults who were exposed to irradiation did not show an increased risk (90,92).
Other putative determinants described in various studies are:

- iodine-intake: both deficient and excessive iodine-intake were found to be associated with thyroid cancer (90,92,94,95). In regions with endemic goiter due to deficient iodine-intake the prevalence of follicular thyroid cancer appeared to be higher (92,94);
- diet: many epidemiological studies were performed to identify dietary factors associated with thyroid cancer. A reduced risk associated with vegetable intake was common to all studies, the results regarding fish intake, however, were inconsistent (90,93,95,96);
- pre-existent thyroid disease: the results of recently published studies have shown a correlation between a pre-existent goiter or pre-existent nodules in the thyroid and the risk of developing thyroid cancer (90,92,93,96,97). At the same time, patients with a chronic lymphocytic thyroiditis appear to exhibit a greatly increased risk of malignant lymphoma of the thyroid (98);
- genetic factors: medullary thyroid cancers are part of the inherited multiple endocrine neoplasia type-2 (MEN-2) syndromes or familial type in about half of the cases, and a small proportion of the papillary types is part of the Gardner's syndrome (92,99,100,101);
- environmental factors: accidental contact with (undefined) chemicals and occupational exposure to dioxins have been associated with an increased risk for (papillary) thyroid cancer (93,102);
- hormonal and reproductive factors: the striking male to female-ratio of 1 to 3 in thyroid cancer (as in other thyroid diseases) suggested that hormonal factors are involved in the development. In studies from Ron et al., Preston-Martin et al. and Kolonel et al. an association between miscarriages and/or multiparity and thyroid cancer was found (96,97,103); Akslen et al., however, failed to confirm this association (104).

Histological types.

The great majority (95%) of thyroid cancers are carcinomas originating from thyroid epithelial cells. The revised World Health Organization (WHO) classification includes as epithelial tumours the well-differentiated papillary (including mixed papillary-follicular) and follicular carcinomas, medullary carcinoma and the undifferentiated (anaplastic) carcinomas (105,106). The papillary, follicular and anaplastic carcinomas all arise from the thyroid follicular cell; medullary carcinoma arises from the calcitonin-producing parafollicular C cell (105,106).
A distinct category are the malignant lymphomas (almost all non-Hodgkin's lymphomas) (105,106). In the past, these malignancies were often diagnosed as small-cell carcinomas. The majority of primary thyroid lymphomas arise on a background of chronic lymphocytic thyroiditis (98,105).
The relative frequencies of the various histological types of the tumours are different in the various geographic regions and populations. This can in part be explained by differences in the distribution of risk factors and variations of diagnostic and pathologic procedures.

TNM and other clinical staging systems.

Clinical staging systems in oncology have been developed for facilitating treatment desicions, for predicting the patient's outcome and for comparison of studies on treatment and prognosis. Various staging classifications for thyroid cancer have been developed in the last decades (107-112). The most wellknown of these staging systems is the TNM classification, which is based on the anatomic extent of the cancer and this classification has been adapted several times. The most recent version is shown in Table 2 (111).

The various staging systems for thyroid cancer have been reviewed and evaluated, and it was concluded that the staging systems yielded comparable results in predicting prognosis. Therefore it was recommended to use the widely accepted and universally available TNM classification for the staging of thyroid cancer (112).

Prognosis and prognostic factors.

The prognosis for patients with papillary and follicular thyroid cancer is very good: the relative 5- and 10-year survival is 80->95% in studies both from selected patients treated in large referral centres and from population-based cancer registries (109,113-118). The prognosis for anaplastic carcinoma patients, however, is extremely poor: the 5- and 10-year survival (crude or relative) is about 5% (116,118). Medullary thyroid cancer patients exhibit a relative 10-year survival of 60-80% (101,116,118).

A multivariate analysis to identify independent prognostic factors for thyroid cancer has been performed in many studies (107,108,109,113-122). Survival appeared to be related to the histological type of the tumour (papillary thyroid cancer showing an extremely good prognosis versus anaplastic showing an extremely poor prognosis), cellular differentiation, stage of disease (extent of disease) and age at diagnosis (107,108,109,113,114,115,117-122). Gender (females doing better than males) was only found to be related to survival in studies on differentiated thyroid cancer (114,117,118,121,122).

Diagnosis and treatment.

Solitary or multiple nodules in the thyroid are frequent: the prevalence is estimated as 4% in the general population in western societies with a male to female ratio of 1 to 4 and an increasing prevalence with age (123,124). The majority of thyoid nodules is benign. Therefore, a correct selection of those goitrous patients who have the highest risk for a malignant tumour is essential to prevent operations in patients who do not have a malignancy; on the other hand, a correct diagnosis is also essential, to treat thyroid cancer patients with the most appropriate therapy. Several diagnostic procedures are thought to distinguish between benign and malignant nodules. In the Netherlands, two consensus development conferences have been organised in order to define recommendations for a diagnostic strategy and treatment (125-129).

Firstly, there was agreement that the medical history and physical examination is important to select patients with nodules suspicious for malignancy (123,124,127). Factors associated with an increased risk are: age <20 or >60 years, male gender, a history of neck irradiation, a rapid growth of the tumour and a family history of medullary or papillary thyroid cancer (123,124,127,130,131). Cancer is found more often in solitary nodules, in fixed tumours, or when enlarged lymph nodes an/or recurrent nerve paralysis are present (123,124,127,130,131). However, most patients with thyroid cancer do not have complaints apart from a (growing) nodule in the thyroid. Secondly, there was agreement that fine-needle aspiration biopsy is of great value in the diagnostic procedure.

Fine-needle aspiration biopsy (FNAB). FNAB is nowadays considered to be the test of choice for pre-operative selection of patients (123,127,130,131,132). FNAB is a safe and inexpensive test and has resulted in a better selection of patients for operation. The sensitivity and specificity of FNAB to detect malignancy are 90-95% and 70-75%, respectively (123,127,130,131,133). The accuracy of FNAB depends upon the experience of the physician:

acceptable results wil be achieved when at least 20-35 FNABs are performed per year (123). The positive predictive value of FNAB is about 30-35%: 2 out of 3 patients with a positive FNAB for malignancy did not exhibit a malignancy when operated (127,131,132,133).

Treatment. Surgery is the initial treatment of choice for differentiated (papillary or follicular) and medullary thyroid cancer. However, there is continuing controversy on the extent of the operation to be performed in cases of differentiated thyroid cancer (110,115,117,127,134-138). In the most recent studies, patients with differentiated thyroid cancer who were treated with more extensive surgical procedures (followed by ^{131}I ablation) did show a better long-term prognosis (115,117,122). These studies involved series of selected patient from referral centres and used different definitions of "extensive" surgery.

The Dutch consensus meeting stated that:

- a hemithyroidectomy is the acceptable approach in case of a well-differentiated papillary thyroid carcinoma confined to one lobe and without extrathyroidial growth, no or ipsilateral lymph node metastases or no distant metastases. Hemithyroidectomy is also an acceptable approach in case of a well-differentiated follicular carcinoma confined to one lobe and with minimal capsular invasion and without lymph node metastases nor distant metastases;
- a total thyroidectomy followed by ^{131}I ablation should be performed in all other cases of differentiated thyroid cancer (127).

^{131}I ablation therapy is recommended for all differentiated thyroid cancer patients with remnant thyroid tissue after surgery (127,139,140). After thyroidectomy and ^{131}I ablation, thyroxine replacement therapy is required. During follow-up, serum thyroglobulin testing might be helpful in detecting recurrences (141).

A total thyroidectomy is the therapy of choice for medullary thyroid cancer because of its multifocal origin, especially in the familial types (99,100,142).

1.4. Brief outline of this thesis.

The studies presented in this thesis focus mainly on epidemiological aspects of the thyroid disorders postpartum thyroid dysfunction (PPTD) and thyroid cancer.

PPTD and related topics. PPTD affects 4-8% of postpartum women in the first year after delivery. The symptomatology of PPTD consists mainly of hypothyroid related complaints. Also, there appears to be an intriguing association between the presence of TPOAb, PPTD and depression. The presence of TPOAb in gestation may serve as a marker for PPTD development, and about 70% of the women developing PPTD are positive for TPOAb in gestation. However, only half of the women with TPOAb in gestation and/or in the postpartum develops PPTD. Therefore, TPOAb testing alone is not a sufficiently reliable method for identifying women who really will experience PPTD. On of our study aims was to see if the predictive value of TPOAb testing could be enhanced by the combination with other anamnestic and immunological determinants. Furthermore, we studied TPOAb and PPTD in relation to depression and child development. The studies are presented as follows:

a. anamnestic and lifestyle-related determinants for PPTD and the usefulness of these determinants in the identification of women who will develop PPTD (besides TPOAb) (Chapter 2.1);
b. cell mediated immunity parameters of PPTD and the usefulness of these parameters in the identification of women who will develop PPTD (Chapter 2.2);

c. the relationship between the presence of TPOAb, thyroid dysfunction and depression during pregnancy and in the first year after delivery; and the usefulness of maternal TPOAb and thyroid dysfunction during pregnancy to predict a postpartum period of depression (Chapter 2.3), and;
d. the consequences of lymphocytic thyroiditis in the mother during pregnancy for the development of the child in the first year (Chapter 2.4).

Thyroid Cancer. The study of diagnostic procedures, treatment and prognostic factors in thyroid cancers has caught the interest of many researchers in the Netherlands. Most studies have concerned selected patient groups referred to large oncologic centres and university hospitals. However, studies on the epidemiology of thyroid cancer in the general population in the Netherlands and the treatment and prognosis of unselected patients referred to community hospitals are lacking. The thyroid cancer studies are population-based and performed in a circumscript geographic area in Southeastern Netherlands. The studies on thyroid cancer are presented as follows:
a. the trends in incidence of thyroid cancer and in the distribution of the different histological types (Chapter 3.1);
b. the (changing pattern of) care of patients referred to community hospitals (Chapter 3.2);
c. the survival and prognosis-related factors of unselected patients (Chapters 3.1 and 3.2);
d. the prevalence of comorbid conditions in relation to possible risk factors and the influence on treatment (Chapter 3.3);
e. the incidence and the spectrum of second tumours after the diagnosis of thyroid cancer (Chapter 3.4).

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Table 1. Incidence of thyroid cancer in different countries or selected populations. (annual rate per 100,000 population, standardized to the World Standard Population; data from Parkin et al., 1997)

	males	females
Denmark	0.8	2.1
Finland	1.8	6.4
France (Bas-Rhin)	1.3	2.6
Germany (Saarland)	2.0	3.5
Iceland	6.1	9.8
The Netherlands	0.9	2.2
Norway	1.7	4.7
Sweden	1.4	3.6
UK (England and Wales)	0.7	1.7
UK (Scotland)	0.9	2.0
US (Connecticut, White)	2.4	4.8
US (Connecticut, Black)	1.2	4.0
US (Hawaii, Hawaiian)	3.0	9.1
US (Hawaii, Filipino)	5.1	25.5
French Polynesia	2.9	15.9

Table 2. TNM Classification of thyroid carcinoma. (International Union Against Cancer, 1992)

Histological type		
Papillary or follicular	under 45 years	45 years and over
Stage I	anyT anyN M0	T1 N0 M0
Stage II	anyT anyN M1	T2 N0 M0
		T3 N0 M0
Stage III		T4 N0 M0
		anyT N1 M0
Stage IV		anyT anyN M1
Medullary		
Stage I		T1 N0 M0
Stage II		T2 N0 M0
		T3 N0 M0
		T4 N0 M0
Stage III		anyT N1 M0
Stage IV		anyT anyN M1
Anaplastic		
StageIV		all cases stage IV

T1: tumour $\leq$1 cm, T2: >1 to 4 cm, T3: > 4 cm, T4: extends beyond gland, N1: metastases in regional lymph node(s).

Chapter 2.1.

Prediction of post partum thyroid dysfunction: can it be improved?

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Eur J Endocrinol 1998; 139: 36-43.

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Abstract

Background. Screening pregnant women for thyroid peroxidase antibodies (TPOAb) to identify women at risk for post partum thyroid dysfunction (PPTD) is controversial, also because of the low positive predictive value (ppv) of TPOAb.

Objectives. To evaluate if ppv of TPOAb can be enhanced, either by taking into account the time of TPOAb testing, or by combination with other putative determinants of PPTD like smoking, family history or other autoimmune diseases.

Methods. A prospective study was performed in the region Kempenland (southeastern Netherlands). 310 unselected women were visited at 12 and 32 weeks gestation and 4, 12, 20, 28 and 36 weeks p.p.. Serial TSH, fT4 and TPOAb testing was performed. Thyroid dysfunction (TD) was defined as abnormal TSH either in combination with abnormal fT4 (overt TD) or without abnormal fT4 (subclinical TD). PPTD was defined as overt TD p.p.. Multivariate regression analysis was performed for determining independent risk factors for PPTD. Sensitivity and specificity of TPOAb at different time points and at different concentrations were calculated and presented in ROC curves. Women who had experienced PPTD were followed for 2.5-3 years.

Results. Data of 291 women were available for analysis. Serum fT4 declined during pregnancy and returned to baseline values p.p.. TD in gestation was present in 23 women (7.9%): serum TSH was transiently decreased in 13 (6 had overt gestational thyrotoxicosis (2.1%)) and increased in 10 (2 had TPOAb). Both point prevalence and concentration of TPOAb decreased during gestation and returned to baseline levels within 12 weeks p.p.. TD in p.p. was present in 36 women (12.4%): 21 had sublinical and 15 overt TD. Out of the 15 women with overt TD (incidence of PPTD: 5.2%) 10 were positive for TPOAb (TPOAb+); 9 had thyrotoxicosis (4 TPOAb+), 5 hypothyroidism (5 TPOAb+) and 1 thyrotoxicosis followed by hypothyroidism (TPOAb+). Independent risk factors for PPTD were TPOAb (RR=27.2), bottle feeding (RR=11.1) and smoking habits (ever smoked: RR=3.1; women with PPTD had smoked more cigarettes for a longer period). The sensitivity of TPOAb testing was highest at 12 weeks gestation (0.67). Ppv of TPOAb was 0.31-0.75 (depending on time of testing and concentration), increasing slightly to 0.38-0.80 when combined with bottle feeding or smoking habits. There appeared to be an autoimmune form of PPTD in 2/3 of cases and a non-autoimmune form; women with the autoimmune form were at risk for developing permanent hypothyroidism.

Conclusions. A maximum of 2/3 of PPTD cases can be predicted from the presence of TPOAb because 1/3 remained negative for TPOAb. The most appropriate time for TPOAb testing is in the first trimester of pregnancy. The combination of TPOAb testing with anamnestic determinants of PPTD does not increase ppv substantially.

Introduction

Post partum thyroid dysfunction (PPTD) was recognized as a clinical entity in the 70's (1,2). The incidence of PPTD in the general population is 4-8% (3,4,5,6). PPTD is thought to be part of the spectrum of autoimmune thyroid diseases (AITD), and is caused in the majority of cases by a lymphocytic thyroiditis exacerbating in the first year post partum (p.p.) as the result of a "rebound" from the suppressed immune system during pregnancy (4,6). Fifty percent of pregnant women positive for thyroid peroxidase antibodies (TPOAb, identical to microsomal antibodies (MsAb)), will develop PPTD (3,4,5,6). PPTD is clinically characterized by symptoms associated with hyper- and/or hypothyroidism and depressive symptoms (4-8).

TPOAb are strongly related with PPTD: women positive for TPOAb have a relative risk (RR) of 20-80 for developing PPTD (3,5). However, the positive predictive value of TPOAb is about 40-60%, and one out of four women with PPTD does not have detectable TPOAb during pregnancy or in the post partum (3,5). Whether screening all pregnant women for TPOAb for predicting PPTD is worthwhile remains controversial. Some promote screening because of the risk of abortion, the risk of developing hypothyroidism in gestation or in future life, or the risk of PPTD (9,10,11). Others state that because of the low predictive value of TPOAb and the absence of severe clinical symptoms in the majority of women with PPTD, screening is not justified (12,13). Screening, however, requires in the first place a test with high sensitivity to identify persons at risk, a high specificity to prevent false positive cases (which might be a great problem in diseases with a low prevalence) and a high predictive value.
The objectives of the present study therefore were to evaluate if the predictive value of TPOAb for PPTD can be enhanced by taking into account the time of TPOAb testing together with other putative determinants of PPTD (like family history, previous autoimmune diseases, smoking behavior).

Subjects and methods

Subjects

The study was performed between january 1994 and april 1996 in the region Kempenland in the southeastern part of the province of Noord-Brabant, the Netherlands. The iodine-intake is low-normal in this region: the mean daily urinary iodide excretion is 111±70 µg (14).
448 consecutive women not using thyroid drugs at their first visit to the local midwife or obstetrical department of the St Joseph Hospital Veldhoven (covering 90% of all pregnancies in the region), were asked to participate. 310 women (69%) consented in participation. Women who experienced spontaneous miscarriages or stillbirth were asked to continue the study; women again pregnant within 6 months after delivery were excluded from analysis. All women were visited at home at 12 and 32 weeks gestation and at 4, 12, 20, 28 and 36 weeks p.p.. A personal and family history for thyroid and autoimmune disease was performed; information on medication, smoking habits and alcohol intake was obtained. In the first post partum visit the obstetrical history was performed. Signs or symptoms of thyrotoxicosis or hypothyroidism were looked for at every visit. Venous blood samples were collected into Vacutainer tubes (8 ml) for thyroid function and thyroid antibody testing every visit; serum was stored at -20°C. Permission for the study was obtained from the Medical Ethics Committee of the Academic Medical Centre, University of Amsterdam.

Methods

Thyroid function tests. The concentration of thyroid stimulating hormone (TSH) was measured by an immunometric technique, based on enhanced luminescence (Kodak Amerlite TSH-30, Kodak Clinical Diagnosticts Ltd., Amersham, UK). The reference interval for TSH was 0.15 - 2.0 mU/l, as defined for 225 non-pregnant women in the age group of 20-40 years and living in the same region, using the IFCC recommendations for defining reference values (15). The interassay coefficients of variation were 20, 4.8, 6.3 and 5.1% at concentrations of 0.04, 0.68, 8.2 and 29.2 mU/l, respectively.

Free thyroxine (fT4) was determined by using the Kodak Amerlite MAB FT4 Assay; its reference interval was 8.7 - 19.6 pmol/l, and was defined as described above. The interassay coefficients of variation were 11.1, 11.3 and 12.2% at concentrations of 6.1, 19.3 and 27.7 pmol/l, respectively.
A free triiodothyronine (fT3) assay for diagnozing a possible T3-toxicosis was performed in case of a decreased TSH but normal fT4 (reference interval: 4.0 - 8.0 pmol/l; Amerlex MAB, Amersham, Amersham, UK).
Thyroid dysfunction (TD) was defined as an abnormal TSH (i.e. outside the reference interval), either in combination with an abnormal fT4 or an abnormal fT3 ("overt" TD), or without an abnormal fT4 or fT3 ("subclinical" TD).
The study group was divided into three subgroups according to the observed thyroid function: I: no TD during the entire study period, II: TD at 12 and/or 32 weeks gestation (overt or subclinical), and III: TD at one or more time points in the post partum (overt (PPTD) or subclinical; women who had TD both in gestation and p.p. were included in this group).
TPOAb were measured by using the Immunometric Enzyme Combikit (Orgentec GMBH, Mainz, Germany); a concentration of >50 U/ml was defined as "positive" (TPOAb+). The interassay coefficients of variation were 18 and 8.5% at concentrations of 18 and 1000 U/ml respectively.
For detection of thyrotropin receptor antibodies (TSH-RAb) in women with TD the TRAK-Assay (B.R.A.H.M.S. Diagnostica GMBH, Berlin, Germany) was used; a concentration of $\geq$15 U/l was considered as positive.
Analysis. Statistical analysis was performed by using the Statistical Package of Social Science (SPSS). Differences between subgroups were analyzed by the Chi-square test or Student's t-test. RR with the corresponding 95% confidence interval (95%CI) for developing PPTD were calculated. Multivariate logistic regression analysis was performed to determine independent riskfactors for PPTD; introduced in the model were all factors with $p \leq 0.1$ in the univariate analysis. Sensitivity, specificity and predictive values of TPOAb for detecting women at risk for PPTD at different time points and at different concentrations were calculated. Sensitivity and specificity were also presented in receiver operating characteristic (ROC) curves (with the corresponding area under the curve (AUC)).
Follow up. All women who had experienced PPTD were visited again 2.5 - 3 years after delivery to perform thyroid function and TPOAb tests.

Results

From the 310 women participating in the study 19 (6.1%) were excluded from analysis. The reasons for exclusion were: 7 women refused further participation after experiencing spontaneous miscarriage or stillbirth (1 TPOAb+), 1 suffered from puerperal psychosis, 9 (1 TPOAb+) were pregnant within 6 months after delivery and 2 women moved out of the region. The study population thus comprised of 291 women.
The different types of TD in relation to TPOAb are shown in Table 1: 232 women (80%) did not develop TD, 23 women (8%) had TD in gestation and 36 women (12%) post partum.
In Figure 1 the results of the serial fT4 and TSH testing are presented. The mean fT4 and TSH levels were comparable to the values for non-pregnant women with the same age, with the exception of fT4 levels at 32 weeks gestation and TSH levels at 20 weeks p.p.. The mean fT4 declined 22% during pregnancy, and returned to the original level within 12 weeks after delivery.

The mean TSH remained stable during gestation, increased gradually to a peak at 20 weeks p.p., and then returned to the original level.
A total of 41 women (14,1%); see Table 1)) had TPOAb at one or more time points. Three patterns of TPOAb could be identified: 5 women had TPOAb only in gestation, 9 women had TPOAb (with increasing concentrations) only in the post partum and 27 women had TPOAb both in gestation and p.p.. Figure 2 shows the point-prevalences of TPOAb at three different concentrations. The proportion of women with TPOAb >50 U/ml at 12 weeks gestation was similar to that at 12, 20, 28 and 36 weeks p.p. (10.0% versus 9.1%, 9.3%, 10.4% and 9.4%, respectively). Both the point prevalence and concentration of TPOAb decreased during gestation. The proportion of women with concentrations of TPOAb ≥100 or ≥300 U/ml increased considerably in the post partum period.
Thyroid function in gestation. TD in gestation was present in 23 women (8%; 3 TPOAb+; see Table 1). Thirteen women had a decreased TSH at 12 weeks, of whom 6 also had an increased fT4; the incidence of gestational thyrotoxicosis can thus be calculated as 2.1% (6/291). TPOAb were present in one women with gestational thyrotoxicosis (and decreased TSH at 12 weeks p.p.). Gestational thyrotoxicosis was not related to the development of PPTD. Ten women had increased TSH levels, from these women 2 had marginally decreased fT4 levels.
The mean fT4 during pregnancy was comparable for TPOAb- and TPOAb+ women; the mean TSH, however, was significantly higher in TPOAb+ women (at 12 weeks: 0.79 (SEM=0.002) versus 1.10 (SEM=0.03) mU/l ($p<0.001$); at 32 weeks: 0.76 (SEM=0.002) versus 0.84 (SEM-=0.01) mU/l ($p<0.001$)).
Thyroid function in the post partum. PPTD was present in 15 women (5.2%; Table 1). When subclinical TD was also taken into account 36 women (12.4%) had TD in the post partum (12 women (6 TPOAb+) had subclinical hypothyroidism and 9 subclinical hyperthyroidism (2 TPOAb+)); from these 36 women 7 (19.4%) had also TD at 12 weeks gestation (6 subclinical hypothyroidism and 1 subclinical hyperthyroidism). From the 15 women with PPTD 9 had thyrotoxicosis without subsequent hypothyroidism (4 TPOAb+), 5 hypothyroidism alone (all TPOAb+) and 1 thyrotoxicosis followed by hypothyroidism (TPOAb+). The 10 TPOAb+ women with PPTD had all decreasing TPOAb concentrations in gestation and increasing concentrations p.p.. All women with PPTD were negative for TSH-RAb. TPOAb+ women with PPTD had more periods with signs and symptoms of hyper- and/or hypothyroidism than TPOAb- women with PPTD (13% versus 4%); two of these women were treated with L-thyroxine for several months because of symptoms of hypothyroidism. All women but one had normal TSH and fT4 at 36 weeks p.p.. Fourteen of the 15 women who had experienced PPTD were visited 2.5 to 3 years after delivery. The results of the thyroid function testing are summarized in Table 2. From the 9 TPOAb+ women 2 had a permanent hypothyroidism and were treated with L-thyroxine, 4 had increased TSH levels and 3 had a normal thyroid function. The 5 TPOAb- women, however, all had a normal thyroid function.
Prediction of PPTD. Neither age, educational level, alcohol-use during pregnancy, a family history of thyroid disease, parity, the number of pregnancy-related complications, nor gender, congenital anomalies and birthweight of the child were related to the development of PPTD. Univariate analysis revealed that PPTD was significantly related to four items: A: the presence of TPOAb: RR at 12 and 32 weeks gestation and 4 weeks p.p. were 18.1 (95%CI 6.6-49.3, $p<0.0001$), 27.6 (95%CI 11.3-67.4, $p<0.00001$) and 22.8 (95%CI 9.1-56.9, $p<0.00001$),

respectively, B: TSH concentration >2.0 mU/l at 12 weeks gestation: RR=5.4 (95%CI 1.7-16.7, p=0.02) C: previous autoimmune disease (mainly AITD): RR=4.3 (95%CI 1.1-16.7, p=0.03), and D: smoking habits ("ever smoked" (women who stopped smoking or still were smoking in gestation) versus "never smoked"): RR=3.6 (95%CI 1.2-11.0, p=0.016). Women with PPTD had smoked more cigarettes per day (46% smoked <10 cig./day, 27% 10-20 cig./day and 27% >20 cig./day versus 55%, 26% and 18% in women without PPTD; differences n.s.) and for a longer period (mean: 12.9 (SD=4.1) yrs. versus 9.8 (SD=3.8) yrs.; t-test $p<0.05$) than women without PPTD. The presence or absence of TPOAb was not related to smoking habits. Women with PPTD experienced more frequently diabetes or hypertension in pregnancy and gave less breastfeeding, but these differences were not statistically significant ($0.05<p<0.1$). In order to determine independent factors related to PPTD a multivariate analysis was performed and three were found: TPOAb (RR=27.2), bottle feeding (RR=11.1) and smoking habits ("ever smoked": RR=3.1) (Table 3).
In Figure 3 the ROC curves for TPOAb testing at 12 and 32 weeks gestation and 4 weeks p.p. are shown. These ROC curves and their AUC's were comparable. The corresponding values of sensitivity and specificity are presented in Table 4. The sensitivity of TPOAb testing alone was highest at 12 weeks gestation: all TPOAb+ women who developed PPTD had TPOAb >50 or $\geq$100 U/ml at that time point. The positive predictive value of TPOAb at each time point increased with increasing concentrations (Table 4). The positive predictive value of TPOAb >50 U/ml was highest at 32 weeks gestation: the presence of TPOAb at that time point indicated a great probability of developing PPTD. The positive predictive values of higher TPOAb concentrations were similar for the different time points (Table 4). Combination of the results of TPOAb testing with the other independent riskfactors (smoking habits and bottle feeding) increased the positive predictive value slightly (Table 4).

Discussion

Our study population consisted of a sample of pregnant women residing in the southeastern part of the Netherlands. Sampling bias is unlikely as at least 90% of the women in the region are attended by the local midwifes or the obstetrical department of the St Joseph Hospital Veldhoven; moreover mean age and parity of the non-participating women were comparable to those of the participants.
Low TSH concentrations in the first trimester and gestational thyrotoxicosis are thought to be the result of a TSH-like effect of human chorionic gonadotropin (hCG) (11,16-19). In this study decreased TSH in early pregnancy was present in 4.5% and gestational thyrotoxicosis in 2.1%. Glinoer et al. found in a region with restricted iodine intake undetectable TSH in 13% and increased fT4 in 3% in the first trimester of pregnancy and in a later study a prevalence for gestational thyrotoxicosis of 2.4% (11,18). The decline of fT4 during pregnancy and return to baseline levels p.p. has been described previously (Figure 1) (11,17,18,20). The mechanism that causes the decline of fT4 without a concomitant rise of TSH during pregnancy is still unknown (11,17).
The prevalence and course of TPOAb concentration and the incidence of PPTD were in accordance with the results of other studies (3,5,6,21,22).
Although fT4 concentrations in gestation in TPOAb+ women were similar to those of TPOAb- women TSH concentrations were slightly but significantly higher in TPOAb+ women. This is in accordance with the findings of Glinoer et al. who reported that TPOAb+ women are at risk

for developing (subclinical) hypothyroidism during pregnancy because of their reduced functional capacity of the thyroid (10,11).

Our study confirmed that TPOAb are the most prominent risk factor for PPTD (4,5,6,8,9,12,21,22,23,24). RR were 18, 28 and 23 at 12 and 32 weeks gestation and 4 weeks p.p., respectively; this was in accordance with a previous study from the same region (5); Gerstein, however, calculated a RR=87, probably due to the use of less sensitive MsAb tests in the 70's and 80's (when TPO≥100 U/ml is taken as cut off point the RR increases to 18, 45 and 31 at 12 and 32 weeks gestation and 4 weeks p.p., respectively) (3).

Women who ever had smoked had an increased risk for developing PPTD (RR=3.1). Fung et al. found also smoking related to PPTD (24); others, however, did not find smoking related to PPTD or autoimmune hypothyroidism (21,25). Arguments in favour of this relation are: the possible dose-response effect that we found, the noxious effect of diverse components of tabacco on the thyroid and the effect of smoking on the immune system (26,27).

This is the first study describing breastfeeding as an independent protecting factor: women not giving breastfeeding had a RR=11.1 for developing PPTD. In the studies from Jansson et al. and Fung et al. PPTD was not related to lactation (21,25). The protective effect can not be explained by the prolonged high prolactin levels during breast feeding: hyperprolactinemia has both immunosuppresive and immunostimulative effects and is associated with the presence of thyroid antibodies (28). Possible explanations are: some other still unknown immunomodulating factors associated with pregnancy which remain operative during lactation or selection (women prone to PPTD would not start breastfeeding).

Anamnestic factors independently related to PPTD (smoking habits, bottle-feeding) had limited additional value for predicting PPTD. The positive predictive value increased slightly, but the sensitivity decreased, which resulted in the identification of a small group of women at risk for developing PPTD with more accuracy, but a large number of cases would be missed (Table 4).

One-third of the women developing PPTD had no TPOAb. All these women experienced only a phase of hyperthyroidism p.p. with slight or no complaints. PPTD characterized by hyperthyroidism alone in the absence of both MsAb and TSAb has been previously described (24,29). The authors supposed that this form of PPTD was not the result of an exacerbation of AITD but had a different etiology, although in some cases thyroiditis was found in fine needle aspiration biopsy (29). The proportion of women with this form of (non-autoimmune) PPTD can be estimated as 10-30% of all PPTD cases (3,5,24). The 10 TPOAb+ women who developed PPTD, in contrast, had more complaints (such as lack of energy and depression) and two needed transient thyroxine replacement therapy. This form of PPTD is the "classical" form presenting with hyperthyroidism followed by hypothyroidism and caused by an exacerbation of a preexisting AITD. These women with high TSH levels in combination with TPOAb appear really at risk for developing permanent hypothyroidism (Table 2) (30,31,32).

We suppose that especially PPTD in TPOAb+ women (the "classical form" with the "classical pattern" of TPOAb decreasing in gestation and increasing p.p.) is of clinical interest. Identification of these women with great accuracy is important when an intervention (e.g. treatment with thyroxine) to prevent PPTD is considered, but also because of the considerable risk to develop permanent hypothyrodisim (30,31). Therefore we calculated the positive predictive values and sensitivity and specificity for TPOAb concentrations ≥100 and ≥300 U/ml respectively for TPOAb+ women at different time points. The positive predictive values

remained unchanged and sensitivity increased: the chance of developing PPTD did not alter but TPOAb+ women at risk were detected more accurately.
The most appropriate moment for screening for TPOAb is in the first trimester of pregnancy if a test with the highest sensitivity is required; on the other hand, if a test with high predicitive value is wanted testing should be performed in the third trimester or 1 month p.p.: when a woman is positive for TPOAb at that time point she has a great chance of developing the autoimmune form of PPTD (see Table 4).
In conclusion, the results of this study indicate that combination of TPOAb testing with independent determinants like smoking habits and bottlefeeding has limited additional value for predicting PPTD. There appeared to be two forms of PPTD: an autoimmune form in twothirds of cases and a non-autoimmune form. An intervention with thyroxine to prevent symptoms of PPTD and long-term follow up for detecting permanent hypothyroidism should be considered only in women with the autoimmune form of PPTD. Further research to evaluate the effects of treatment with thyroxine, and to study the etiology and long-term effects of the non-autoimmune form is needed.

Acknowledgements. This study was supported by grants from the Dutch Praeventiefonds (no: 002822380) and the Dr de Grood Foundation. We thank Marco van de Paal for preparing the figures, and Kodak Clinical Diagnostics Ltd., Amersham, Uk, for the TSH and fT4 kits and Diagnostic Products Co. Nederland bv. for the TPOAb kits.

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Table 1. Thyroid dysfunction (TD; subclinical: TSH abnormal; overt: TSH and fT4 abnormal) in gestation or in the post partum in relation to the presence of thyroid peroxidase antibodies (TPO-Ab) in gestation and/or in the post partum.

	no TPO-Ab (≤50 U/ml)	TPO-Ab (>50 U/ml)	total (%)
no TD	212	20	232 (80%)
TD in gestation:			
- subclinical	14	1	15 (5%)
- overt	6	2	8 (3%)
TD in the post partum:			
- subclinical	13	8	21 (7%)
- overt	5	10	15 (5%)
total (%)	250 (86%)	41(14%)	291(100%)

Table 2. The results of 2.5-3 years follow-up in 14 women who had experienced post partum thyroid dysfunction. (TPOAb+: positive for TPOAb when PPTD occurred; TPOAb-: negative for TPOAb).

	TPOAb+ n = 9	TPOAb- n = 5
thyroid function testing: - fT4 (pmol/l) - TSH (mU/l) -TPOAb+ (>50 U/ml)	mean (range) 17 (14-21)* 3.2 (0.9-5.4)* 9	mean (range) 19 (14-22) 1.0 (0.2-1.8) 0
thyroid (dys-)function: - hypothyroidism - subclinical hypothyroidism - normal - hyperthyroidism	 2 4 3 0	 0 0 5 0

TPOAb+: TPOAb present at follow up.
*: 2 women on L-thyroxine treatment were excluded.

Table 3. Results of the multivariate regression analysis to determine independent factors related with post partum thyroid dysfunction. Introduced in the model were factors with $p \leq 0.1$ in the univariate analysis.

	RR (95%CI)
smoking habits (ever vs. never)	3.1 (1.2-7.5)*
previous auto immune disease	2.0 (0.1-37.7)
family history thyroid disease	1.4 (0.3-6.7)
parity >1	2.3 (0.4-13.6)
pregnancy complications:	
- diabetes	5.9 (0.5-66.1)
- hypertension/toxicosis	3.7 (0.4-37.8)
bottle feeding	11.1 (1.4-75.1)*
TPO-Ab>50 U/ml at 12 weeks gestation	27.2 (6.4-115.6)**

RR (95%CI): relative risk (95% confidence interval)
*: p=0.04
**: p<0.0001

Table 4. Positive and negative predictive value, sensitivity and specificity of TPO-antibody testing at different time points and concentrations separate and in combination with independent anamnestic risk factors for developing post partum thyroid dysfunction.

	npv[1]	ppv[2]	sens.	spec.
TPO-antibodies:				
- TPO>50 12 weeks gestation	0.98	0.31	0.67	0.93
- TPO≥100 12 weeks gestation	0.98	0.50	0.67	0.97
- TPO≥300 12 weeks gestation	0.97	0.75	0.40	0.99
- TPO>50 32 weeks gestation	0.97	0.64	0.64	0.97
- TPO≥100 32 weeks gestation	0.99	0.71	0.33	0.99
- TPO≥300 32 weeks gestation	0.95	0.67	0.13	0.996
- TPO>50 4 weeks post partum	0.97	0.44	0.53	0.96
- TPO≥100 4 weeks post partum	0.96	0.63	0.33	0.99
- TPO≥300 4 weeks post partum	0.96	0.75	0.20	0.996
TPO>50 12 wks gest.+smoking	0.97	0.50	0.47	0.97
TPO>50 4 wks p.p.+smoking	0.97	0.67	0.40	0.99
TPO>50 12 wks gest.+bottle-feeding	0.97	0.38	0.53	0.95
TPO>50 4 wks p.p.+bottle-feeding	0.97	0.47	0.47	0.97

[1]: negative predictive value;
[2]: positive predictive value.

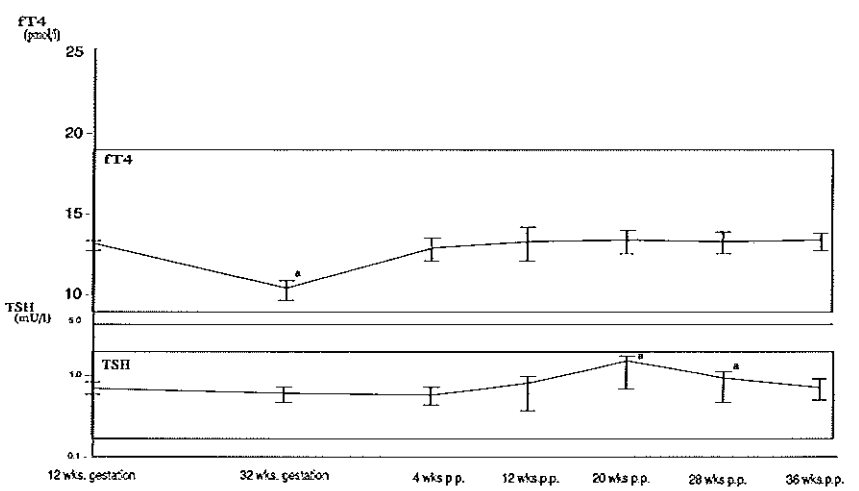

Figure 1. Results of serial fT4 and TSH testing in 291 women. Represented are mean ±standard error of the mean (SEM). Reference limits are 0.15-2.0 mU/l for TSH and 8.7-19.6 pmol/l for fT4 (shaded areas). [a]: $p<0.05$ versus 12 weeks gestation.

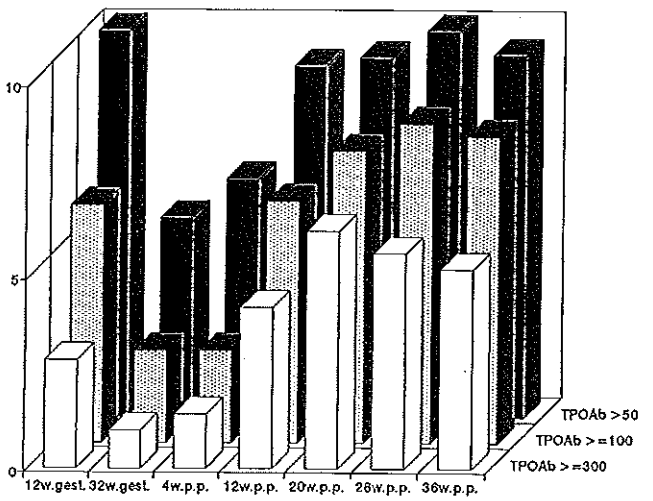

Figure 2. Point prevalences (%) of thyroid peroxidase antibodies (TPOAb) for 3 different concentrations at 7 different time points. Point prevalence was calculated as: the number of TPOAb positive women/ total number of women X 100% for each time point separatedly. (n=291).

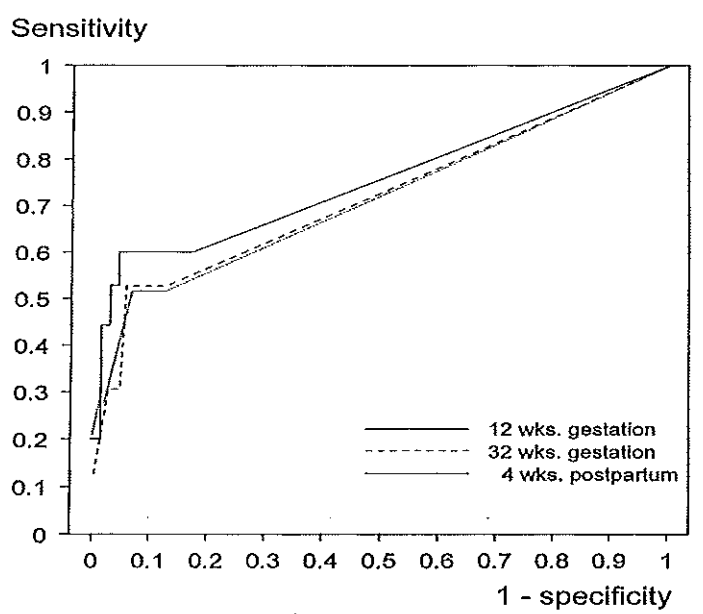

Figure 3. Receiver operating characteristic (ROC) curves for serum concentrations >50 U/ml of thyroid peroxidase antibodies (TPOAb) measured at 12 and 32 weeks gestation and 4 weeks post partum, respectively (n=291).

Chapter 2.2.

Cell mediated immunity and post partum thyroid dysfunction: a possibility for the prediction of disease?

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J Clin Endocrinol Metab 1998; 83: 1959-66.

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Abstract

Post partum (p.p.) thyroid dysfunction (PPTD) is thought to be due to an autoimmune destruction of thyroid follicles during the p.p. period. The chronic thyroid autoimmune (AI) process - already present in pregnancy as shown by the positivity for TPO-antibodies (TPO-Ab) - becomes overt disease in the p.p. period, and one assumes that this exacerbation represents a rebound phenomenon following a general immunosuppression during pregnancy. The presence of TPO-Ab in pregnancy has been suggested as a predictor for later PPTD development. Apart from B cells, e.g. production of autoantibodies, various functions of the cell mediated immune (CMI) system, including those of peripheral T cells, monocytes and dendritic cells (DC) are also disturbed in autoimmune states.

The objectives of the present study were determining alterations in various CMI parameters in pregnancies followed by PPTD versus those not followed by PPTD, and determining the usefulness of these parameters in the prediction of PPTD.

In a prospective study (region Kempenland, southeast Netherlands) a random sample of 291 women was tested at 12 and 32 weeks gestation and 4 weeks p.p. for TPO-Ab. Women were followed till 9 months p.p. for developing PPTD. PPTD was defined as both an abnormal TSH and fT4 p.p.. Women developing PPTD and/or positive for TPO-Ab (n=26) and "thyroidological uneventfull" control women of the same cohort matched for age and parity (n=21) were tested for thyroid stimulating antibodies (TSAb), percentages of peripheral blood lymphocyte subsets using FACS analysis (CD3, CD4, CD8, CD16, CD56, MHC-class II), for monocyte polarization and for cluster capability of monocyte-derived dendritic cells (DC).

Results were: a) 31 women (10.7%) were positive for TPO-Ab (TPO-Ab$^+$) in gestation (12 and/or 32 weeks); b) 15 women (5.2%) developed PPTD, of whom 10 were TPO-Ab$^+$ in gestation; c) pregnancy related CMI alterations consisted of low percentages of CD16$^+$CD56$^+$ NK cells and a low DC clustercapability at 12 weeks gestation. These functions were normalized at 32 weeks gestation; d) the TPO-Ab$^+$ PPTD$^+$ women (4 hyper, 5 hypo and 1 hyper/hypo) were characterized by a persistently low percentage of NK cells, a lowered monocyte polarization and a raised percentage of MHC-class II$^+$CD3$^+$ T cells; e) the TPO-Ab$^-$ PPTD$^+$ women (all 5 hyper) had neither TSAb, nor CMI alterations apart from those normally seen in pregnancy; f) 21 women were positive for TPO-Ab in pregnancy, but did not develop PPTD; they had the same lowered NK cell percentages and monocyte polarization as the TPO-Ab$^+$ PPTD$^+$ cases, but they had normal percentages of activated peripheral T cells and a lower titre of TPO-Ab; g) determination of the number of NK cells and monocyte polarization hardly contributed to the prediction of PPTD (as compared to TPO-Ab status) due to strong interindividual variation and close association with the presence of TPO-Ab; h) combining TPO-Ab assays with testing for activated T cells was the most optimal parameter for the prediction of TPO-Ab$^+$ cases of PPTD in our small testset.

We conclude that TPO-Ab$^+$ pregnant women who develop PPTD show several CMI abnormalities other than those seen in normal pregnant women, such as persistently lower percentage of NK cells, a lowered monocyte polarization and a raised percentage of activated T cells. The latter seems rather specific for the actual PPTD development and is not found in TPO-Ab$^+$ but PPTD uncomplicated pregnancies. TPO-Ab$^-$, but PPTD$^+$ women had no signs of CMI abnormalities (apart from those specific for the pregnancy state). Although numbers of studied cases are low our data are hence suggestive for the existence of two forms of PPTD: a TPO-Ab$^+$ ("autoimmune") form (2/3 of patients, classical PPTD pattern) and a TPO-Ab$^-$ ("non-

autoimmune") form (1/3 of patients, only hyper). Such assumption implies that at best 2/3 of PPTD cases can be predicted using either humoral and/or cellular immune tests.

Introduction

The syndrome of post partum thyroid dysfunction (PPTD) is characterized by periods of hyperthyroidism and/or hypothyroidism in the first post partum (p.p.) year; the hyperthyroidism is usually very mild, the hypothyroidism, however, is attended with symptoms such as lack of energy and depression (1-3). The incidence of PPTD ranges from 4-8% (4-6).
PPTD is considered to be part of the spectrum of autoimmune thyroid diseases (AITD) and caused by an autoimmune destructive lymphocytic thyroiditis (3,6,7). Basic to autoreactive processes are immunodysregulations such as defective tolerance mechanisms and an enhanced autoagression towards target antigens. As signs of such immunodysregulations various humoral and cell mediated immune (CMI) abnormalities have been reported in thyroid and other endocrine autoimmune patients: autoantibodies (in the case of lymphocytic thyroiditis thyroid peroxidase antibodies, TPO-Ab) are present in serum, and there is often a rise in the number of activated (MHC-class II^+) peripheral T cells, a lowering of the number of peripheral natural killer (NK) cells, a lowered monocyte polarization and an impaired T cell cluster capability of monocyte-derived dendritic cells (DC) (8,9).
The presence of TPO-Ab has been reported as the most prominent riskfactor for developing PPTD: about 70% of women developing PPTD are positive for TPO-Ab ($TPO\text{-}Ab^+$) during pregnancy or p.p. as compared to around 10% in the normal female population (4-6). The positive predictive value of TPO-Ab positivity, however, is about 40-60%: only one out of two $TPO\text{-}Ab^+$ women develops PPTD (4,5). Therefore TPO-Ab testing alone is not a sufficiently reliable method for identifying women at risk for PPTD.
The objectives of the study reported here are to determine possible alterations in the number of subsets of T cells, activated T cells and NK cells in the peripheral blood, and the capability of monocytes to polarize and of monocyte-derived DC to form cellular clusters in pregnancies followed by PPTD versus those pregnancies not followed by PPTD. In addition the possible usefulness of these alterations for the prediction of PPTD was studied. We therefore performed a prospective study of a sample of women who were followed during pregnancy and in the first p.p. year. Serial testing of thyroid function, serum TPO-Abs and the mentioned CMI functions was carried out.

Subjects and Methods

Subjects

Permission for the study was obtained from the Medical Ethics Committee of the Academic Medical Centre, University of Amsterdam.
Between january 1994 and april 1996 a prospective study on thyroid dysfunction (TD) in gestation and in the p.p. was performed. 448 consecutive women at their first visit to the local midwife or the obstetrical department of the St Joseph Hospital Veldhoven were invited to participate. Informed consent was obtained from 310 women (69%; none on thyroid drugs at entry); 291 women completed the study and 19 (2 $TPO\text{-}Ab^+$ (10.5%)) were withdrawn from analysis. All women with TPO-Ab in gestation ($TPO\text{-}Ab^+$) (irrespective of developing PPTD), all women with PPTD ($PPTD^+$) also those negative for TPO-Ab ($TPO\text{-}Ab^-$) were introduced

in the study together with for age and parity matched controls (TPO-Ab$^-$, PPTD$^-$).
All women were visited at home at 12 and 32 weeks gestation, and in the p.p. period at regular intervals (starting 4 weeks p.p. every 8 weeks until 36 weeks). Signs and symptoms of hyper- or hypothyroidism (3) were recorded at every visit; depression was assessed at every visit using the Research Diagnostic Criteria (RDC) (10).
Venous blood samples were collected into Vacutainer tubes: every visit 8 ml for thyroid function and TPO-Ab testing, and at 12 and 32 weeks gestation and 4 weeks p.p. 40-50 ml heparinized blood for peripheral blood mononuclear cell separation.

Methods

Thyroid function tests. The thyroid function was assessed by measuring the concentration of thyroid stimulating hormone (TSH; reference interval 0.15-2.0 mU/l, defined for non-pregnant women aged 20-40 years originating from the same region; Kodak Amerlite TSH-30, Kodak Clinical Diagnostics Ltd., Amersham, UK), and by measuring the free thyroxine concentration (fT4; reference interval 8.7-19.6 pmol/l; Kodak Amerlite MAB FT4 Assay). PPTD was defined as an abnormal TSH in combination with an abnormal fT4 in the p.p. period.
TPO-Ab were measured using the Immunometric Enzyme Combikit (Orgentec GMBH, Mainz, Germany); a concentration >50 U/ml was defined "positive" (TPO-Ab$^+$).
Thyroid stimulating antibodies (TSAb) were measured using the TRAK-Assay (Brahms Diagnostica GMBH, Berlin, Germany); reference values are: <9 U/l antibody negative, 9-14 U/l borderline, ≥15 U/l positive.
Peripheral mononuclear cell separation. Peripheral blood mononuclear cell separation was performed at the Clinical Laboratories of the St Joseph Hospital Veldhoven, using Ficoll Paque density gradient centrifugation (density 1.077 g/ml; Pharmacia, Uppsala, Sweden). The cells were washed twice in phosphate buffered saline (PBS). Aliquots of 40-80 x 10^6 cells were stored in a solution of 20% DMSO (Dimethylsulphoxide) in RPMI 1640 supplemented with 10% fetal calf serum (Gibco, Breda, The Netherlands). The actual immunological tests were performed at the Department of Immunology, Erasmus University Rotterdam.
Monocyte polarization assay for peripheral blood monocytes. This assay has proven to reflect the responsiveness of blood monocytes to chemoattractants and is a measure of preactivated monocytes in the peripheral blood; it is disturbed in endocrine autoimmune diseases (11,12). Monocytes were isolated from separated and deepfrozen lymphoid cells. An enrichment for the monocytes in the Ficoll-Isopaque isolated fraction was obtained by Percoll gradient centrifugation (13): after washing, the Ficoll-isolated pellet containing both monocytes and lymphocytes was resuspended in RPMI 1640 10% FCS and carefully layered on top of an equal volume of Percoll 1.063 (Pharmacia, Diagnostics AC, Uppsala, Sweden). After centrifugation (40 min, 450 g) the cells were collected from the interface, washed twice in medium (10 min, 500 g) and counted: the suspension now contained 70-95% monocyte-specific esterase positive cells. This suspension was directly used for the monocyte polarization assay or for the maturation of monocytes to obtain DC.
For monocyte polarization aliquots (0.2 ml) of the Percoll purified cell suspension containing 200.000 monocytes were added to 12*75 mm polypropylene tubes (Falcon Labware Division of Becton Dickinson, Oxford, CA, USA) containing 0.05 ml of either medium or N-formyl-methionyl-leucyl-phenylalanine (fMLP) in medium, to reach a final concentration of 10 nm.

The tubes were incubated at 37°C in a waterbath for 15 min. The incubation was stopped by addition of 0.25 ml ice-cold 10% Formaldehyde in 0.05% PBS (pH 7.2). The cell suspensions were kept at 4°C until counting in a hemocytometer using an ordinary light microscope (magnification 250X). The test was read blindly by two persons; 200 cells were counted, manually, from each tube. A cell was "polarized" if any of the following occurred: elongated or triangular shape, broadened lamellopodia, and/or membrane ruffling. The responsiveness of a monocyte population was expressed as the percentage of polarized monocytes in the presence of fMLP minus the percentage of polarized monocytes in the absence of fMLP. The percentage of polarized monocytes was calculated as follows:

(% cells polarized / % monocyte-specific esterase positive cells) x 100%

Of the 77 healthy control individuals tested during the last two years a mean of 30% polarized monocytes was found (SD 8%; range 18-70%). There were no differences between females and males: females, a mean of 33% (SD 9%; n=36); males, a mean of 32% (SD 13%; n=41). Nor were differences found between individuals <50 years and >50 years of age: respectively, a mean of 34% (SD 11; n=66), and a mean of 31% (SD 5%; n=11). The interassay variation never exceeded 17% (n=13), the intra-assay variation never exceeded 15% (n=77). On the basis of these outcomes fMLP induced polarization values of less than 20% polarized monocytes are considered to be abnormal.

The maturation of dendritic cells from blood monocytes, clustering of dendritic cells. DC were prepared from peripheral blood monocytes according the method described by Mooy et al (14). Cells from the Percoll-isolated monocytic fractions were exposed to T3 in suspension culture for 30 minutes. Thereafter, the cells were washed (culture fluid was added slowly to prevent osmotic lysis of the cells), and further cultured under non-adhering conditions for 16 hours in polypropylene tubes (5% CO2 and 37°C, 100% humidity). This procedure yields 40-60% cells with a dendritic morphology, showing class-II MHC positivity, a decreased expression of the monocytic CD14 determinant, a decreased phagocytic capability, but an enhanced stimulator capability in the MLR. The full technical details of this method are given in Mooy et al (14). Fifty thousand DC prepared from peripheral blood monocytes exposed to T3 were allowed to cluster with 5.000 allogenic lymphocytes isolated from healthy controls (4 hours, 37°C 5% CO2) in 250 microliter flat-bottomed wells. The lymphocytic isolation was performed according to standard procedures with Ficoll-Isopaque and Nylon wool adherence (Leuko-Pak, Fenwall Laboratories, IL, USA). Formed cellular clusters were counted using an inverted microscope and values were expressed as the number of clusters per 6 microscopic fields (X250). A cluster was defined as an accumulation of 4-25 cells. Of the 25 healthy control individuals tested during the last two years a mean of 187 clusters was found (S.D. 54, range 150-230). On the basis of these outcomes values of less than 150 clusters are considered as abnormal.

FACS analysis. Peripheral blood mononuclear cell subsets were analized using a FACScan flow cytometer (Becton Dickinson). The technique has been described in detail elsewhere (15). Mononuclear cells were incubated with monoclonal antibodies for detection of surface markers. The monoclonal antibodies were conjugated with fluorescein isothiocynate (FITC) or phycoerythrin (PE) for double marker analysis. The following markers were used: the B cell markers CD19 (Leu-12 PE, Becton Dickinson, San Jose, CA, USA) and CD20 (B1 FITC,

Coulter Clone, Hialeah, FL, USA), the T cell markers CD3 (Leu-4, FITC, Becton Dickinson), CD4 (Leu-3 PE, Becton Dickinson) and CD8 (Leu-2 PE, Becton Dickinson), the T and B cell marker CD5 (Leu-1 FITC, Becton Dickinson), the HLA-DR marker (L243 PE, Becton Dickinson), the NK cell markers CD56 (Leu-19 PE, Becton Dickinson) and CD16 (Leu-11c PE, Becton Dickinson), and the monocyte marker CD14 (MY4 PE, Coulter Clone). Percentages of the total mononuclear cells were calculated. Reference values were obtained from 14 concommitantly tested non-pregnant TPO-Ab$^-$ women 20-40 years: CD19$^+$ CD20$^+$ B cells 10.9% (SD=5.6), CD4$^+$ CD3$^+$ T helper cells 40.4% (SD=5.8), CD8$^+$ CD3$^+$ T suppressor/cytotoxic cells 23.4% (SD=6.9), activated (HLA-DR$^+$/CD3$^+$) T cells 6.4% (SD=3.1) and CD16$^+$ CD56$^+$ NK cells 7.9% (SD=1.8).

Statistical analysis. For statistical testing the Chi-square test and Student's t-test were performed. $P<0.05$ was considered significant.

Results

From the 291 women completing the prospective study 31 (10.7%) were TPO-Ab$^+$ at 12 and/or 32 weeks gestation (Table 1). In total fifteen women (5.2%) developed PPTD; of these 10 were TPO-Ab$^+$ and 5 TPO-Ab$^-$. From the remaining 276 women 21 were TPO-Ab$^+$ and 255 TPO-Ab$^-$; the latter were considered as thyroidological uneventfull pregnancies. CMI testing was carried out for 47 selected women: 21 blindly selected TPO-Ab$^-$ and PPTD$^-$ women (thyroidological uneventfull pregnancies = controls), the 5 TPO-Ab$^-$ but PPTD$^+$ women, the 21 TPO-Ab$^+$ but PPTD$^-$ women and the 10 TPO-Ab$^+$PPTD$^+$ women. None of these 47 women was positive for TSAb. No differences between the groups were found concerning educational level, family history for thyroid disease, alcohol use during pregnancy, pregnancy complications and gender and birthweight of the child.

Pregnancy related CMI alterations. In all groups (irrespective of thyroid status) alterations were found during pregnancy in the percentage of peripheral CD16$^+$ CD56$^+$ NK cells and in the DC cluster capability (Figure 1). The DC cluster capability was decreased at 12 weeks gestation and returned to normal in all groups within 32 weeks (Figure 1). Percentages CD16$^+$ CD56$^+$ NK cells were significantly decreased at 12 weeks gestation; in TPO-Ab$^-$ women a gradual return to normal levels occurred (Figure 1), in TPO-Ab$^+$ women (irrespective of PPTD development), however, percentages NK cells remained low (Figure 1). The percentages CD19$^+$ CD20$^+$ B cells and the number of CD3$^+$, CD4$^+$ and/or CD8$^+$ T cells were within the reference limits for all tested groups at all three time points.

PPTD related CMI alterations. In the women who later developed PPTD two different patterns of CMI alterations were found that correlated with the presence or absence of TPO-Ab:

- in TPO-Ab$^-$ PPTD$^+$ women no CMI alterations were found with the exception for those related with the pregnancy state (see Figure 1);
- in all TPO-Ab$^+$ women persistent decreases were found in NK cell numbers and the monocyte polarization assay regardless the development of PPTD (Figure 1). The percentages NK cells remained significantly decreased in TPO-Ab$^+$ women as compared to non-pregnant healthy women (but not in comparison to the healthy pregnant (= TPO-Ab$^-$ PPTD$^-$) women). The monocyte polarization also remained lower in TPO-Ab$^+$ women and significant in comparison to both healthy pregnant and non-pregnant women. The percentage of activated (MHC-class II$^+$ CD3$^+$) T cells was in general not raised in TPO-Ab$^+$ women. However, in TPO-Ab$^+$PPTD$^+$

women percentages were significantly higher at all time points studied as compared to PPTD$^-$ TPO-Ab$^+$ women (Figures 1 and 2).
Two forms of PPTD could hence be identified on the basis of immune abnormalities: a form of PPTD lacking any sign of both humoral and cellular immune alterations (n=5) and a form of TPO-Ab$^+$ PPTD with also cellular immune alterations (n=10).
The 5 PPTD$^+$ women without humoral and cellular immune alterations all had a period with hyperthyroidism at different time points p.p., but no signs of hypothyroidism while symptoms were relatively mild. None of these women had indications for an ingestion of excess iodine or thyroxine; one woman had a (probably viral) infection preceding the hyperthyroidism.
From the 10 TPO-Ab$^+$ CMI abnormality$^+$ PPTD$^+$ women 4 had only hyperthyroidism, 5 only hypothyroidism, and 1 had hyperthyroidism followed by hypothyroidism. Women in this group had a significantly higher frequency of TSH >2.0 mU/l at 12 weeks gestation as compared to the TPO-Ab$^-$ PPTD cases (30% versus 0%). They also had more signs and symptoms. Although numbers of cases are low, data are nevertheless given as an illustration. The number of signs and symptoms of hyperthyroidism reported during the consecutive p.p. home visits was comparable within the TPO-Ab$^+$ and the TPO-Ab$^-$ PPTD group: weight loss in 13% versus 16%, increased sweating in 18% versus 24%, heat intolerance in 3% versus 20%, nervousness in 5% versus 4%, palpitations in 5% versus 0% and increased appetite in 3% versus 4% respectively. The number of signs and symptoms characteristic of hypothyroidism, however, was higher in the TPO-Ab$^+$ PPTD cases vs the TPO-Ab$^-$ PPTD cases: lassitude/ fatigue 26% versus 8%, cold intolerance 16% versus 4%, hoarseness 13% versus 0%, dry/ fragile hair 13% versus 0%, paresthesia 11% versus 0%, and lethargy 11% versus 0%. Depression was diagnozed in 17% of home visits in TPO-Ab$^+$ and in 12% in TPO-Ab$^-$ PPTD cases, respectively. Two of the TPO-Ab$^+$ PPTD cases were treated for several months with l-thyroxine because of the indicated symptoms of hypothyroidism.
In our study group of 291 women, 12 women (6 TPO-Ab$^+$) had one or more post-partum periods with elevated TSH only in the absence of fT4 abnormalities (i.e. not cases of PPTD in our definition - see materials and methods). None of these women did experience more complaints of either hyper- or hypothyroidism as compared to the healthy control post-partum women.
Prediction. With regard to our second objective we determined the usefulness of the various CMI parameters in predicting PPTD in general, i.e. both the TPO-Ab$^+$ plus the TPO-Ab$^-$ cases. Table 2 shows that the predictive values of monocyte polarization, activated T cells or NK cells are low at 12 weeks gestation, and actually not much higher as compared to the TPO-Ab status. CMI values at 32 weeks gestation or 4 weeks pp were also not better in predicting PPTD. The combination of TPO-Ab status and abnormalities in the monocyte polarization assay, the number of activated T cells or NK cells at 12 weeks gestation slightly increased the positive predictive value but sensitivity decreased in comparison to TPO-Ab status alone (Table 2).
Because the number of activated T cells apparently is an independent predictor of PPTD within the group of TPO-Ab$^+$ women (fig. 1 and 2) we assessed the predictive power of the test "activated T cells" within the group of TPO-Ab$^+$ women for the development of PPTD. Table 3 shows that with such approach we were able to reach a sensitivity of around 70% - although admittedly numbers are limited -: 71% of the women with TPO-Ab 50 U/ml plus mean activated T cells > 10% in follow-up (i.e. 12 and 32 weeks gestation and 4 weeks p.p.,

see also fig. 2) went on to develop TPO-Ab$^+$ PPTD. However 5/10 TPO-Ab$^+$ PPTD cases would have been missed in such approach; whereas 2/7 of the TPO-Ab$^+$ women with mean raised activated T cells would have been falsely predicted to develop TPO-Ab$^+$ PPTD.

Discussion

Our study is suggestive for the concept that there might exist two forms of PPTD: a TPO-Ab$^+$ ("autoimmune") and a TPO-Ab$^-$ ("non-autoimmune") form. The TPO-Ab$^+$ PPTD was immunologically characterized by the presence of CMI disturbances normally related to endocrine autoimmune diseases and clinically by periods of hyper- and/or hypothyroidism. The TPO-Ab$^-$ form lacked cellular immune abnormalities and was characterized by hyperthyroidism in conjunction with mild symptoms. However numbers of identified cases are small in our study and further larger studies to confirm a dichotomy in PPTD are clearly needed.

We consider it unlikely that the TPO-Ab$^-$ PPTD cases suffered from Graves' disease; arguments are that all were TSAb negative and that Graves' disease patients do show CMI abnormalities (11). In fact the etiology of our TPO-Ab$^-$ PPTD is obscure, it is possible that one case was the result of a subacute thyroiditis following viral infection (16). In previous studies comparable proportions of TPO-Ab$^-$ cases of PPTD were found. Pop et al. described in an earlier study from our region that 28% of PPTD cases were negative for MsAb in the third trimester of pregnancy and p.p. (all hyper) (5). Gerstein found in his review of studies on the incidence of PPTD also a group of cases with hyperthyroidism negative for MsAb and also came to the conclusion that these cases could not be considered as Graves' disease cases (4).

Adaptation of the immune system of the mother is required for acceptation of the fetus and maintaining pregnancy because the fetus expresses next to maternal also paternal HLA-molecules. Despite extensive research the precise mechanisms of the immune tolerance for the fetus remains unclear (17). Both local placental and systemic alterations in the immune system are responsible (17). In the very early pregnancy an accumulation of NK cells (with distinctive phenotype: CD56$^+$CD16$^-$ CD3$^-$) and of macrophages/dendritic cells occurs in the decidua; these cells are supposed to play a role in the acceptation of the early pregnancy and in the regulation of the local immune responses (17-21). It is well established that these local immune adaptations are associated with various alterations in the number and activity of peripheral leucocytes, amongst which a decreased number and activity of NK cells (17,22). In our study we confirmed that the percentages of blood NK cells were lowered during early pregnancy. Our study is special in that it is the first study describing a diminished function of the monocyte-derived DC in the first trimester of human pregnancy. Morphological changes indicating alterations in the function of skin-localized DC (Langerhans cells) of pregnant guinea pigs have been described before (23).

Recent research suggests that a normal pregnancy is accompanied by a shift from predominant T helper-1 (TH1) to a predominant T helper-2 (TH2) driven immune response characterized by a decreased production of type-1 cytokines (e.g. IL-2 and gamma-IFN) and an increased production of type-2 cytokines (22,24). Because IL-2 is a stimulator of NK cells and gamma-IFN induces DC activation and MHC-class II expression this Th1 to Th2 shift might explain both the lowered numbers and activity of peripheral NK cells and the diminished peripheral DC clustering.

We found percentages of activated T cells and the CD4/CD8 ratio in normal pregnancies within reference limits. Results from other studies are conflicting in this respect: both lowered and increased numbers of activated T cells and altered CD4/CD8 ratios have been found (22,25). These differences in outcomes are probably the result of a difference in methods of identifying the lymfocyte subsets (we used the very sensitive double labelling technique, see materials and methods) (15).

Although the mechanisms of the adaptive immune alterations in pregnancy are thus far from clear it is the generally held view that the pregnancy state represents a state of relative immunosppression, and that in the p.p. period the function of the immune system is restored with a rebound phenomenon. Indeed the fall in the titre of TPO-Abs in pregnant women with a p.p. rise is suggestive for such an assumption, and TPO-Abs likely contribute to the development of PPTD (26-28). However the prime pathogenetic role of TPO-Abs in thyrocyte destruction is questionable, and Th1 cell mediated processes are nowadays considered to be the most important mechanisms of action in thyroid and other destructive endocrine autoimmune diseases. The here reported data show that TPO-Ab$^+$ women already have alterations in various CMI functions from the first trimester of pregnancy onwards, about 1 year before a possible onset of clinical symptoms. These alterations included a lowered fMLP-induced monocyte polarization and a persistently lower number of NK cells. We assume that the lowered monocyte polarization and the lowered NK cell numbers reflect a state of subclinical chronic autoimmune thyroiditis. Identicle CMI abnormalities have been found in other clinically overt autoimmune endocrine diseases (8,11,12,29). The persistently lowered number of NK cells might be a representation of an autoimmune related immunodysregulation since NK cells are not only involved in target cell lysis but also in the regulation of the immune response (30). The lowered polarization of blood monocytes towards fMLP might also represent such immunodysregulation. Polarizing capability of monocytes not only reflects the chemotactic ability, it also reflects the activation state of the peripheral monocytes and their recruitment capacity into peripheral tissues (31), both important functions in immunoregulation.
It is remarkable that we found the percentages of activated MHC-class II$^+$ T cells already increased in the first trimester of pregnancy in TPO-Ab$^+$ women who later developed PPTD. This parameter of enhanced T cell activity might indicate that effector functions of T cells are out of balance in future PPTD patients and our observations might thus be compatable with a view that Th1 cells play an important pathogenic role in thyrocyte destruction. However a pattern of suppression during pregnancy and a rebound phenomenon in the p.p. period was not evident in the number of MHC class II$^+$ T cells in the PPTD patients (neither was that seen for NK cells and monocyte polarization disturbances). It is important to note in this respect that Stagnaro-Green et al. found increased percentages of activated T cells (CD4$^+$DR$^+$) in TPO-Ab$^+$ women (including those with later PPTD) in the second trimester of pregnancy with a peak at 3 months p.p. (25). Clearly future studies should more closely investigate numbers of activated T cells in relation to PPTD complicated pregnancies.
If our assumption of two forms of PPTD holds true, then identifying women at risk for the TPO-Ab$^+$ ("autoimmune") form of PPTD is more important than identifying those with the TPO-Ab negative form because our data suggest that women with the TPO-Ab$^+$ form are prone to develop more symptomatology of hypothyroidism (lassitude, hoarseness, fragile hair, paresthesia and depression). Moreover and more importantly, the literature indicates that

they have a higher chance for permanent hypothyroidism (32,33). Also reinvestigation of the here reported TPO-Ab$^+$ PPTD$^+$ cases after 2-3 years shows that 25-30% of the cases now has a permanent hypothyroidism (to be published). Also, when prophylactic treatment with thyroxine is considered to prevent symptoms during the hypothyroid period a correct identification is essential to prevent under- and/or overtreatment. On the basis of the here reported results the most feasible strategy to identify women at risk for the TPO-Ab$^+$ form of PPTD might be a testing for TPO-Ab followed by measuring of percentages of activated T cells in TPO-Ab$^+$ women only. In fact a practical approach for implementing a screening program would be the testing of all pregnant women at 12 weeks gestation for the identification of TPO-Ab$^+$ women, since at 12 weeks all women are regularly tested for bloodgroup/Rhesus, rubella-antibodies, Hepatitis B surface antigen and syphilis in our country. Moreover at that time the prevalence and titres of TPO-Abs are the highest. Thereafter the TPO-Ab$^+$ women could be tested and followed for percentages of activated T cells which are probably high throughout pregnancy (see fig. 1 and 2). The financial costs of this strategy are limited: about 10% of women aged 20-40 years have TPO-Ab and only these women need follow up with tests for activated T cells. In the Netherlands it accounts for 18.000 women per year. Further study to evaluate a feasibility of such screening strategy and the effect of treatment on symptoms is however clearly needed.

In conclusion the results of this study are an indication for the existence of two forms of PPTD: a TPO-Ab$^+$ ("autoimmune") form (about twothird of cases) and a TPO-Ab$^-$ ("non-autoimmune") form. The first form shows the more severe symptomatology and a possible strategy for identifying women at risk for this form of PPTD would perhaps be a TPO-Ab testing in combination with a follow-up for activated T cells. Further research on larger cohorts of pregnant women to confirm our findings is however clearly needed.

Acknowledgements

We would like to acknowledge the excellent typographical assistance of Petra Assems. Tar van Os prepared the figures. The analytical staff of the St. Joseph Hospital Clinical Laboratories was very helpfull in preparing the frozen lymphoid cells. The TSH and fT4 kits were made available by Kodak Clinical Diagnostics Ltd., Amersham, U.K., and the TPO-Ab kits by Diagnostic Products Corporation Nederland B.V.

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Figure 1A

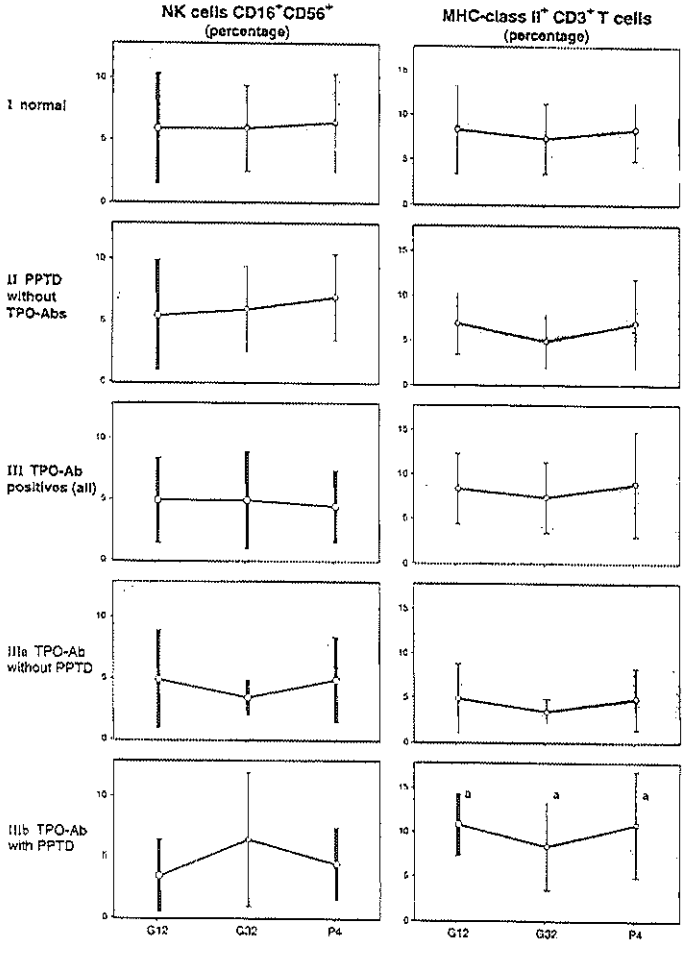

Figure 1B

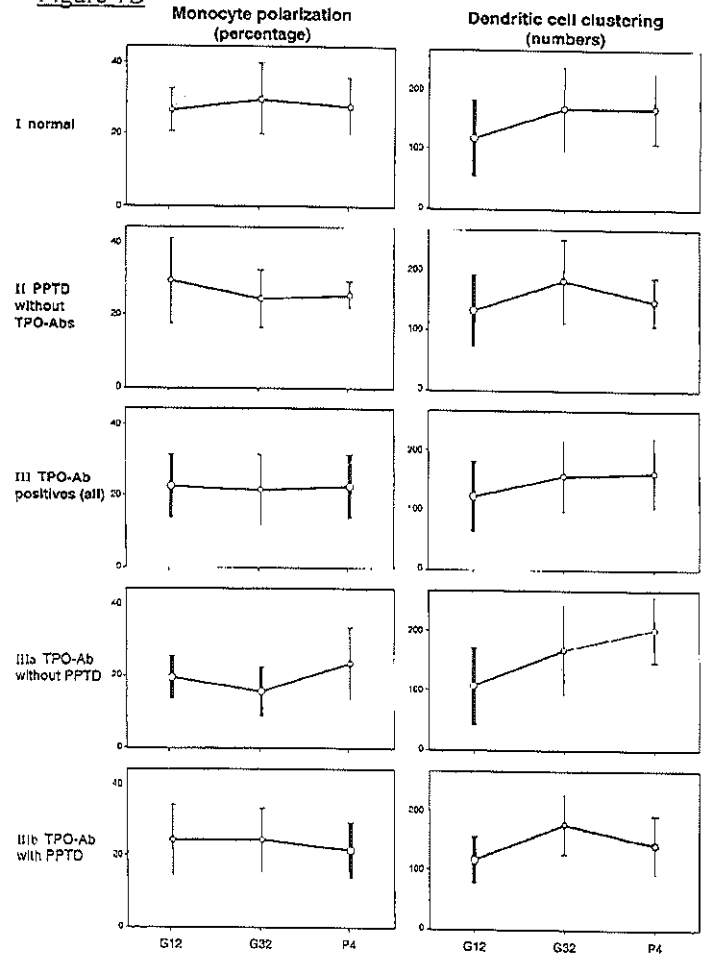

Fig. 1 The percentages of $CD16^+$ $CD56^+$ NK cells (norm: 7.9±1.8%), activated (MHC-class II^+) $CD3^+$ T cells (norm: 6.4±3.1%) (fig. 1a), the percentage of monocytes capable to polarize under the influence of the chemoattractant fMLP (norm: 30±8%) and the capability of monocyte-derived dendritic cells to form cellular clusters (norm: 187±54 clusters/6 microscopic fields) (fig. 1b) in normal ("thyroidological uneventful") pregnancies (I), in PPTD cases without TPO-Abs in gestation (II) and in pregnancies positive for TPO-Abs (III) at 12 and 32 weeks of gestation (G12 and G32). The latter group was subdivided in those women developing PPTD (IIIb) and those not developing PPTD (IIIa). Shaded areas represent values found in healthy, non-pregnant controls. Mean (°) ± standard deviations are given.
Accentuated bars represent values significantly different from those of healthy, non-pregnant controls ($p<0.05$, Student's t-test, Instat® programme) P4=4th week post partum. a = see figure 2.

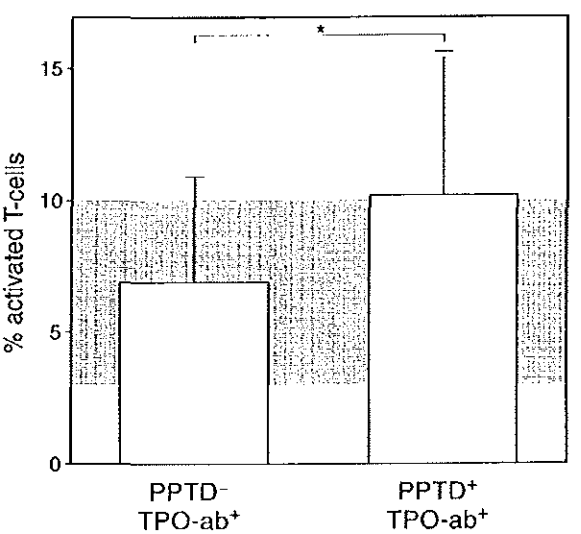

Fig. 2 Of each $TPO\text{-}Ab^+$ pregnant women at G12 the mean of the percentages of MHC-class II^+ $CD3^+$ T cells at G12, G32 and P4 was calculated and used as the value (percentage) of MHC-class II^+ $CD3^+$ T cells representative for that pregnant women (G12+G32+P4/3). The figure represents the means (± standard deviation) of these latter values in $TPO\text{-}Ab^+$ women not developing PPTD (n=16) and in $TPO\text{-}Ab^+$ women who did develop PPTD (n=10). The difference is statistical significant (Student's t-test, $p<0.05$, Instat® programme). The hatched area represents values found in non-pregnant, healthy controls.

Table 1. Study population, number (%) of women positive for TPO-antibodies in gestation (TPO-Ab$^+$) and/or developing post partum thyroid dysfunction (PPTD$^+$).

study population:	n = 310	100%
excluded:	n = 19	6.2%
in analysis:	n = 291	93.8%
- TPO-Ab$^+$, PPTD$^-$	n = 21	10.7%
- TPO-Ab$^+$, PPTD$^+$	n = 10	3.4%
	n = 15	5.2%
- TPO-Ab$^-$, PPTD$^+$	n = 5	1.7%

Table 2. Positive predictive value, sensitivity and specificity for all forms of PPTD of some CMI parameters and of TPO-Ab positivity at 12 weeks gestation. Firstly the values are given for an abnormal monocyte polarization assay, activated T cells and an abnormal percentage of NK cells in the peripheral blood alone. Secondly values are also given when combined with TPO-Ab status.

		pos-pred value	sensitivity	specificity
I.	Decreased monocyte polarization#	0.44	0.29	0.84
	Increased activated T cells^	0.46	0.43	0.77
	Decreased NK cells@	0.36	0.71	0.42
II.	Positivity for TPO-Abs irrespective CMI parameters*	0.31	0.67	0.93
	Positivity for TPO-Abs in combination with			
	decreased monocyte polarization	0.43	0.21	0.87
	increased activated T cells	0.56	0.36	0.87
	decreased NK cells	0.55	0.43	0.84

#: monocyte polarization <20% polarized monocytes;
^: activated T cells >10% MHC-class II$^+$ CD3$^+$ cells;
@: NK cells <6% CD16$^+$ CD56$^+$ cells;
*: TPO-Ab > 50

Table 3. The development of the more severe TPO-Ab$^+$ ("autoimmune") form of PPTD in the various groups of pregnant women tested for TPO-Abs and for percentages of activated circulating T cells

I.	TPO-Ab$^+$ ("autoimmune") PPTD cases developing from pregnant women who are negative for TPO-Abs[a] at 12 weeks gestation	0% (0/260)
II.	TPO-Ab$^+$ ("autoimmune") PPTD cases developing from pregnant women who are positive for TPO-Abs[a] at 12 weeks gestation	32% (10/31)
III.	TPO-Ab$^+$ ("autoimmune") PPTD cases developing from pregnant women who are positive for TPO-Abs at 12 weeks gestation *plus* increased numbers of activated circulating T cells[b] at 12 weeks gestation	58% (7/12)
IV.	TPO-Ab$^+$ ("autoimmune") PPTD cases developing from pregnant women who are positive for TPO-Abs at 12 weeks gestation *plus* increased numbers of activated circulating T cells in follow-up[c]	71% (5/7)

[a] TPO-Ab > 50 U/ml; [b] activated T cells > 10% MHC-class II$^+$ CD3$^+$ cells at 12 weeks gestation; [c] mean activated T cells > 10% MHC-class II$^+$ CD3$^+$ cells (mean of values measured at G12, G32 and P4, see also fig. 2

Chapter 2.3.

Can thyroid peroxidase antibodies be regarded as a marker for depression?

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Submitted for publication.

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Abstract

Background. Depression is a major health problem with a high prevalence in women 20-40 years of age. The presence of thyroperoxidase antibodies (TPOAb) has been associated with postpartum thyroid dysfunction and postpartum depression. However, most if not all of the studies investigated the relationship at an univariate level and used a cross-sectional design.
Objectives. To investigate the relationship between TPOAb and depression during pregnancy and in the 1st year postpartum, particularly in relation to other determinants of depression, and to investigate whether elevated TPOAb levels in pregnancy are associated with depression in the postpartum period.
Methods. A prospective study was performed in the region Kempenland, south-eastern Netherlands. 310 unselected women were visited at 12 and 32 weeks gestation and 4, 12, 20, 28 and 36 weeks postpartum. TSH, fT4 and TPOAb testing was performed at each visit. Depression was assessed according to the Research Diagnostic Criteria (RDC). Multiple logistic regression analysis was performed to determine independent risk factors for depression in gestation and/or postpartum. Calculated were odds ratios (ORs) with 95% confidence intervals (95%CI).
Results. Data of 291 women were available for analysis. 41 women (14.1%) had TPOAb at one or more time points. Depression occurred more frequently in women with TPOAb women. The multiple logistic regression analysis showed that TPOAb were independently related to depression at 12 weeks gestation and at 4 and 12 weeks postpartum (OR (95%CI): 2.4 (1.1-6.0), 3.8 (1.3-7.3) and 3.6 (1.2-7.1), respectively). After exclusion of women depressed at 12 weeks gestation (n=70), the presence of TPOAb during early pregnancy was also related with the development of postpartum depression (OR (95%CI): 2.8 (1.7-4.5); after exclusion of women who had a depression in earlier life (n=51), TPOAb during early gestation remained related with postpartum depression (OR (95%CI): 2.9 (1.8-4.3).
Conclusions. The presence of TPOAb during gestation (a predictor for postpartum thyroid dysfunction) are also related to the occurrence of subsequent depression during the postpartum period and as such can be regarded as a marker for depression.

Introduction

Depression is a major health problem with an 1-year prevalence of 4-8% and has been associated with an increased morbidity, a high risk for suicidal death and a threefold increased risk of overall mortality (1,2,3,4). A major problem of depression is its social and psychological burden: it is estimated that more than half of the subjects with depression does not seek professional care. Moreover, in subjects who visit their general practitioner, the diagnosis is missed in up to 50% of the cases (5). Inadequately treated depression causes over-medicalisation: depressed patients show an increased consumption of medical care. Therefore, it is important to have reliable and objective markers for the disease which make it possible to detect it at an early stage.
Women are particular at risk to develop depression with an 1-year prevalence of 8-12% (1,2,3). During the first postpartum year depression has been reported to occur in up to 15% of the young mothers, and the negative impact of maternal depression on infant development is well established (6,7). Moreover, 5 years after parturition, up to 50% of the women still suffer from not resolved or a renewed episode of depression (8).
The aetiology of depression is thought to be multifactorial: biological, genetic and psychosocial

factors interact in order to provoke depression (4). A biological factor which relationship with depression has often been described is thyroid dysfunction, which is mostly caused by thyroid autoimmunity. An early sign of autoimmune thyroid disease - years before clinically overt thyroid dysfunction develops - may be the presence of thyroid autoantibodies, i.e. antibodies to thyroperoxidase (TPOAb). Around 10% of women over 20 years do have elevated conentrations of TPOAb (9,10,11). These women are particular at risk to develop overt thyroid dysfunction, especially during the postpartum period: up to 7% of all childbearing women suffer from postpartum thyroid dysfunction (PPTD) whereas up to 50% of the women with TPOAb develops PPTD (12-15). Women suffering from PPTD have been reported to have higher prevalence rates of depression in the postpartum period (9,16,17).
Most if not all of the studies showing a relation between thyroid autoimmune disease and depression used an univariate design while depression has a multivariate origin which means that when looking at the effect of one variable on depression, the influence of other determinants of depression should be simultaneously taken into account (4). Moreover, the design of the studies was retrospective and cross-sectionally in the majority of cases.
Therefore, we have investigated within a multivariate model the relationship between postpartum depression and thyroid dysfunction cross-sectionally. Subsequently, we have investigated within a longitudinal design whether the presence of thyroid autoimmune disease during pregnancy is correlated with the occurrence of a depression after delivery.

Subjects and methods

Subjects

The study was performed between January 1994 and April 1996 in the region Kempenland, a semi-rural area in the south-eastern part of the Netherlands. In this region the iodine-intake is low-normal (mean daily urinary iodide excretion 111±70 ìg (18)). All consecutive women (n=448) who booked in for antenatal controls to the local midwives or the obstetrical department of the St Joseph Hospital Veldhoven, were invited for a prospective study. None of the women used thyroid medication. Of these, 310 women (69%) consented in participation. All women were visited at home at 12 and 32 weeks gestation and at 4, 12, 20, 28 and 36 weeks postpartum. Nineteen women (6.1%) were excluded from analysis: 7 women refused further participation after experiencing spontaneous miscarriage or stillbirth, 1 suffered from puerperal psychosis, 9 were pregnant again within 6 months after delivery (and therefore it was impossible to evaluate postpartum depression) and 2 women moved out of the region. Data analysis refers to the remaining 291 women.
At baseline visit, a family and personal history of autoimmune thyroid disease and previous episodes of depression was performed; moreover lifestyle habits (medication, smoking habits and alcohol intake) and social-economic status were registered. Determinants which are known from literature to be related to depression (demographic features [such as educational level, marital state, employment, number of children], the occurrence of major life events [such as bereavement, severe disease, accidents], or a previous episode of depression) were carefully assessed. During the first postpartum visit the obstetrical history was performed. During all visits venous blood samples were collected into Vacutainer tubes (8 ml) for assessment of thyroid function and TPOAb testing; serum was stored at -20°C.
Permission for the study was obtained from the Medical Ethics Committee of the Academic Medical Centre, University of Amsterdam.

Methods

Thyroid function tests. The concentration of thyroid stimulating hormone (TSH) was measured by an immunometric technique, based on enhanced luminescence (Kodak Amerlite TSH-30, Kodak Clinical Diagnosticts Ltd., Amersham, UK). The reference interval for TSH was 0.15 - 2.0 mU/l, as defined for 225 non-pregnant women in the age group of 20-40 years and living in the same region. The interassay coefficients of variation were 20, 4.8, 6.3 and 5.1% at concentrations of 0.04, 0.68, 8.2 and 29.2 mU/l, respectively. Free thyroxin (fT4) was determined by using the Kodak Amerlite MAB FT4 Assay; its reference interval was 8.7 - 19.6 pmol/l, and was defined as described above. The interassay coefficients of variation were 11.1, 11.3 and 12.2% at concentrations of 6.1, 19.3 and 27.7 pmol/l, respectively.

A free triiodothyronine (fT3) assay for diagnosing a possible T3-toxicosis was performed in case of a decreased TSH but normal fT4 (reference interval: 4.0 - 8.0 pmol/l; Amerlex MAB, Amersham, Amersham, UK). Thyroid dysfunction was defined as an abnormal TSH in combination with an abnormal fT4 (or fT3), subclinical thyroid dysfunction referred to an abnormal TSH with normal fT4 (or fT3). TPOAb were measured by using the Immunometric Enzyme Combikit (Orgentec GMBH, Mainz, Germany); a concentration of >50 U/ml was defined as "positive" (TPOAb+). The interassay coefficients of variation were 18 and 8.5% at concentrations of 18 and 1000 U/ml, respectively.

Depression was defined according to the Research Diagnostic Criteria (RDC) (19), which discriminate between major and minor depression. During a short interview, syndromal diagnosis was established by one investigator who was unaware of the thyroid function.

Statistical Analysis. Statistical analysis was performed by using SPSS-7. Differences between groups were determined using the Chi-square test. Multiple logistic regression analysis (using the method Enter) was performed to determine factors independently related with depression. Introduced into the model were factors related with depression in the univariate analysis. Calculated were Odds ratios (OR) with 95% confidence intervals (95%CI).

Results

A total of 41 women (14.1%) were TPOAb+ at one or more time points. During the study 232 (80%) women remained euthyroid, 7 (2.4%) women showed clinical and 30 (10.4%) subclinical thyroid dysfunction during pregnancy, 15 women (5.2%) developed clinical (PPTD) and 21 (7.2%) subclinical thyroid dysfunction during the postpartum period. The characteristics of the TPOAb+ women did not differ from those without TPOAb with respect to demographic and psychosocial features or obstetrical complications (Table 1).

In Figure 1 the point prevalences of (sub)clinical thyroid dysfunction, TPOAb concentrations >50 U/ml and depression are shown for the whole study group. The highest prevalences of thyroid dysfunction were found at 12 weeks gestation (largely due to gestational thyrotoxicosis) and 20 and 28 weeks postpartum; the highest prevalences of depression were found at 12 and 32 weeks gestation and 12 weeks postpartum.

In Figure 2, the percentages of women with depression at each assessment point in relation to the TPOAb status are shown. During pregnancy and early postpartum (up until 12 weeks postpartum) women with depression presented more often elevated TPOAb concentrations. Although not correlated in time (Figure 1), an association between TPOAb and thyroid dysfunction and/or depression existed: both (sub-)clinical thyroid dysfunction and depression were significantly more prevalent in TPOAb+ women (Table 1).

In Table 2, a multiple logistic regression analysis shows the independent relations between psycho-social determinants of depression, (sub-)clinical thyroid dysfunction and TPOAb, and depression at each time point separately. The occurrence of a major life event was significantly associated with depression at each assessment. The presence of TPOAb was related with depression at 12 weeks gestation (OR=2.4; 95%CI 1.1-6.0) and during the first 3 months postpartum (4 weeks postpartum: OR=3.8 (95%CI 1.3-8.9) and 12 weeks postpartum: OR=3.6 (95%CI 1.3-7.3). Within the first 3 months after delivery, complications during labour were also significantly related with the occurrence of depression (OR=3.7; 95%CI 1.3-5.7). Clinical nor subclinical thyroid dysfunction were significantly related with depression (Table 2).

In order to answer the question whether TPOAb+ women in gestation but without an actual depression were at risk for future (postpartum) depression all women who were depressed at 12 weeks gestation (n=70) were excluded from the analysis. Of these excluded women 9 (12%) were TPOAb+ at 12 weeks gestation. In the 221 remaining women, the presence of TPOAb at 12 weeks gestation was significantly related with the occurrence of postpartum depression (OR= 2.8; 95%CI 1.7-4.5). The presence of TPOAb at 32 weeks gestation was not significantly related with the development of postpartum depression (OR= 2.4; 95%CI 0.6-8.7). Subsequently, in order to exclude the possibility that a previous episode of depression in a woman's' life might interfere with the occurrence of TPOAb, these women (51; 5 (10%) TPOAb+ and 21 (41%) depressed at 12 weeks gestation) were also excluded from the analysis. In the 191 remaining women, again the presence of TPOAb at 12 weeks gestation was significantly related with postpartum depression (OR=2.9; 95%CI 1.8-4.3) which was not the case for TPOAb at 32 weeks gestation (OR=2.3; 95%CI 0.5-7.1).

Discussion

This study shows that there is an association between the presence of TPOAb and depression in women during pregnancy and up to 3 months after delivery: 30-40% of women with TPOAb had a depression, contrasting to 15-20% of TPOAb negative women (see Figure 2). This relation was also found within a multivariate model taking into account other determinants of depression, such as the occurrence of a major life events and a family history of depression. The presence of TPOAb at 12 weeks gestation did also increase the risk for the development of a depressive period after delivery (OR=2.9; 95%CI 1.8-4.3).

So far, an association between thyroid disease (both overt and subclinical thyroid dysfunction) and depression has only been described using an univariate model in which higher prevalence rates of depression and/or more severe complaints of depression were reported in TPOAb+ women (9,11,16,17). However, depression is thought to have a multifactorial origin which implies that when investigating the effect of thyroid disease on depression other independent factors should also be taken into account (4). Within this model we found that 'classical' determinants of depression also in our study were significantly associated with depression: the occurrence of a major life event was significantly associated with depression at all assessment points (ORs varying from 2.2 to 4.7). High ORs (varying from 3.0 to 4.5) were also found for a previous episode of depression at several assessment points (Table 2). It is noteworthy that another cross-sectional survey in perimenopausal women originating from the same region also found an independent relation between TPOAb positivity and depression using a multivariate model (10).

An explanation for the relation between early forms of autoimmune thyroid disease (with normal TSH and fT4 or fT3) and depression is still lacking. In psychoneuroimmunological studies (which have been reviewed elsewhere) the relation between depression and alterations in the immune system have been studied and they present rather speculative conclusions (20,21). However, the question whether depression precipitates immune alterations or immune dysfunction precedes depression is far from being resolved. Within this discussion, we excluded women who had been suffering from a previous episode of depression (in earlier life and/or at 12 weeks gestation) in order to investigated whether women with TPOAb are at risk to develop subsequent (postpartum) depression. An OR of 2.9 (95%CI 1.8-4.3) is suggestive for the assumption that women with an already existing autoimmune thyroid disorder - without a history of a previous episode of depression - are at risk for a first period of depression (in the postpartum period).

As mentioned earlier, one major problem of depression (which is a very common, serious but treatable disease) in general is its hidden course: a substantial proportion of patients suffering from depression does not seek for medical care and once the patient contacts a physician a proper diagnosis is often not made (1-5). It is wellknown that TPOAb are an important risk factor or a marker for the development of future overt thyroid dysfunction which also often presents with atypical complaints. This study does suggest that TPOAb could be regarded as a marker for future depression to occur.

Several limitations of the study need to be mentioned. The numbers are rather small and other putative biological determinants of depression were not included in the analysis which means that the association between thyroid autoimmunity and depression should be interpreted with caution.

What could be the clinical implications of this study? It has been suggested earlier that screening of women in the first trimester of pregnancy for TPOAb might be worthwhile, since these antibodies are markers for later development of PPTD (14,17,22,23). Also, women with TPOAb during pregnancy have an increased risk for an impaired development of their offspring (8). The present study would add yet another argument for TPOAb screening: women with TPOAb during early pregnancy in the absence of a present or previous depression have a 3-fold increased risk to develop a subsequent depression. Because of its high incidence (10-15%) but its hidden nature, knowing the TPOAb status of a woman might help the clinician to detect depression at an early stage after parturition. Subsequent adequate treatment might prevent symptoms in the postpartum, might prevent possible negative effects on child development, and might reduce the recurrence rate of depression.

This study was supported by grants from the Dutch Praevention Fund (002822380) and the Dr. de Grood Foundation.

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Table 1. Characteristics of 41 women tested positive for TPO-antibodies (TPO+) and 250 women negative for TPO-antibodies (TPO-).

	TPOAb+	TPOAb-
mean age (yrs.) (±SD)	30.8(±2.7)	29.5(±3.2)
educational level (%)		
- primary/secondary school	26	22
- low college degree	51	53
- high college/ academic degree	23	25
smoking habits (%)		
- never smoked	56	57
- stopped	33	27
- currently smoking	12	16
parity (%)		
- 0	33	42
- ≥1	67	59
complications in pregnancy (%)	14	10
complications during labour (%)	35	35
male gender of the child (%)	54	56
breastfeeding (%)	23	33
previous episode of depression (%)	14	19
major life events (%)	54	61
major life events before 16 yrs. of age (%)	42	37
depression* (%)	70	52 (p=0.03)
subclinical thyroid dysfunction* (%)	44	18 (p=0.0001)
clinical thyroid dysfunction* (%)	26	4 (p<0.00001)

*: at one or more time points, during pregnancy and/or postpartum.

Table 2. Multiple logistic regression analysis (method Enter) in 291 women as assessed separatedly at 7 time points. Dependent variable: depression according to RDC. Odds ratio's (95%CI).

Variable	12 wks ges	32 wks ges	4 wks pp	12 wks pp	20 wks pp	28 wks pp	36 wks pp
low education level	1.5(0.9-2.4)	**1.6(1.1-2.6)**	1.3(0.8-2.3)	1.4(0.8-2.5)	**1.8(1.1-3.2)**	1.4(0.8-2.1)	1.3(0.7-2.2)
higher age	1.2(0.6-2.1)	1.3(0.5-1.9)	1.2(0.7-2.4)	1.5(0.8-2.2)	1.5(0.7-1.9)	1.2(0.6-2.1)	1.3(0.5-1.8)
multiparity	1.3(0.9-2.1)	1.0(0.7-2.5)	1.2(0.6-1.9)	1.1(0.7-1.8)	1.1(0.7-1.9)	1.3(0.5-1.8)	1.4(0.8-2.4)
occurrence of major life events	**3.0(1.5-5.8)**	**2.6(1.4-5.8)**	**2.2(1.1-4.6)**	**2.5(1.2-5.8)**	**4.7(1.4-6.8)**	**4.3(2.0-7.1)**	**2.7(1.1-4.3)**
smoking	1.5(0.8-2.1)	1.2(0.9-2.0)	1.4(0.7-2.1)	1.3(0.7-2.2)	1.1(0.7-1.9)	1.0(0.6-1.7)	2.0(0.5-2.3)
previous depression	**4.5(2.0-7.9)**	**3.0(1.5-5.8)**	1.2(0.6-2.5)	1.5(0.6-3.7)	1.1(0.4-2.7)	1.4(0.6-3.9)	**3.5(1.2-4.2)**
subclinical thyroid dysfunction	1.5(0.6-8.1)	1.9(0.3-24)	1.8(0.5-16)	1.8(0.4-19)	1.1(0.3-17)	1.4(0.6-14)	2.0(0.3-21)
clinical thyroid dysfunction	7.6(0.6-53)	*	*	4.9(0.4-35)	2.2(0.2-43)	9.8(0.3-62)	*
TPO-Ab >50 U/ml	**2.4(1.1-6.0)**	2.4(0.7-8.9)	**3.8(1.3-7.3)**	**3.6(1.2-7.1)**	2.8(0.8-7.4)	1.5(0.4-6.6)	1.0(0.3-6.1)
complications in pregnancy	1.4(0.8-4.2)	2.1(0.6-7.4)	-	-	-	-	-
complications during labour	-	-	**3.7(1.3-5.7)**	**2.6(1.2-6.1)**	2.1(0.9-4.9)	-	-
breastfeeding	-	-	1.2(0.7-2.2)	1.5(0.8-1.9)	1.3(0.8-1.9)	1.1(0.7-2.1)	1.1(0.6-2.1)

-: not relevant; *: to few cases.

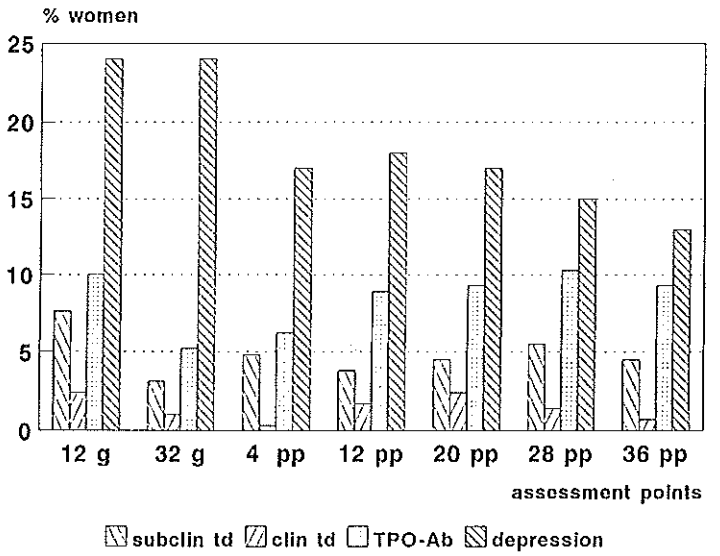

Figure 1.
The point prevalences of subclinical (abnormal TSH) and clinical (abnormal TSH and abnormal fT4) thyroid dysfunction, TPO-antibody concentration >50 U/ml and depression according to RDC criteria in 291 women during gestation and in the postpartum period. (12g, 32g, 4pp, 12pp, 20pp, 28pp and 36pp: 12 and 32 weeks gestation, 4, 12, 20, 28 and 36 weeks postpartum, respectively).

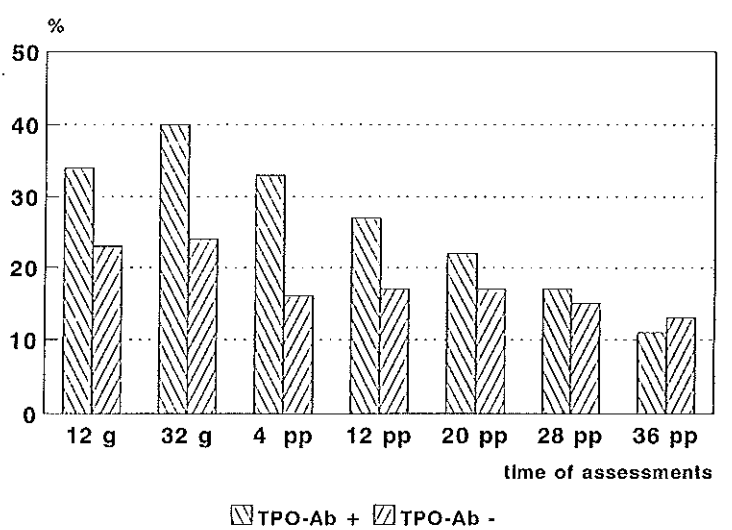

Figure 2.
The percentage of women with depression according to the presence of TPOantibodies.

Chapter 2.4.

Low maternal fT4 concentrations during early pregnancy are associated with impaired psychomotor development in infancy.

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Clin Endocrinol 1998; in press.

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Abstract

Background. Maternal thyroid function during early pregnancy is an important determinant of early fetal brain development because the fetal thyroid is unable to produce any T4 before 12-14 weeks' gestation. Overt maternal hypothyroidism as seen in severe iodine-deficient areas is associated with severely impaired neurological development of the offspring. At present, it is not known whether low fT4 levels during pregnancy in healthy women from iodine sufficient areas may affect fetal neurodevelopment.

Methods. Neurodevelopment was assessed at 10 months of age in a cohort of 220 healthy children, born after uncomplicated pregnancies and deliveries, using the Bayley Scales of Infant Development. Maternal TSH, fT4 and TPO antibody status were assessed at 12 and 32 weeks' gestation. Maternal gestational fT4 concentration was defined as an independent parameter for child development.

Results. Children of women with fT4 levels below the 5th (<9.8 pmol/l, n=11) and 10th (<10.4 pmol/l, n=22) percentiles at 12 weeks' gestation had significantly lower scores on the Bayley Psychomotor Developmental Index (PDI) scale at 10 months of age, compared to children of mothers with higher fT4 values (t test, mean difference: 14.1, 95% CI: 5.9 - 22 and 7.4, 95% CI: 1.1 - 13.9, respectively). At 32 weeks' gestation, no significant differences were found. In the group of women with the lowest 10th percentile fT4 concentrations at 12 weeks' gestation, a positive correlation was found between the mothers' fT4 concentration and children's PDI scores (linear regression, R: 0.46, p = 0.03). After correction for confounding variables, an fT4 concentration below the 10th percentile at 12 weeks' gestation was a significant risk factor for impaired psycho-motor development (OR: 5.8, 95% CI: 1.3 - 12.6).

Conclusions. Low maternal plasma fT4 concentrations during early pregnancy may be an important risk factor for impaired infant development.

In pregnant women suffering from thyroid dysfunction, decreased maternal fT4 levels play a critical role in the neurological development of the fetus, especially during the first trimester, since the fetus does not produce thyroid hormone itself until 16-20 weeks' gestation (Vulsma et al., 1989; Porterfield & Hendrich, 1993; Burrow et al., 1994; De Zegher et al., 1995; Emerson, 1996; Fisher, 1996). Similarly, animal and human studies have shown that impaired maternal thyroid function during early gestation is associated with impaired fetal neurological development, in contrast to maternal thyroid dysfunction in late gestation (Morreale de Escobar et al., 1990; Calvo et al., 1992; Contempre et al., 1993). To date, the relationship between the thyroid hormone status of healthy pregnant women and infant neurodevelopment has not been investigated in iodine sufficient areas. In a recent study, no relationship could be demonstrated between maternal plasma fT4 levels at 32 weeks' gestation and the infant's neurodevelopment at 5 years of age (Pop et al., 1995). However, it might be argued that it is the maternal plasma fT4 concentration earlier in gestation which is important for fetal maturation and, consequently, for infant development (Calvo et al., 1992; Contempre et al., 1993). The present study overcomes these limitations. Firstly, the maternal thyroid hormone status was assessed in healthy women with no previous thyroid dysfunction, who experienced normal pregnancies and deliveries. Secondly, in order to avoid possible bias on child development from environmental factors (e.g. psycho-social aspects, diseases), child development was assessed at an early age (10 months). Finally, the outcome of maternal fT4

levels at 12 weeks' gestation on child development was compared with that of fT4 levels at 32 weeks' gestation.

Subjects and Methods

Sample

The study was carried out in an iodine-sufficient area in the south-east of the Netherlands, in and around the city of Veldhoven (Rees-Wortelboer et al., 1987). Between January and November 1994, 448 pregnant women at 12 weeks' gestation were invited to participate in a longitudinal study of postpartum thyroid dysfunction. Women receiving antithyroid drugs and/or thyroid hormones were excluded. The participants were examined at 12 and 32 weeks' gestation, four weeks' postpartum, and at eight-week intervals thereafter until 36 weeks' postpartum. The characteristics of the study group are shown in Table 1.

Maternal thyroid determinants (fT4, TSH and TPO-Ab) were assessed in early and late gestation and in the postpartum period. Neonatal thyroid function was assessed on the fifth to seventh postpartum days, as part of the Dutch national screening program for congenital hypothyroidism. 310 Women (69%) consented to participate, 291 of them (94%) completed the study. At ten months' postpartum, 268 women were still eligible to be asked for informed consent to evaluate child neurodevelopment. Of the 23 women excluded, three had experienced neonatal deaths related to preterm birth, five had had children with congenital abnormalities, and 15 women had moved outside the area. Of the remaining 268 women, 244 (91%) consented to participate. Of these, a further 24 were excluded for reasons of prematurity (4), severe neonatal asphyxia (4), twins (3), severe eclampsia (2), IUG retardation (2) and a birth weight of < 2500 g (9). Data analysis is based on the remaining 220 women and their children, none of whom had serious complications during pregnancy or delivery and the details of whom are shown in Table 1.

Permission for the study was obtained from the Medical Ethics Committee of St Joseph Hospital in Veldhoven.

Methods

Thyroid function was assessed by measuring the concentrations of thyroid stimulating hormone (TSH, Kodak Amerlite TSH-30, Ultrasensitive Assay, Kodak Clinical Diagnostics Ltd, Amersham, UK), free thyroxine (fT4, Kodak Amerlite MAB FT4 Assay), and thyroid peroxidase antibodies (TPO-Ab, Immunometric Enzyme, Combikit, Orgentec GMBH, Mainz, Germany). Evaluation of the assays throughout the study showed interassay coefficients of variation for a TSH of 20%, 4.8%, 6.3% and 5.1% at concentrations of 0.04, 0.68, 8.2 and 29.2 mU/l, respectively, for an fT4 of 11.1%, 11.3% and 12.2% at concentrations of 6.1, 19.3, and 27.7 pmol/l, respectively, and for a TPO-Ab of 18% and 8.5% at concentrations of 18 and 1000 IU/ml, respectively.

Child neurodevelopment was assessed by means of the Dutch version of the Bayley Scales of Infant Development (Bayley, 1969). The Mental Developmental Index (MDI) scale of the Bayley test evaluates aspects of functioning such as eye-hand coordination, manipulation, understanding of object relations, imitation, and early language development. The Psychomotor Developmental Index (PDI) scale assesses gross motor development. The Dutch Bayley scales (published in 1983) have a mean of 100 and a standard deviation of 16 (these are still considered reliable) (Van der Meulen & Smrkovsky, 1983). All children were visited at home by one

developmental psychologist who was blind to the thyroid hormone and TPO-Ab status of the mother during pregnancy.
Several confounding variables which have been reported in the literature to be related to child neurodevelopment were assessed such as: maternal depression (using Research Diagnostic Criteria, RDC) (Spitzer et al., 1978), psycho-social factors, demograhpic features, life-style habits during pregnancy (smoking, alcohol), breastfeeding and the occurrence of stressful life events.
Statistical Analysis. Statistical analyses were performed using the Statistical Package of Social Science (SPSS). Statistical testing was by Student's t test, linear regression and logistic regression analysis. In the logistic regression analysis, an unadjusted model with low scores on the Bayley Scales (below 1 SD of the mean, <84) was used as the dependent variable. The independent variables were entered into the regression at a univariate level in order to assess significant independent associations with the Bayley scores and, subsequently, at a multivariate level, to control for confounding effects regarding the association between maternal fT4 and these scores.

Results

Figure 1 shows the childrens' scores on the two Bayley subscales in relation to the maternal plasma fT4 concentrations at 12 weeks' gestation. The scores on the Psychomotor Developmental Index (PDI) of children of mothers with fT4 concentrations in the lowest 5th and 10th percentiles at 12 weeks' gestation were significantly lower than the scores of the remainder of the group (mean difference: 14.1, 95% CI: 5.9-22.3, and 7.4, 95% CI: 1.1-13.9, respectively). At 32 weeks' gestation, no differences in scores could be demonstrated between any of the subgroups (data not shown). Similarly, children of mothers with fT4 concentrations in the lowest fT4 5th and 10th percentiles had lower scores on the Mental Developmental Index subscale (MDI), although these differences were not significant. Therefore, the PDI scores were studied more closely.
Figure 2 presents a scatter diagram of the group of women with the lowest 10th percentile plasma fT4 concentrations at 12 weeks' gestation and correlates maternal fT4 concentrations with their children's scores on the Psychomotor Developmental Index scale (PDI). From this, it can be seen that, the lower the mother's fT4 concentration, the lower the child's score (linear regression, R: 0.46, $p = 0.03$).
All children who were assessed at 10 months of age had T4 and TSH values within the normal range by approximately one week after birth, as assessed by the national screening programme for congenital hypothyroidism (data not shown).
Table 2a shows the results of the independent associations between several maternal variables and the low PDI scores of the children. Alcohol use, maternal TPO-Ab status during pregnancy, fT4 in the lowest 10th percentile (<10.4 pmol/l) at 12 weeks' gestation, gestational depression, low educational level of the mother, and the occurrence of a negative life event, were all significantly associated with a low PDI score. An fT4 concentration at 32 weeks' gestation in the range of the lowest 10th percentile (< 8.5 pmol/l) was not related to a low PDI score. In order to correct the fT4 effect on the PDI scores for possible confounders of infant development, a multivariate logistic regression analysis was carried out (Table 2b) with the PDI score as the dependent variable. An fT4 concentration in the range of the lowest 10th percentile (< 10.4 pmol/l) at 12 weeks' gestation, alcohol intake by the mother during pregnancy, maternal

depression during pregnancy, and the occurrence of negative life events (as rated by the mother), were all significantly related to a low score (below 1 SD of the mean) on the PDI scale. Again, fT4 concentrations in the range of the lowest 10th percentile (<8.4 pmol/l) at 32 weeks' gestation were not related to impaired psychomotor development, neither were high titres of TPO-Ab during pregnancy.

Discussion

This is the first study to show that low maternal fT4 concentrations in apparently healthy women during early gestation implicate a significantly increased risk (RR 5.8) of impaired neurodevelopment in the infant.

Animal studies have shown that thyroid hormone is of major importance to early fetal cerebral development, possibly due to its direct effect on the development of the cerebral T3 nucleus receptor (Brent, 1994). Moreover, animal studies have shown, that during early pregnancy, the fetus is totally dependent on maternal fT4 concentration, since it is unable to produce thyroid hormone (Calvo et al., 1992). In humans, clinical studies have shown that fetal and/or neonatal thyroid hormone deficiency, due to congenital hypothyroidism or iodine deficiency, has a dramatic negative impact on cerebral development (Contempre et al., 1993; Delange, 1996; Foley, 1996; De Vijlder & Vulsma, 1996). Moreover, premature neonates show psychomotor retardation associated with low postnatal thyroxine concentrations (Den Ouden et al., 1996; Reus et al., 1996; Vulsma & Kok, 1996). These are all examples of mothers and infants with serious health problems.

In contrast, this study questioned whether low normal plasma fT4 concentrations during pregnancy in healthy women with no previous thyroid dysfunction guarantees an adequate thyroid hormone status for the fetus, and we hypothesised that there might be differences in the individual thyroxine requirements of mother and child. Since fetal development is completely dependent on the maternal thyroid hormone supply, we measured fT4 at 12 weeks' gestation. The regression line in Figure 2 suggests that, within the lower range (10th percentile) of maternal fT4 concentrations during early pregnancy, the young child's psychomotor development is directly related to the maternal thyroid hormone status. In contrast, after the first trimester of pregnancy, if there is sufficient iodine intake, the increasing fetal thyroid hormone production gradually becomes responsible for fetal growth and development (Calvo et al., 1992; Contempre et al., 1993). Indeed, at 32 weeks' gestation, low maternal fT4 concentrations were not correlated with impaired development.

What is the clinical relevance of a statistically significant impaired score on the PDI scale in children of mothers with low fT4 during early gestation? A difference of 10 points on the psychomotor developmental index score reflects a delay of one month in the development of the retarded group (Bayley, 1969). Although the impact of this delay might be barely perceptible at the age of 10 months, the consequences will be important if the difference persists in later life. While it may be argued that child neurodevelopment on the Bayley Scales is more reliable if the child is assessed at 18-24 months of age, the literature on prematurity (33 weeks' gestation) and the outcome following prenatal complications show that results from assessments at as early as six months of age are able to predict the later outcome (Siegel, 1982; Van Baar & De Graaff, 1994; Van Wassenaer et al., 1997). The children in the present study were all born after pregnancies and deliveries with no serious complications, and were free of any explicit abnormalities during the first postpartum year. In order to evaluate whether there is an

association between child development and a prenatal factor in a cohort of children in whom a barely perceptible difference could be expected, the investigation should be carried out as early as possible (for example, during a neonatal examination).
The clinical implications of these findings could be impressive. If children of women from the general population in iodine-sufficient areas, with fT4 concentrations in the lowest 5th to 10th percentiles during early gestation, are more likely to have impaired neuro-development, the question arises as to whether this impairment could be prevented by the administration of thyroxine to pregnant women with low maternal fT4 levels. The implications of this supplementation for the offspring of women from iodine-deficient areas could be even greater. From this study, one preliminary conclusion could be that maternal fT4 values in the low normal range during early pregnancy are associated with impaired child development. Further research is needed to determine whether these 'borderline' concentrations of maternal fT4 can any longer be accepted as 'normal', with regard to infant development.

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Acknowledgements.
This study was kindly supported by a grant from the Dutch Praevention Foundation (No:002822380) and the Dr. De Grood Foundation. We are indebted to Dr. J. Rovet from the Hospital of Sick Children, Toronto, for her critical comments on the manuscript.

Table 1. Characteristics of the study group.

	A	B	C
Number of women	291	71	220
Educational level:	%	%	%
- 1 basic school	0.7	1.3	1.0
- 2	22.1	27.1	20.2
- 3	53.0	45.4	55.4
- 4 graduated/academic	24.2	26.2	23.4
Mean age of women (SD)	29.6 (3.2)	29.4 (3.2)	29.5 (3.1)
Parity: - primipara	105 (36)	27 (38)	78 (35)
- multipara	186 (64)	40 (62)	142 (65)
Smoking habits:			
- never	165 (57)	38 (54)	127 (58)
- no smoking in pregnancy	80 (28)	22 (31)	58 (26)
- smoked in pregnancy	46 (16)	11 (15)	35 (16)
Alcohol intake:			
- never	90 (31)	22 (31)	68 (31)
- no intake in pregnancy	151 (51)	32 (46)	119 (54)
- intake in pregnancy	50 (17)	17 (23)	33 (15)
Mean birth weight (SD)	3441 (579)	3386 (624)	3471 (550)
Sex: no. of girls (%)	129 (44)	34 (47)	99 (45)
no. of boys (%)	162 (56)	37 (53)	121 (55)
No. of women breastfeeding* (%)	200 (69)	40 (57)	160 (73)
Mean fT4 concentrations (SD)			
- 12 weeks' gestation	13.2 (2.5)	13.6 (2.7)	13.1 (2.6)
- 32 weeks' gestation	10.4 (1.9)	10.8 (2.0)	10.4 (1.8)
No. with TPO-Ab (%)			
- 12 weeks' gestation			
>50 U/ml	29 (10)	5 (7)	24 (11)
≥100 U/ml	18 (6.2)	3 (4)	15 (7)
- 32 weeks' gestation			
>50 U/ml	15 (5)	2 (3)	13 (6)
≥100 U/ml	8 (3)	2 (3)	6 (3)
No. with postpartum thyroid dysfunction (%)	15 (5)	2 (3)	13 (6)
No. with depression (%)			
- during pregnancy	70 (24)	19 (26)	51 (23)
- in the postpartum period	110 (38)	29 (40)	81 (37)

A: characteristics of the women in the original sample (n=291).

B: characteristics of the women not included in the follow-up (n=71).

C: characteristics of the women in the follow-up study (n=220)

*: breastfeeding: at least four weeks of exclusive breastfeeding.

Table 2. FT4 and TSH concentrations in relation to TPO-Ab titers of 220 women at 12 and 32 weeks' gestation. Reference ranges: fT4: 8.8-18 pmol/l; TSH: 0.14-2.2 mU/l.

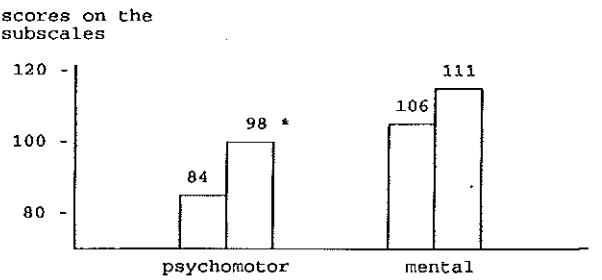
	12 weeks gestation N	32 weeks gestation N
A. fT4 (10th percentile)	10.4 pmol/l	8.5 pmol/l
fT4 ≤ 10th percentile	22	22
* TPO-Ab >50 U/ml	6	7
* TPOAb ≥100 U/ml	5	2
fT4 > 10th percentile	198	198
* TPO-Ab >50 U/ml	18	6
* TPO-Ab ≥100 U/ml	10	4
B. TSH		
TSH <0.14 mU/ml	10	4
* TPO-Ab >50 U/ml	2	0
* TPO-Ab ≥100 U/ml	1	0
TSH >2.2 mU/l	3	1
* TPO-Ab >50 U/ml	2	0
* TPO-Ab ≥100 U/ml	2	0

Table 3. Logistic regression analysis, method Enter; dependent variable: low score of the Psychomotor Scale (PDI) of the Bayley scale of Infan Development (SD=16, Mean=100). Low score: more than 1 SD below the mean. N=220.

A. Univariate regression	O.R>	95%CI
1. Pregnancy related factors:		
- smoking during gestation	1.7	0.6-5.2
- obstetrical factors	1.2	0.6-2.9
- alcohol use during pregnancy	3.0	1.4-6.6
- TPO-Ab ≥100 U/ml at 12 weeks' gestation	3.8	1.3-10.2
- TPO-Ab ≥100 U/ml at 32 weeks' gestation	2.9	0.6-13.8
- fT4 of lowest 10th percentile at 12 wks gest	3.6	1.1-12.1
- fT4 of lowest 10th percentile at 32 wks gest	1.1	0.4-3.2
- breastfeeding	1.2	0.6-2.5
- female	1.3	0.5-3.1
2. Maternal mood state:		
- gestational depression	3.1	1.3-6.3
- postpartum depression	1.4	0.8-2.7
- postpartum major depression	1.3	0.4-4.0
- depression in parents	1.0	0.5-1.9
3. Demographic features		
- marital state	1.9	0.7-5.4
- low educational level	1.8	1.1-2.9
- previous episode of depression	1.5	0.7-3.2
- occurrence of negative life events	1.9	1.1-3.7
- work outside home	1.9	0.8-3.8
B. Multiple regression	O.R.	95%CI
1. Pregnancy related factors:		
- smoking during gestation	1.2	0.5-2.8
- obstetrical factors	1.2	0.6-2.9
- alcohol use during pregnancy	3.3	1.3-8.7
- TPO-Ab ≥100 U/ml at 12 weeks' gestation	3.4	0.3-14.0
- TPO-Ab ≥100 U/ml at 32 weeks' gestation	2.7	0.2-42.0
- fT4 of lowest 10th percentile at 12 wks gest	5.8	1.3-12.6
- fT4 of lowest 10th percentile at 32 wks gest	1.0	0.4-3.2
- breastfeeding	1.4	0.5-3.4
- female	1.5	0.4-4.1
2. Maternal mood state		
- gestational depression	3.3	1.1-10.3
- postpartum depression	1.9	0.8-4.6
- postpartum major depression	2.5	0.3-16.2
- depression in parents	2.3	0.9-5.7
3. Demographic features		
- marital state	1.1	0.4-6.2
- low educational level	2.0	1.1-4.8
- previous episode of depression	3.1	0.9-9.5
- occurrence of negative life events	2.6	1.1-6.1
- work outside home	1.9	0.6-4.6

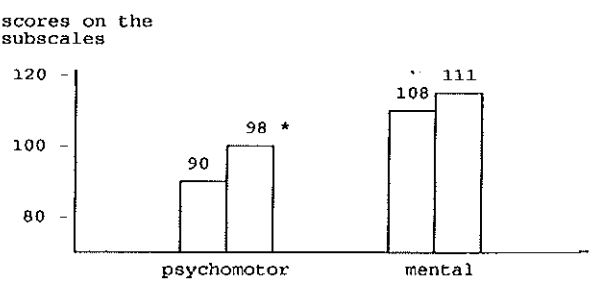
figure 1. Differences in mean scores on the two Bayley subscales comparing different percentiles of fT4 at 12 weeks' gestation (t test).

A. Lowest 5th percentile (<9.8 pmol/l n=11) versus remaining group (n=209).



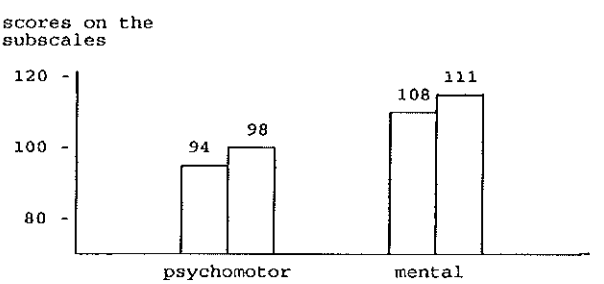
* mean difference: 14.1 (95% CI: 5.9 - 22.3)

B. Lowest 10th percentile (< 10.4 pmol/l, n=22) versus remaining group (n=198).



* mean difference: 7.4 (95% CI: 1.1 - 13.9)

C. Lowest 15th percentile (< 10.9 pmol/l, n=34) versus remaining group (n=186).



D. Lowest 20th percentile (<11.4 pmol/l, n=45) versus remaining group (n=175).

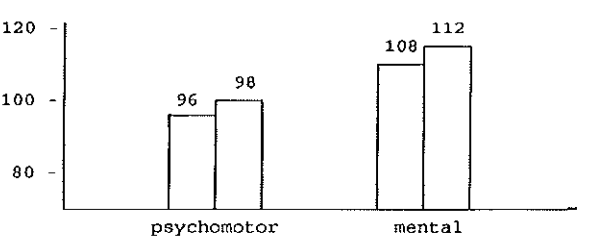
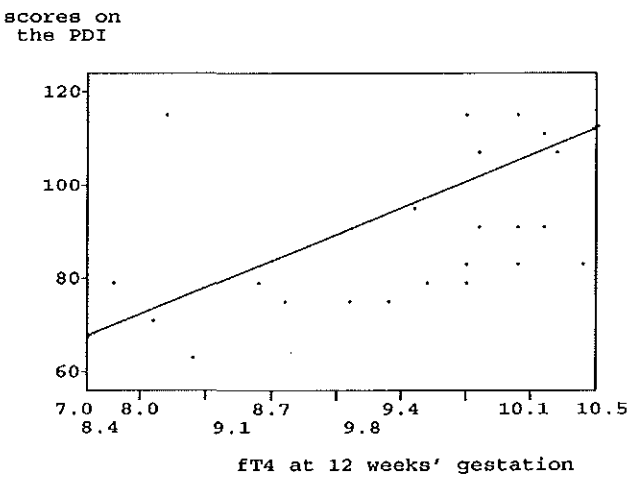


Figure 2. Scatter diagram correlating the scores on the Psycho-Motor Developmental Index Scale of children of women with the lowest 10th percentile fT4 concentrations at 12 weeks' gestation (< 10.4 pmol/l, n=22).



Linear Regression: Correlation: 0.46, p = 0.03

Chapter 3.1.

Thyroid cancer in the South-east of the Netherlands, 1970-1989 trends in incidence, treatment and survival.

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Ned Tijdschr Geneeskd 1994; 138: 464-8.

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Abstract

Objective. To describe the (changes in) incidence, treatment and prognosis of thyroid cancer (TC) in the period 1970-89 in the South-east of the Netherlands.

Setting. Eindhoven Cancer Registry, Comprehensive Cancer Centre South (IKZ), Eindhoven.

Design. Retrospective.

Patients and methods. Data were collected from al TC patients (ICD-O code 193 and non-Hodgkin lymphoma originating from the thyroid) diagnosed in the period 01-01-1970 - 31-12-1989. Histological, treatment and survival (on 01-07-1991) data were collected. The standardised incidence, prevalence, (relative) survival and mortality were calculated for men and women.

Results. The mean age of the 297 TC patients was 52 years; the male-female ratio was 1:2.3. 46% Of the TC patients had papillary TC, 35% follicular TC. The incidence of TC increased from 1.4 to 3.0/100,000/yr for females, the incidence remained unchanged for males (1.1/100,000/yr). The point prevalence (01-07-1991) was 25.6/100,000 for females and 8.2/100,000 for males. TC patients were treated in all hospitals in the region and were increasingly first seen by an internist. There was a trend to more extensive surgical treatment and iodine-131 treatment in differentiated TC. For all TC patients the crude 10-year survival rate was 61%, the relative 10-year survival rate was74%. Survival was related with sex, age and histological type. Mortality from TC remained very low.

Conclusions. The incidence and prognosis of TC were similar to the surrounding countries. In general the recommendations from the consensus meetings for treatment of TC in 1985 and 1987 appear to be followed.

The (changing pattern of) diagnostic procedures and treatment of thyroid cancer (TC) in the Netherlands has been described frequently (1-9); however, the incidence and the prognosis of TC (and the problable changes that occurred) have not been described so far. The patient groups described originated from university hospitals and oncologic centres (2,4,7-9). Little is known about the treatment and the prognosis of unselected TC patients referred to general hospitals.

TC is a rare malignancy: in 1989 311 new patients were registered by the joined cancer registries in the Netherlands, accounting for 0.6% of all new cancers (10). National data before 1989 are not available.

In this study the prevalence and incidence, the treatment and the survival of patients with TC residing in Southeastern-Netherlands are described based on data derived from the cancer registry of the Comprehensive Cancer Centre South (IKZ). The incidence and the survival are being compared with data from the Netherlands and the surrounding ciountries; the treatment wil be related to the recommendations of the consensus meetings in 1985 and 1987 (3,6).

Patients and methods.

The cancer registry of the Comprehensive Cancer Centre South (formerly the Cooperative Association of Hospitals in Oncology; SOOZ) comprises a defined region with about 1 million inhabitants in the southeastern of Noord-Brabant and middle and northern Limburg, and can be considered as "complete" since the early seventies. All hospitals and the radiotherapy institute in the region participate in the cancer registry. Additional patient data are being derived from oncologic clinics and university hospitals (11).

Diagnosis. Introduced in this study were all patients diagnosed in the period 1 January 1970 - 31 December 1989. TC was defined as any malignant tumour primary originating from the thyroid or aberrant thyroid tissue, or a distant metastase of a true thyroid tumour (International Classification of Diseases for Oncology, 8th and 9th edition, (ICD-O)-code 193). The data of the cancer registry were also screened for non-Hodgkin's lymphoma (NHL; ICD-O-code 202) primary originating from the thyroid.
Personal data and date of diagnosis, histology of the tumour, hospital, first specialist and treatment were obtained from the cancer registry. From 265 patients residing in the nucleus of the registry area, survival up to 1 July 1991 was asked for in the municipal population registries according to the last address. Based on the pathologist's reports, five types of TC were discerned: papillary, follicular, medullary and anaplastic TC, and other types (including NHL) (12).
Analysis. The incidence was calculated per 100,000 personyears for men and women and standardised using the European Standard Population with a 3-year-mean for trend (10). Based on all TC diagnosed since 1 January 1970, the point prevalence on 1 July 1991 was calculated. The actuarial survival curves were estimated using a computer program of the Finnish Cancer Registry (13,14). The "observed (crude) survival rate" is the survival based on death, irrespective of the cause of death. The "relative survival rate" is the ratio of the observed (crude) survival rate and the expected survival (for a population similar in age- and sex-distribution) and can be interpreted as the chance not to die of TC (13). With data derived from the Central Bureau of Statistics (CBS), mortality related to TC per 100,000 per year for males and females was calculated in the same manner as the calculation of the incidence.

Results

Incidence. In the period 1970-1989 297 new patients were registered. In particular the number of new patients with papillary and follicular TC increased in the last 5-year period (Table 1). Amongst the different histological types, papillary TC was the most frequent (46%), followed by follicular TC (35%). In total 10 patients (3%) with medullary TC were registered; 3 of these patients were relatives with a hereditary form of medullary TC. Six cases (2%) with a primary thyroid NHL were registered. A summary of the patient characteristics is shown in Table 1. The mean age was 53 years for males and 52 years for females.
The incidence of TC in males remained stable around 1.1/100,000/year, in females the incidence increased from 1.4 to 3.0/100,000/year due to an increase of papillary and follicualr TC (Figure). The point prevalence on 1 July 1991 was 8.2 and 25.6/100,000 for males and for females, respectively.
Treatment. Patients with TC were treated in all hospitals in the region, approximately 1-3 per year. Two of the patients were initially treated outside the region in a university hospital or an oncologic centre. From almost all patients data on the first specialist and the initial therapy were known (Table 2). Compared with the first 10 years period, a shift occurred in the second 10 years period from the surgeon to the internist as the first specialist performing the diagnostic process. The initial therapy was in almost all cases surgical. There was a trend to more extended surgical procedures (see Table 2). External radiotherapy and chemotherapy were scarcely administered. Three per cent of all patients did not receive oncological treatment. In the second 10 years period, patients with papillary TC underwent surgical treatment in the majority of cases (79%; 40% total thyroidectomy, 23% hemithyroidectomy and 10% thyroidectomy with lymph node dissection). just as patients with follicular TC (88%; 63% total thyroidectomy,

13% hemithyroidectomy and 8% subtotal thyroidectomy). From 142 patients data on one or more follow-up therapies were reported. Only patients with differentiated TC received radioactive iodine (^{131}I) therapy; the proportion patients treated with ^{131}I increased from 21% to 28% in papillary and from 32% to 39% in follicular TC patients in the second 10 years period. Radiotherapy was administered in total in 45 cases, most frequently in anaplastic TC (of the 24 patients with anaplastic TC 14 received radiotherapy). Chemotherapy was administered in 11 patients. Nine per cent of all patients were referred for further treatment to a hospital outside the region (university hospital or oncologic centre).

Survival. Information about vital status up to 1 July 1991 was obtained for 260 patients. The 5- and 10-year survival rates are summarized in Table 3. The crude 10-year survival rate for TC patients was 61%; the relative 10-year survival rate was 74%, indicating that about a fourth part of the patients with TC had died of TC. Survival appeared to be related to gender (relative survival rates for males 67% and for females 77%), age (patients <30 years 98%, 30-60 years 76% and >60 years 54%) and histological type of the tumour (papillary 93%, follicular 68%, medullary 77% and anaplastic TC 7%).

The relative survival increased from 69% in the first 10 years to 79% in the second 10 years. The relative 10-year survival rates for papillary and follicular TC patients increased from 85% to 100% and from 61% to 81% in the second 10 years period, respectively.

The mortality related to TC remained very low around 0.7/100,000/year for both males and females during the whole study period (see Figure).

Discussion

Incidence. In a twenty-year period 297 new patients with TC were registered. In the most recent years papillary and follicular TC cases appeared to increase (see Table 1). The incidence in Southeastern Netherlands in the early 80's (1.1/100,000/year in males and 2.0/100,000/year in females; see Figure) was similar to that in the surrounding countries (Denmark, Germany, France, United Kingdom), but lower than in Norway and Sweden (15). The incidence in the Netherlands in 1989 was 1.0 and 3.0/100,000 for males and females, respectively (10). An increase of the incidence (particular in papillary TC) did also arise in Norway and Denmark (16,17). This increase of papillary TC was explained by earlier detection of the tumour (16,17). The fact that (benign) thyroid disorders are more prevalent in women than in men is an explanation for the excess changes in incidence in females (18,19). Through that, thyroid disorders are looked for more frequently. Changes in the prevalence of risk factors for TC, such as external radiation of the head and neck region, environmental exposure to radioactive iodine or hormonal and fertility-related disturbances most likely did have a limited effect (16, 20-22).

Prevalence. Based on the point prevalence on 1 July 1991 in Southeastern-Netherlands, the number of TC patients treated since 1970 could be extrapolated as 1920 women and 615 men for the Netherlands as a whole.

Histological types. In a study from the Rotterdamsch Radio-Therapeutisch Instituut (the Rotterdam Radiotherapy Institute; RRTI) on 429 selected patients with a mean age of 55 years and diagnosed in the period 1950-1981, 46% of the patients had papillary, 20% follicular, 5% medullary, 15% anaplastic TC, and 14% an other histological type (2% NHL) (4). The distribution of histological types in patients registered by the Dutch cancer registries was: papillary 48%, follicular 23%, medullary 10% and anaplastic TC 7%, and others 12% (Dutch

Cancer Registry 1989, personal communication 1993). The mean ages at diagnosis for the different histological types were comparable. The distribution of the histological types did change in the course of years: the proportion anaplastic TC decreased gradually, whereas the proportion differentiated TC increased. This could explain the differences in results.
The male-to-female ratio was 1:2.3 (see Table 1); this was comparable with the results of the RRTI study (4). In a population-based study from Norway, the male-to-female ratio was 1:3.1 (23).
In Southeastern-Netherlands, patients with (a probable) TC were increasingly first seen by an internist (see Table 2). This appeared to be the result of the introduction of ultrasonographic examinations and, in particular, the introduction of fine-needle aspiration biopsy, which facilitates a better pre-operative selection of patients (2,3,5-7,24). As a consequence, the number of thyroid operations for thyroid nodules has decreased (19).
Treatment. The majority of patients with TC has been treated in one of the regional hospitals. Only 1 out of 11 patients has been referred for additional treatment to a hospital outside the region. More than 90% of all patients underwent initially surgical therapy; the proportion extended surgical procedures increased (see Table 2). These findings are in accordance with the recommendations described in the Dutch "Leerboek Chirurgie" (1988) and the guidelines developed during the consensus meeting in 1987: an increasing number of total thyroidectomies performed in follicular TC and an increasing number of thyroidectomies with lymph node dissection in papillary TC (6,25). Data on one or more follow-up treatments were available for 142 patients. ^{131}I ablation therapy was the most frequent type of follow-up therapy. Additional ^{131}I therapy was increasingly administered to patients with differentiated TC. This was also in accordance with the recommendations from the consensus meeting (6).
External radiotherapy and chemotherapy were of limited value in the treatment of TC: a small number of patients received these therapies supplementary to surgical treatment. This is also in accordance with the recommendations formulated for the Netherlands (6,25). Besides, radio- and chemotherapy were prescribed months to years after the initial therapy, probably when a relapse occurred.
Prognosis. The prognosis for TC patients was relatively good: the relative 10-year survival rate was 67% for men and 77% for women compared to 27% for men and 44% for women in cancer patients in general (13). The prognosis appeared to be related with age and histological type (see Table 3). In the RRTI study the disease-free 10-year survival was 52% and the prognosis was related with age, histological type and stage of disease (4).
The prognosis of TC patients improved in the course of years: in the RRTI study the 10-year survival for patients diagnosed before 1965 was 45% and since 1965 56%, in our study the relative 10-year survival rate was 69% for patients treated in 1970-1979 and 79% for those treated in 1980-1989 (4). Explanations for the improvement of the prognosis are the increasing proportion of less aggressive histological types (in particular papillary TC), an earlier detection (resulting in less extended disease) and a better treatment, e.g. an increase of ^{131}I ablation therapies.
The prognosis for patients with papillary and follicular TC has improved in the second 10-year period (see Table 3). The 10-year survival rate of papillary TC is similar to that for the general population. Schelfhout et al. found a disease-free survival of 95% in papillary and 67% in follicular TC patients (9). Our findings are also comparable with the findings of the Norwegian cancer registry in a comparable period (1970-1985) (23)**Mortality.** The mortality

from TC was low: for men and women around 0.7/100,000 per jaar, accounting for only a few men and women per year in Southeastern-Netherlands. In 1989 28 men and 70 women died of TC in the Netherlands (10). This accounted for 0.14% and 0.44% of all cancer deaths in men and women, respectively. The mortality from TC was similar to that in the surrounding countries (Belgium, Denmark, France, West-Germany and the United Kingdom) (26).

Acknowledgements. We thank mrs. M. van Daal-Wijnen for preparing the manuscript.

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Table 1. Numbers and clinical characteristics of patiensts with thyroid cancer diagnosed in the period 1970-1989 in Southeastern-Netherlands, per histological type and 5-year period.

Histological	1970-1974	1975-1979	1980-1984	1985-1989	total (%)	mean age years (range)	male:female
papillary	26	26	27	56	135 (46)	45.1 (16-83)	1 : 3.2
follicular	15	26	21	41	103 (35)	55.3 (13-85)	1 : 2.1
medullary	1	3	4	2	10 (3)	45.4 (16-61)	1 : 1
anaplastic	4	6	7	7	24 (8)	68.1 (51-87)	1 : 1
other	6	6	4	9	25 (8)	63.2 (40-83)	1 : 2.6
total	52	67	63	115	297 (100)	52.0 (13-87)	1 : 2.3

Table 2. First specialist and initial treatment in 297 newly diagnosed patients with thyroid cancer in the period 1970-1979 and 1980-1989. Numbers are percentages.

	1970-1979 %	1980-1989 %
first specialist		
internist	35	58
surgeon	58	38
other	7	3
unknown	1	1
initial treatment		
excision/biopsy*	21	15
surgery (total)	65	79
- hemithyroidectomy	15	20
- subtotal thyroidectomy	13	7
- total thyroidectomy	34	44
- thyroidectomy with lymph node disection	3	8
external radiotherapy	4	3
chemotherapy	1	-
no therapy	6	1
unknown	3	3

* Only excision of the tumour or biopsy performed.

Table 3. Cumulative crude and relative 5- and 10-year survival rates in 260 patients with thyroid cancer in the southeastern of Noord-Brabant and middle and northern Limburg diagnosed in the period 1970-1989, registered in the Eindhoven Cancer Registry. The relative survival rate is the ratio of the observed of the expected survival (expected in a population similar in age- and sex-distribution. SE: standard error).

	numbers	observed 5-year survival %	relative 5-year survival (SE) %	observed 10-year survival %	relative 10-year survival (SE) %
total	260	68	74 (3.3)	61	74 (4.2)
men	78	58	66 (6.8)	50	67 (8.6)
women	182	72	78 (3.7)	67	77 (4.7)
age (years)					
- <30	46	98	98 (2.2)	98	98 (2.2)
- 30-60	107	79	81 (4.3)	72	76 (5.5)
- >60	107	44	54 (6.1)	34	54 (8.7)
histological type					
- papillary					
1970-1979	44	81	87 (6.3)	74	85 (7.9)
1980-1989	74	92	97 (3.8)	92	100 (3.9)
- follicular					
1970-1979	35	64	71 (9.1)	49	61 (10.8)
1980-1989	53	67	74 (7.8)	67	81 (8.5)
- medullary	9	86	90 (13.6)	69	77 (20.9)
- anaplastic	23	4	5 (5.2)	4	7 (6.6)
- other		22	36 (11.2)	32	43 (13.3)

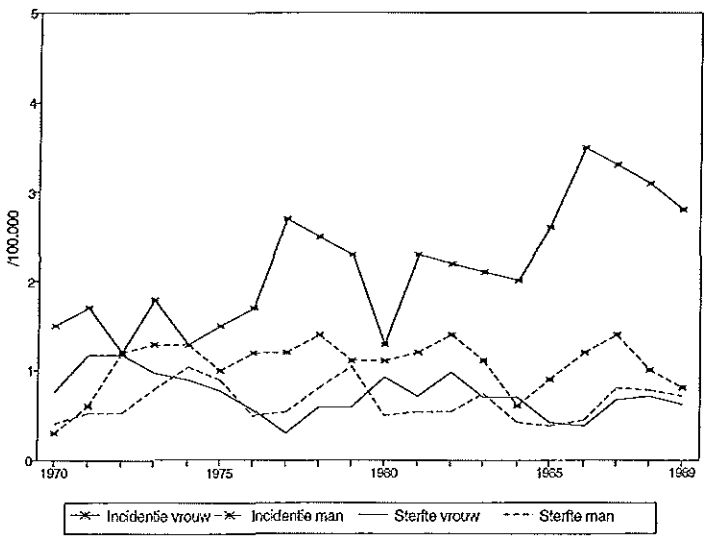

Figure Trends in incidence and mortality of thyroid cancer in Southeastern-Netherlands in the period 1970-1989, for men and women separadetly, calculated with a 3-year-mean and standardised using the European Standard Population.

Chapter 3.2.

Trends in treatment and long-term survival of thyroid cancer in Southeastern Netherlands, 1960-1992.

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Eur J Cancer 1998; 34: 1235-41.

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Abstract

Background. Thyroid cancer (TC), comprising less than 1% of all cancers in the Netherlands, has a good prognosis in general. Controversy still remains on the extent of surgical treatment and the indication for additional Iodine-131 (^{131}I) therapy in the management of differentiated TC.

Objectives. To describe (changes in) the treatment of TC and to determine independent prognostic factors for crude and relative survival of differentiated TC diagnosed in general hospitals.

Setting. Eindhoven Cancer Registry, Comprehensive Cancer Centre South (I.K.Z.), Eindhoven, the Netherlands.

Design. Population-based, retrospective study.

Subjects and methods. Data were collected on all 343 TC patients diagnosed from 01-01-1960 to 31-12-1992. All available information on treatment (initial and additional) and survival (on 01-04-1994) were recorded. Initial surgical treatment was defined as limited or extended. Multivariate analysis of crude and relative survival to determine prognostic factors for differentiated TC was performed.

Results. Mean follow-up was 7.6 years. The proportion patients with differentiated TC increased from 60% to 84%. TC patients were treated in all hospitals in the region, approximately 2-4/year. Ninety percent of all TC patients initially underwent surgical treatment; the extended procedures increasing from 27% to 61%. ^{131}I was also administered increasingly (from 18% to 44%) to patients with differentiated TC. The relative 5, 10 and 20 year survival rates for all TC were 79%, 75% and 74%, respectively. In the first 5 years after diagnosis the crude death ratio was higher with the rise of age and for the follicular type and after 5 years for males and advanced disease. After inclusion of surgical treatment into the model, the estimates of the other death ratios did not change. Patients treated with ^{131}I did better only during the first 5 years.

Conclusion. Although the prognosis for TC patients treated in general hospitals in Southeastern Netherlands was similar to that found for patients treated in referral centers, concentration of treatment should be considered.

Introduction

The incidence of thyroid cancer (TC) is low in the Netherlands: in 1993 340 new patients (96 male, 244 female) were registered by the Dutch Cancer Registry (0.5% of all cancer cases); the European standardized incidence rates were 1.3 and 2.7 per 100.000 inhabitants per year for men and women, respectively (1). In general 80% of newly diagnosed TC are differentiated (papillary or follicular) tumours which have a relatively good prognosis.

A consensus conference on the management of differentiated TC in the Netherlands (1987) developed guidelines for the diagnostic strategy and for surgical and additional Iodine-131 (^{131}I) therapy (2). However, controversy remained on the extent of surgical treatment both in the Netherlands and abroad (2,3,4,5). Some authors promote total thyroidectomy with or without (modified) neck dissection (3,6,7,8); others state that patients subjected to less extensive surgery (e.g. lobectomy incl. ishtmusectomy) have a similar prognosis with fewer complications (postoperative hypoparathyroidism, vocal cord paralysis) (9,10). Three recent studies of patients with papillary and/or follicular TC concluded that more extensive forms of surgery followed

by ^{131}I ablation led to a better long-term prognosis (5,8,11), although the optimal dose for ^{131}I ablative therapy is unknown (5,12).
Multivariate analysis has shown that crude and/or relative survival are related to age at diagnosis, histological type and cellular differentiation, and stage (5,8,11,13-22); gender was only found to be related to survival in five studies of mainly differentiated TC (5,11,14,21,22). Various forms of extended or radical surgery were related to better prognosis, but the results were not conclusive (5,8,11,20,21). Few studies are population-based (20,22), whereas most studies stem from large referral centers and introduced selected patients.
The objectives of this study are: to describe the (changing) pattern of treatment, also in relation to the recommendations of the 1987 consensus meeting, and to determine factors related to long-term survival of differentiated TC.

Subjects and methods

The data used for this study came from the Eindhoven Cancer Registry, which was founded in 1955 and became part of the Comprehensive Cancer Centre South in 1983. The registry covered a growing area; between 1960 and 1969 it consisted of 15 municipalities with approximately 300,000 inhabitants, since then it has increased to encompass 51 municipalities with about 1 million inhabitants in an area covering 2500 km2. All hospitals are served by the Radiotherapy Institute as well as the cancer registry. Data on histological type of the tumour, stage and initial and following therapy were obtained from copies of the pathologist's reports and from the patient records of the hospitals and the Radiotherapy Institute, which also provided ^{131}I treatment.
The records of all 343 patients with a tumour originating from the thyroid diagnosed from 01-01-1960 to 31-12-1992 were studied; the 6 patients with a non-Hodgkin's-lymphoma (NHL; 1 male, 5 females, age 40-83 yrs.) were excluded from analysis because of the different nature and therapy of this malignancy.
The pathological classification was in accordance with the recommendations of the World Health Organization: papillary, follicular, medullary (C-cell) and anaplastic carcinoma, and others (including NHL) (23).
Postoperative stage could be classified according to the recommendations of the Union Internationale Contre le Cancer (24), except for 88 patients who were mostly diagnosed before 1975.
Initial surgical treatment was classified as limited (excision of the tumour or surgical biopsy, lobectomy, subtotal thyroidectomy) or extended (total thyroidectomy with or without lymph node dissection); initial external radiotherapy or chemotherapy was also reported. Additional treatment consisted of radioactive iodine ablation (^{131}I), radiotherapy, other (surgery, chemotherapy) or none.
A teaching hospital was presumed to have training facilities for residents in surgery and/or internal medicine, "other hospitals" were hospitals outside the region, mainly referral centers.
Information about vital status up to 01-04-1994 was obtained for 327 patients (95.3%); 16 patients (4.7%) were lost to follow up.
Analysis. Eight TC patients (4 males, 4 females; age 63-85 yrs.) who died within 1 month of diagnosis were excluded from survival analysis. Survival (time from diagnosis) was calculated as crude and relative survival, the latter being the ratio of the crude rates to the expected rates

(25). Expected survival rates for the regional population were calculated from life tables (supplied by the Netherlands Statistics) compiled according to gender, age and period of diagnosis (1960-74, 1975-84, 1985-92) for the regional population. Crude survival curves were calculated using the Kaplan-Meier method. Comparisons between groups were made by means of the log-rank test. Cox's proportional hazard regression model was used to assess the prognostic value (calculated as rate ratio (RR) and 95% confidence interval (95%CI)) of several factors simultaneously for crude and relative survival. Relative survival was modelled with the Relsurv program (version 1.0n) which uses Cox's proportional hazard approach (26). Possible interaction terms expected to have influence on survival and interaction terms possibly related to treatment were investigated in the model of crude survival. None of these were significant, maybe also as a result of low numbers. The Cox model assumes that the various factors have a proportional effect on the outcome. This assumption was checked graphically as well as by adding the covariates as time-dependent factors to the model. Since the assumption of proportionality appeared to be violated when the total follow-up time after diagnosis was considered, separate analyses were performed for the first 5-year interval and after 5 years. For the first interval patients were censored at 5 years. For the second interval only patients who were still alive at the beginning of the next period were considered. The landmark of five years was chosen on the basis of an observed shift in survival around the five-year follow-up point. We were not able to calculate RR using the Relsurv program for the period after five years because few events occurred. The factors introduced in the main model were period of diagnosis, age, age category (<45 yrs., 45-60 yrs., >60 yrs.), gender, histological type (papillary or follicular; the other histological types were excluded because the numbers were small) and stage. The model was extended with initial and additional treatment.

Results

The mean follow-up of the 337 patients was 7.6 years (range 1.3-34 yrs.); 30% of patients were followed for ≥10 and 10% ≥20 years. The clinical characteristics of the patients are listed in Table 1. The male/female ratio was 0.4. The mean age at diagnosis for papillary, follicular, medullary or anaplastic TC, which was 43 (range: 5-83), 55 (13-85), 43 (16-61) and 67 years (43-87), respectively, remained stable for all histological types during the entire period.

The percentage patients with papillary or follicular TC increased from 37% and 23% in 1960-74 to 50% and 34% in 1985-92, respectively. Medullary TC was diagnosed in 12 patients (4%); 3 patients had a familial form of medullary TC. The percentage patients with medullary or anaplastic TC remained stable; the percentage patients with TC classified as "others" decreased.

For 249 patients the stage was known. Papillary TC patients had more stage I-II disease compared with follicular TC patients: 83% versus 61%. Anaplastic TC was classified as stage IV according to the recommendations of the UICC. The percentage stage I-II disease increased from 77% to 85% for papillary and from 50% to 67% for follicular TC in 1975-84 and 1985-92, respectively.

Treatment. TC patients were treated in all hospitals in the region, approximately 2-4 per year. The initial diagnosis of 47% of the TC patients was made by an internist, 48% by a surgeon. Initial treatment is summarized in Table 2. Nine out of ten patients underwent surgery; the proportion initially receiving limited surgery decreased from 63% in 1960-74 to 34% in 1985-

92; whereas the proportion subjected to extended surgery increased from 27% in 1960-74 to 61% in 1985-92. Extended surgery was performed increasingly in all age groups (<30 yrs: 39 vs. 58%; 30-59 yrs: 32 vs. 72%; ≥60 yrs: 36 vs. 51% in 1960-74 vs. 1985-92). Papillary, follicular and medullary TC patients received more extended surgery compared to anaplastic TC patients: 49%, 62% and 67% vs. 29%. External radiotherapy was prescribed predominantly for anaplastic TC patients, both initially and during follow-up. Patients treated in teaching hospitals underwent more extended surgery compared to non-teaching hospitals (57 vs. 49%). The initial and additional treatment of differentiated TC patients only is illustrated in Figure 1. ^{131}I therapy was available in the region during the whole study period: 46 papillary and 39 follicular TC patients were treated with ^{131}I after surgical therapy. ^{131}I therapy was administered relatively more often to follicular than to papillary TC patients (35 vs. 31%), more often to female than male patients (36 vs. 22%), and more often to younger than older patients (<30 yrs: 31%; 30-59 yrs: 38%; ≥60 yrs 23%). There was no association with stage or type of initial surgical therapy. In teaching hospitals patients received ^{131}I therapy more frequently than in non-teaching hospitals.

Survival. Figure 2 shows the crude and relative survival for the whole study group. It is clear that after 10 years there is no excess mortality. In Table 1 crude and relative survival are related to putative prognostic factors. In the univariate analysis, better survival was related to female sex, age <45 yrs., papillary type of the tumour and stage I-II disease.

Papillary TC had the best prognosis, followed by follicular and medullary TC (log-rank test: p=0.004) (Figure 3). Differentiated TC patients treated with ^{131}I did better than those not treated with ^{131}I (log-rank test: p=0.046).

The results of multivariate analysis of crude survival for patients with differentiated TC are shown in Table 3A. In the first five years the observed death rate was related to increasing age and the follicular type of tumour. Introduction of treatment into the model did not influence the other factors; patients who were not treated with ^{131}I exhibited an increased RR (Table 3A). After five years females exhibited a decreased and patients with stage III-IV disease had an increased death rate. After five years the effects of age and histological type declined and introduction of treatment into the model resulted only in a decreased risk of dying for patients treated in 1975-84. The RR of patients treated with ^{131}I became similar to those not treated with ^{131}I.

Table 3B shows the results of multivariate analysis for the relative survival of differentiated TC patients. The results for the first five years were similar to those for crude survival. However, the RR patients initially treated with radiotherapy increased to 15.

Discussion

The present study indicates that patients with differentiated TC admitted to general hospitals in our area received therapy as recommended by a consensus conference in 1987 and that the prognosis of these patients was similar to those treated in large referral centers. The mean ages and male/female ratios for the different histological types were in accordance with other European studies (13,16,17,19,27), whereas differentiated TC patients were younger in studies originating from the USA (5,8,11,22). Compared to other population-based studies the proportion with papillary TC was lower (Table 1): 43% versus 60-74% (20,22,28).

Treatment. At a consensus conference on the management of differentiated TC (1987) hemithyroidectomy was considered acceptable for treatment of well-differentiated papillary

or follicular TC confined to one lobe, with no lymph node metastases (or only on the side of the tumour in papillary TC) and no distant metastases and total thyroidectomy was to be performed in all other cases (2). Stable percentages for lobectomy and increasing percentages for total thyroidectomy (extended surgery) were found, especially among those with differentiated TC (Table 2, Figure 1). It appeared that the recommendations of the consensus meeting were already common practice in the region during the period 1975-84.

A total-body scan with ^{131}I was performed in the majority of cases 6 to 8 weeks after surgery and patients with a positive scan then received an ablation dose of 50 mCi ^{131}I. The increasing percentage patients who received ^{131}I (Figure 1) was also in accordance with the recommendations of the consensus meeting and other authors: ^{131}I should be given to all patients with follicular and advanced papillary TC to ablate remaining normal or neoplastic tissue and metastases (2,29,30).

A 1993 Dutch Health Council report on the quality of care in oncology recommended a certain degree of regional concentration of care for TC patients and quality improvement could be achieved by regional agreements between specialists (31). The differences in treatment between teaching and non-teaching hospitals in our region with only general hospitals were small but nonetheless not negligable. The small number of TC patients per hospital and the decreasing number of thyroid operations in The Netherlands may be an argument for regional concentration because the results and postoperative complications of thyroidectomy depend upon the experience of the surgeon (4,6,8,32).

Survival. The results of the univariate analysis of survival (all histological types) were comparable to those of studies from both referral centres and cancer registries. The relative 5- and 10-year survival was 76% and 72% for males and 81% and 78% for females, respectively. In a population based study from Norway (1970-85), 5- and 10-year survival (only TC deaths) was 76% and 66% for males and 82% and 79% for females, respectively, while in a study from Denmark (1978-82), 5- and 10-year relative survival was relatively low: 52% and 48% for males and 65% and 59% for females, respectively (20,33). In the population-based SEER program in the United States (1973-91), 5- and 10-year relative survival was 93% and 93% for males and 96% and 95% for females, respectively (22). The good results are likely to be explained by the greater proportion of papillary TC (74%), possibly also due to overdiagnosis. In our study relative survival was related to age at diagnosis, histological type and stage (Table 1), as in other studies (13,16,20,22,33).

The fact that patients who underwent extended surgery did slightly better compared to patients who underwent limited surgery (Table 1) can largely be explained by selection (patients with differentiated TC received more extended surgery compared to the other histological types which have a worse prognosis).

The multivariate analysis was performed only for differentiated TC. In most other studies independent factors related to the prognosis were age, histological type and cell differentiation and extent of disease (stage) (5,8,13-22); gender was related to prognosis in studies with relatively long-term follow-up (5,11,14,21,22). In the present study the effect of these prognostic factors was clearly different in the first five years (when younger patients, patients with papillary TC and those treated with ^{131}I did better) compared to later years (when females and patients with stage I-II disease did better). This may also explain the differences in outcome between studies.

Inclusion of initial and follow-up treatment in the multivariate analysis did not affect the other

prognostic factors. A favourable effect on prognosis for differentiated TC patients undergoing more extended forms of surgery was found in three studies of selected patient groups, moreover with different definitions of extended surgery (5,8,11). In this study the extent of surgical therapy was not related with a better prognosis (Table 3).
Patients treated with ^{131}I had a better prognosis compared to patients without this treatment only in the first 5 years. The latter group, however, most likely consisted of patients without indications for ^{131}I treatment (negative diagnostic scans) or patients who were not referred for performing a diagnostic scan and eventual treatment (patients with all stages of disease; some of these patients can be considered as "undertreated", mainly in the period before 1984 (Figure 1)). Initially more advanced disease (e.g. metastases on the diagnostic scan) and/or the development of second tumours may be explanations for the fact that the long-term prognosis of patients treated with ^{131}I did not differ from those not treated with ^{131}I.
The results of multivariate analysis for crude and relative survival were more or less identical in the first 5 years (Table 3), because correction for expected death has only a limited effect among relatively young patients with a good prognosis (see also Table 2: relative survival for papillary and follicular TC).
Conclusion. The prognosis for unselected TC patients treated in general hospitals in Southeastern Netherlands was similar to that for selected series of patients treated in referral centres. The prognosis of patients with differentiated TC was in the first 5 years of follow-up better for younger patients and papillary type of tumour, and after 5 years better for females and stage I-II disease. Additional ^{131}I treatment was related to a favourable prognosis only in the first five years. Regional co-operation (e.g. by developing regional guidelines for diagnostic procedures and therapy) of endocrinologists, pathologists, surgeons and radiotherapists may further improve the results of treatment.

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Table 1. Clinical characteristics (n=337) and 5-, 10- and 20-year crude and relative survival (excluded 8 patients dying <1 month; n=329; standard error: SE) of patients with thyroid cancer in Southeastern Netherlands, 1960-1992.

			5-year crude relat.(SE)		10-year crude relat.(SE)		20-year crude relat.(SE)	
	n	%	%	%	%	%	%	%
total:	337	100	71(3)	80(3)	62(3)	75(7)	52(4)	75(7)
gender:								
- males	102	30	64(5)	76(5)	54(6)	72(6)	42(7)	70(7)
- females	235	70	73(3)	81(3)	64(4)	78(4)	56(5)	77(5)
age:								
- <45 yrs.	135	40	94(2)	95(3)	92(3)	94(4)	83(5)	94(7)
- 45-60 yrs.	73	22	71(6)	74(6)	57(7)	67(7)	43(8)	67(16)
- >60 yrs.	129	38	45(5)	53(6)	32(5)	43(7)	22(7)	43(21)
hist. type:								
- papillary	149	44	89(3)	95(3)	79(4)	94(3)	68(6)	94(4)
- follicular	111	33	70(5)	82(5)	59(5)	80(6)	53(6)	79(8)
- medullary	12	4	81(12)	87(17)	58(16)	85(19)	45(17)	84(22)
- anaplastic	28	8	3(4)	5(4)	0	0	0	0
- other	37	11	44(9)	52(11)	44(9)	47(10)	34(8)	45(10)
stage:								
- I-II	172	51	90(2)	97(2)	88(3)	96(2)	83(4)	95(3)
- III-IV	77	23	43(6)	43(6)	14(5)	28(7)	0	0
- unknown	88	26	59(6)	77(6)	53(6)	68(7)	39(6)	65(8)
period:								
- 1960-74	82	24	67(5)	79(5)	60(6)	76(6)	50(6)	76(7)
- 1975-84	115	34	66(4)	74(5)	59(5)	70(5)	-	-
- 1985-92	140	42	77(4)	85(4)	-	-	-	-
hospital category:								
- teaching	179	53	68(4)	78(4)	61(4)	74(5)	47(6)	73(6)
- non-teaching	134	40	73(4)	80(4)	62(5)	77(5)	58(6)	76(5)
- other	24	7	75(9)	88(8)	65(10)	86(9)	53(11)	85(10)
therapy:								
- lim. surgery	146	43	67(4)	79(4)	61(4)	75(5)	57(5)	74(6)
- ext. surgery	163	48	80(3)	88(3)	68(5)	85(4)	46(10)	86(6)
- other/none	28	8	30(10)	29(10)	14(8)	22(9)	0	0

Table 2. The initial treatment of 337 patients with thyroid cancer in the region of the Eindhoven Cancer Registry, 1960-1992. Six patients with non-Hodgkin lymphoma excluded.

	1960-74 n=82	1975-84 n=115	1985-92 n=140
	%	%	%
Surgery			
- exc. tumour/biopsy	24	15	11
- lobectomy	22	18	18
- subtotal/near total thyroidectomy	17	8	4
- total thyroidectomy (± lymph node diss.)	27	49	61
External radiotherapy	4	3	2
Chemotherapy	1	-	-
None/unknown	5	7	4

Table 3. Rate ratio (95%CI) for 257 patients with differentiated thyroid cancer 1960-92 before and after 5 years of follow-up. Values calculated by Cox regression, without and with treatment in the model. (*: p<0.05)

	Follow-up ≤5 yrs Without treatment	Follow-up ≤5 yrs With treatment	Follow-up >5 yrs Without treatment	Follow-up >5 yrs With treatment
3A. crude survival.				
Age (yrs.):				
<45	1	1	1	1
45-59	6.4 (1.7-25)*	6.5 (1.7-25)*	3.5 (0.24-49)	1.8 (0.13-25)
>60	12 (3.5-43)*	10 (3.0-39)*	4.2 (0.30-59)	1.9 (0.13-28)
Gender:				
male	1	1	1	1
female	0.71(0.38-3.9)	0.93 (0.44-2.0)	0.22 (0.09-0.57)*	0.29 (0.09-0.94)*
Histology:				
papillary	1	1	1	1
follicular	2.0 (1.0-3.9)*	2.4 (1.2-4.8)*	1.1 (0.45-2.6)	0.84 (2.7->100)*
Stage:				
I-II	1	1	1	1
III-IV	1.3 (0.59-3.1)	1.3 (0.54-3.3)	19 (2.2->100)*	28 (2.7->100)*
unknown	0.69 (0.23-2.1)	0.65 (0.21-2.0)	2.1 (0.16-29)	4.1 (0.29-57)
Period of diagnosis:				
1960-74	1	1	1	1
1975-84	0.99 (0.36-2.7)	1.1 (0.39-3.1)	0.22 (0.05-1.1)	0.14 (0.03-0.73)*
1985-92	0.44 (0.13-1.6)	0.62 (0.17-2.3)	0.47 (0.06-3.8)	0.47 (0.05-4.2)
Initial therapy:				
limited surgery		1		1
extended surgery		0.87 (0.44-1.7)		1.5 (0.54-4.3)
other/none		1.3 (0.36-4.7)		17 (2.9->100)*
Follow-up therapy:				
Iodine-131		1		1
Radiotherapy		5.6 (1.4-22)*		0.76 (0.10-5.6)
None		4.6 (1.5-14)*		0.31 (0.10-1.02)
3B relative survival.				
Age (yrs.):				
<45	1	1		
45-59	6.4 (0.94-45)*	9.4 (1.6-55)*		
>60	10.0 (1.7-63)*	12 (2.4-57)*		
Gender:				
male	1	1		
female	0.76 (0.26-2.3)	1.1 (0.32-3.8)		
Histology:				
papillary	1	1		
follicular	2.1 (0.70-6.2)	2.7 (0.97-7.2)*		
Stage:				
I-II	1	1		
III-IV	1.7 (0.44-6.6)	1.2 (0.33-4.1)		

Table 3. (Continued)

unknown	0.71 (0.13-3.8)	0.44 (0.10-2.0)		
Period of diagnosis:				
1960-74	1	1		
1975-84	0.90 (0.22-1.5)	1.1 (0.26-4.4)		
1985-92	0.22 (0.04-1.5)	0.62 (0.06-2.1)		
Initial therapy:				
limited surgery		1		
extended surgery		0.72 (0.29-2.0)		
other/none		1.1 (0.17-6.9)		
Follow-up therapy:				
Iodine-131		1		
radiotherapy		15 (1.6->100)*		
none		5.9 (0.85-41)*		

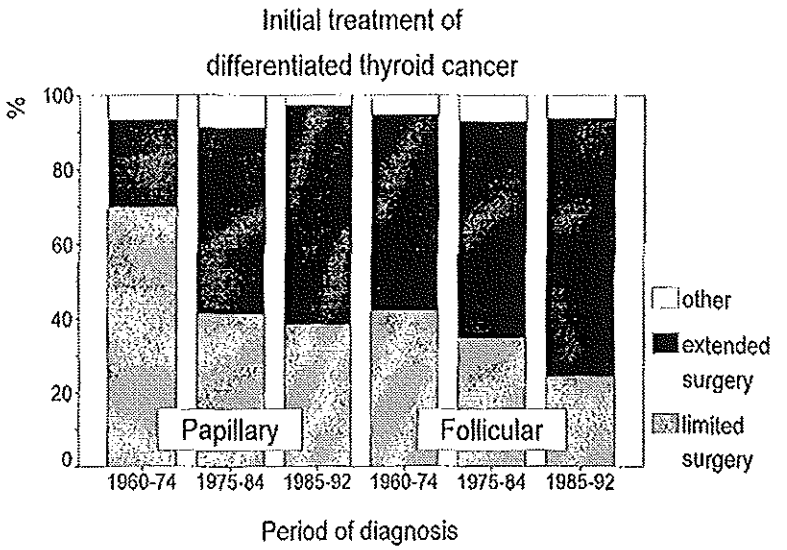


Figure 1. Trends in initial and additional treatment for differentiated (papillary or follicular) thyroid cancer in southeastern Netherlands, 1960-92. (n=260). A: initial treatment; limited surgery: biopsy, excision of tumour, lobectomy or subtotal thyroidectomy, extended surgery: total thyroidectomy with/without lymph node dissection, other: radiotherapy, chemotherapy, none or unknown. B: additional treatment: radioactive iodine ablation (^{131}I), radiotherapy, other/none.

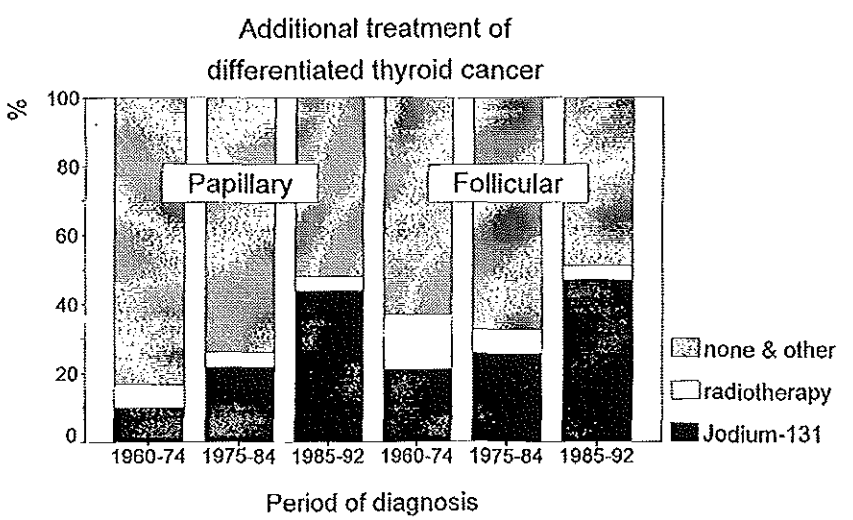
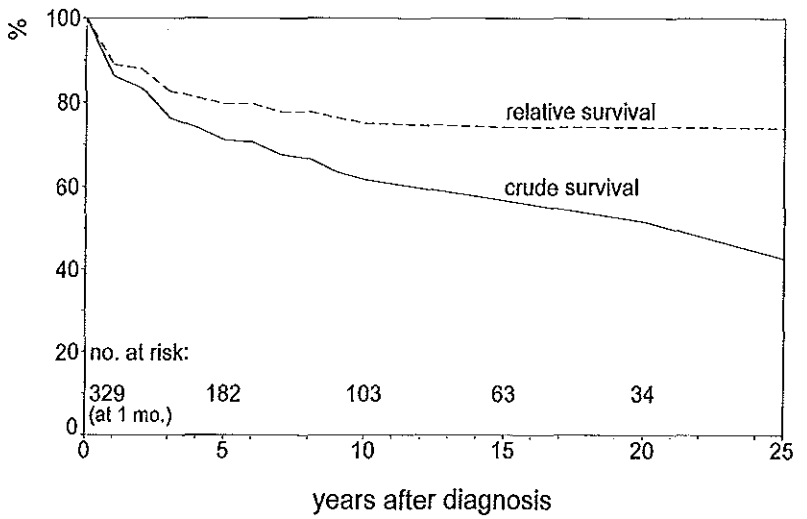


Figure 2. Crude and relative survival of 329 patients with thyroid cancer, 1960-92. Patients who died < 1 month and/or with non-Hodgkin's lymphoma were excluded.



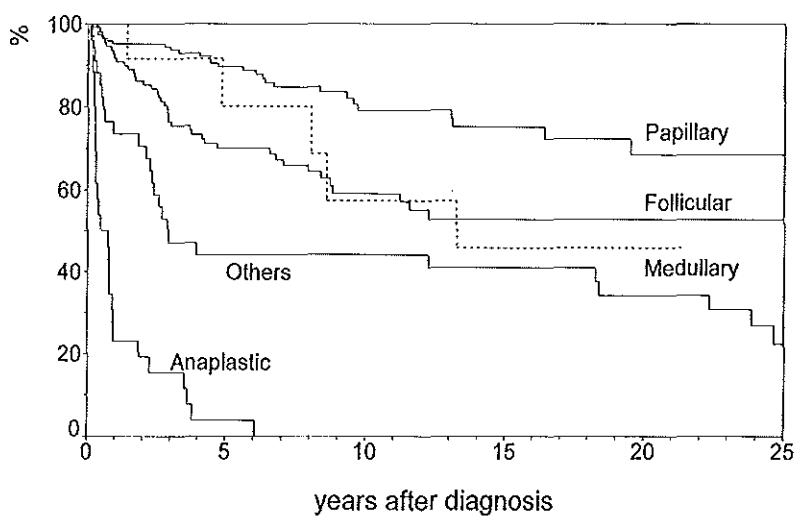


Figure 3. Crude survival of 329 patients with thyroid cancer according to histological type, 1960-92. Patients who died <1 month and/or with non-Hodgkin's lymphoma were excluded.

Chapter 3.3.

Co-morbidity in newly diagnosed thyroid cancer patients: a population-based study.

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Abstract

Background. Concomitant diseases can be an important reason for differences in the treatment and outcome of cancer. Moreover, their presence might provide aetiological clues. The objective of this study was to describe the spectrum of concomitant diseases in patients with newly diagnosed thyroid cancer (TC).

Design. Cross-sectional study.

Setting. Eindhoven Cancer Registry, Comprehensive Cancer Centre South, The Netherlands.

Methods. Histological and treatment data on all 164 TC patients diagnosed between 01-01-1993 and 31-12-1996 were collected. An adapted version of the list of Charlson (J Chron Dis 1987, 40, 373-383) was used for registration of clinically relevant concomitant diseases. The prevalence of co-morbidity at diagnosis was analysed according to age, histological type and therapy.

Results. Information about concomitant diseases was available for 151 patients (92%). Co-morbidity was present in 32% of TC patients; the prevalence was 21% for patients <60 years and 69% for patients ≥60 years, respectively. Hypertension was present in 18%, followed by other cancers (8%), diabetes mellitus (7%), cardiovascular diseases (4%), chronic obstructive pulmonary disease (2%) and cerebrovascular disease (2%). Five patients ≥60 yrs. had had tuberculosis. The proportion of patients ≥60 yrs. who underwent surgery decreased as the number of comorbid conditions per patient increased.

Conclusions. The use of external radiation for diagnostic and therapeutic procedures for tuberculosis might explain the relatively high prevalence of former tuberculosis in elderly TC patients. The number of comorbid conditions affected the choice of surgical therapy for elderly patients.

Introduction

Comorbidity in cancer patients may have prognostic significance and it may increase the complexity of care. Moreover, excessive rates of comorbid conditions may give aetiological clues. Patients treated in referral centres or included in clinical trials represent a selected population with fewer comorbid conditions and therefore probably a better prognosis than those treated in general hospitals (1,2).

The prevalence of concomitant diseases and their effect on prognosis have been described previously for several cancer types (3,4,5,6). The results of these studies indicated that the number of comorbid conditions increased with age and that patients with concomitant diseases were treated less aggressively and/or had a worse prognosis (after adjustment for age and stage of disease) (3,4,5).

We studied the age-specific prevalence and distribution of concomitant diseases in thyroid cancer (TC) patients in relation to age, histological type of the tumour and treatment in a series of unselected patients treated in general hospitals in southern Netherlands since 1993.

Subjects and methods

The Eindhoven Cancer Registry (part of the Comprehensive Cancer Centre South) has collected data on patients with newly diagnosed cancer since 1988 in a region in the southern Netherlands with 2.1 million inhabitants. About 11,000 newly diagnosed cancers are registered annually.

Data on histological type of the tumour, stage, therapy and co-morbidity were obtained from the pathologist's reports and from the patient records in both the hospitals and the two regional radiotherapy institutes.
The pathological classification was in accordance with the recommendations of the World Health Organization (7); stage was classified according to the TNM-classification (8). Patients with non-Hodgkin's lymphoma (NHL) originating from the thyroid were excluded because of the different nature of this malignancy.
Data on clinically relevant concomitant diseases listed in the patient's clinical record, have been registered for all newly diagnosed cancer patients since 1993, using an adapted version of the list of Charlson (9). Hypertension and diabetes mellitus were only included in case of current treatment. A validation study of consecutive patients with lung, endometrial and prostate cancer was performed in 1996-97 by checking the completeness and accuracy of the data on co-morbidity as recorded by the registry (5,6). There were some indications of underregistration of cardiovascular diseases.
Between 01-01-1993 and 31-12-1996 164 new TC patients (41 males, 123 females) were registered: 101 papillary (63%), 32 follicular (19%), 12 medullary (7%), 13 anaplastic TC (7%) and 5 "other" (4%), with a mean age of 48, 53, 46, 66 and 76 years, respectively.
The prevalence of co-morbidity was analysed according to gender, age, histological type of the tumour and stage; furthermore the association with therapy was studied.

Results

Information on co-morbidity was available for 151 TC patients (92%); 32% of these patients had at least one concomitant disease (see Table 1).
The most frequent concomitant condition was hypertension (18%); other concomitant conditions were other cancers (8%), diabetes mellitus (7%), cardiovascular diseases (4%), chronic obstructive pulmonary disease (COPD; 2%) and cerebrovascular disease (2%). Five (all ≥65 yrs.) out of the 8 patients with "other diseases" had had tuberculosis. Of the 13 (previous or simultaneous) other malignancies 2 were Hodgkin's lymphoma, 1 NHL, 1 multiple myeloma, 1 breast, 1 ovary, 1 kidney and 1 skin cancer and 1 cancer of the oral cavity (4 unknown). The time intervals between treatment of the lymphomas and diagnosis of TC were 3, 15 and 15 years, respectively; one patient had received radiotherapy and one radiotherapy and chemotherapy (1 unknown). The tumour site and/or treatment of the other malignancy was similar for all histological types of TC.
Males had more smoking related concomitant diseases (COPD, cardiovascular diseases) and hypertension than females (Table 2). The proportion patients without concomitant diseases decreased from 86% among patients <45 yrs of age to 31% for patients ≥60 yrs. In patients ≥60 yrs hypertension, diabetes, other malignancies and cardiovascular and cerebrovascular diseases were clearly more common.
The percentages papillary, follicular and medullary TC patients without comorbid conditions were 64%, 63% and 67%, respectively; the proportion anaplastic TC patients without comorbid conditions was, however, 31%, due to the fact that these patients were older. Hypertension was more prevalent in papillary TC (18%); follicular TC patients had more other malignancies (19%). Number or type of co-morbid diseases was not related to stage .
The proportion patients <60 yrs receiving surgical therapy (93%) was not affected by the number of concomitant diseases, whereas the proportion patients ≥60 yrs who underwent

surgery decreased with increasing number of concomitant diseases (surgery was performed on 15 out of 17 patients without concomitant diseases (88%), on 13 out of 16 patients with one (81%) and on 8 out of 15 patients with >1 concomitant disease (53%), respectively (Chi-square for trend: 4.95; p=0.026)).

Discussion

An increase in the prevalence and number of concomitant diseases with age has also been found in both general practice registrations and studies on other cancers in the Netherlands (6,10). In the present study the number of comorbid conditions only affected the choice of treatment and therefore prognosis for patients ≥60 yrs. It was not possible to study the effect of co-morbidity on prognosis because of the short follow-up period and the good prognosis of TC in general.

The prevalence of previous or simultaneous malignancies in TC patients was in accordance with percentages reported for other cancer patients (6). However, an unusually high number of previous haematological malignancies was found. The treatment of these haematological malignancies with intensive external radiotherapy and/or chemotherapy could have been carcinogenic (11).

The prevalence of diabetes mellitus (type I and II) in the Netherlands in general practice registrations and in studies on co-morbidity in other cancer types (<45 yrs. 0.6%, 45-59 yrs. 2.0% and 60-74 yrs. 6.3%, respectively) was lower than that registered in this study (6,10); the prevalence established in case-finding screening projects, however, was higher (≥50 yrs. 18-26%, including impaired glucose intolerance) due to the detection of unrecognized asymptomatic cases (12). The relatively high prevalence in this study may be explained by the fact that most patients with TC were treated by an internist with endocrinological interest who is more likely to screen for glucose intolerance.

Five patients ≥60 yrs. had suffered from tuberculosis. The expected number of cases of tuberculosis would be 1-2, based on data derived from the Netherlands Tuberculosis Register (15). A possible explanation for this increase could be the frequently repeated relatively high doses of radiation to the chest and head and neck region for diagnostic purposes during long-term surveillance (personal communication, R.Daemen MD, Dept. of Tuberculosis Control, Municipal Health Service, Eindhoven) (13,14).

Conclusions: among TC patients the incidence of haematological malignancies and tuberculosis was increased, both probably due to exposure to external radiation. The high diabetes rate is likely to be due to screening. In the elderly, an increasing number of comorbid conditions led to less surgical treatment. The registration of co-morbidity needs to be continued to confirm our findings and to study the effects of co-morbidity on prognosis.

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Table 1. Number of concomitant diseases per patient.

Number of concomitant disease	males n=41	females n=123
	%	%
none	61	60
1	15	23
2	12	5
3	2	2
4	5	1
unknow	5	9

Table 2. Co-morbidity according to gender and age in patients with thyroid cancer, 1993-96. Patients with unknown co-morbidity are excluded. Numbers are percentages; total >100% because some patients had more than one co-morbid condition.

	males n=41	females n=123	≤45 yrs. n=59	45-59 yrs. n=41	≥60 yrs. n=64
	%	%	%	%	%
none	61	60	86	68	31
other malignancy	7	8	5	5	13
COPD	5	2	2	-	5
cardiovasc. diseases	7	3	-	-	11
hypertension	22	17	2	10	39
cerebrovasc. disease	2	2	-	-	5
diabetes mellitus	5	7	-	5	14
other	10	3	3	-	9

COPD: chronic obstructive pulmonary disease.

Chapter 3.4.

Second malignancies following thyroid cancer diagnosed since 1960: a population-based study.

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Abstract

Background. Thyroid cancer (TC) has been associated with an increased risk of subsequent tumours and some of these tumours (e.g. leukaemia and urinary tract cancer) are thought to be due to the use of radioactive iodine (^{131}I). We studied the incidence and spectrum of second cancers to determine cancers related to TC and possible carcinogenesis of ^{131}I.

Design. Retrospective study.

Setting. Cancer Registry, Comprehensive Cancer Centre South, Eindhoven, the Netherlands.

Methods. Data on histological type and treatment (e.g. ^{131}I ablation) were collected on all 343 TC patients registered from 01-01-1960 to 31-12-1992; vital status was determined up to 01-04-1994. A subsequent tumour was defined as any tumour with an incidence date following the diagnosis of TC. The total cohort of TC patients was matched with the register of the Eindhoven Cancer Registry and all subsequent tumours up to 01-04-1994 were introduced. Person-years at risk were calculated for males and females. After determining the expected numbers for the different cancers, the standardised incidence ratio's (SIR's) with the 95% confidence intervals (95%CI) were calculated. The Kaplan-Meier method was used for calculating cumulative incidence curves.

Results. The mean follow-up was 7.6 years. A subsequent tumour was found in 23 TC patients which accounted for a SIR of 1.4 (95%CI 0.9-2.1). Not significantly increased SIRs were found for cancer of the oral cavity, biliary tract, pancreas, uterus, prostate and kidney, melanoma of the skin and leukaemia; no SIRs were found for cancer of the larynx, stomach and bladder, and non-Hodgkin's lymphoma. For papillary TC separatedly, increased SIRs for developing leukaemia (SIR=16.7; 95% CI 2.0-60) and prostate cancer (SIR=9.5; 95%CI 1.1-34) were found. These increased SIRs were not related with ^{131}I ablation therapy.

Conclusion. An etiological association between TC and a spectrum of other cancers such as cancer of the breast, pancreas or urinary tract or leukaemia may exist. ^{131}I treatment is not related with an increased risk for developing a subsequent tumour.

Introduction

Thyroid cancer (TC) is a rare cancer type in The Netherlands affecting relatively young patients. TC has a good prognosis: the relative 10-year survival for differentiated (papillary or follicular) TC patients is about 90% (1,2,3).

The precise etiology of TC is unknown. Geographic, genetic, ethnic, hormonal and environmental factors, and pre-existing thyroid diseases are all considered to be related with TC (4,5). However, the results of the various studies were not conclusive (4). The only well described risk factor for TC is previous irradiation for diagnostic and/or therapeutic purposes (4,5,6).

In the majority of studies originating either from population-based cancer registries or large referral centres, TC patients had a slightly increased overall risk for developing a second cancer: standardised incidence ratio's (SIRs) ranged from 0.95 to 1.51 (7-14); the spectrum of second cancers, however, consisted of a selected number of cancer types, indicating a possible relation between TC and some other cancer types.

Radioactive ^{131}Iodine (^{131}I) therapy is nowadays considered to be a safe procedure for the ablation of remnant thyroid tissue and/or metastases (13-16). Earlier studies of patients who received relatively high doses suggested an association between ^{131}I treatment and an increased

risk for developing subsequent leukaemia and bladder cancer (12,17).
We studied the incidence and the spectrum of second cancers following TC to determine cancers related to TC and to determine the possible role of ^{131}I treatment in initiating a malignancy.

Subjects en methods
The Eindhoven Cancer Registry (part of the Comprehensive Cancer Centre South (IKZ) since 1983) collects data on patients with newly diagnosed cancer since 1955. The registry covers a region with about 1 million inhabitants in the southeastern part of The Netherlands. All hospitals and the regional radiotherapy institute participate in the cancer registry. The patient data, concerning the incidence date, histological type and therapy of TC and the incidence date and site of the subsequent tumour(s), were derived from copies of the pathologists' records and patients' files in the hospitals and the radiotherapy institute.
The pathologic classification of TC was in accordance with the recommendations from the World Health Organization (18).
Information about vital status up to 01-04-1994 was obtained for 327 patients (95.3%).
In the period 01-01-1960 - 31-12-1992 343 patients (103 males, 240 females) with newly diagnosed TC (ICD-O code 193 or non-Hodgkin's lymphoma (NHL) primary originating from the thyroid) were registered. Papillary TC was present in 149 patients (43%), follicular TC in 111 patients (32%), medullary TC in 12 patients (4%), anaplastic TC in 28 patients (8%) and other types in 49 patients (13%; including 6 NHL).
Forty-six (31%) papillary and 39 (35%) follicular TC patients were referred to the radiotherapy institute for ^{131}I ablation therapy; almost all patients received a dose of 50 mCi.
A subsequent tumour was defined as any tumour with an incidence date following the incidence date of TC. To allow comparison with the results of studies from other cancer registries (who excluded non-melanoma skin cancer because of the incompleteness of data), non-melanoma skin cancer was analyzed separatedly. The registration of non-melanoma skin cancer (basal cell and squamous cell cancer of the skin) can be considered as "complete" for the region of the Eindhoven Cancer Registry (19).
Analysis. The total cohort of 343 TC patients was matched with the register of the Eindhoven Cancer Registry and all subsequent tumours until 01-04-1994 were introduced. Person-years at risk were calculated separatedly for males and for females and for 5-year intervals. The expected numbers for the different cancer types were calculated from the age- and sex-specific incidence rates for the regional population. The standardized incidence ratio (SIR) was calculated as the ratio of the observed to the expected numbers; the 95% confidence interval (95%CI) was determined by assuming the observed number of cases to be distributed as a Poisson variable. Cumulative incidence curves of subsequent tumours were calculated using the Kaplan-Meier method; comparisons between groups were made by means of the log-rank test. The Cox's regression model was used to assess the relative risk (RR) with 95%CI for developing a subsequent tumour.

Results
The mean follow-up of the 343 patients was 7.6 years; 30% of patients were followed for $\geq$10 and 10% $\geq$20 years. In total 23 TC patients (6.7%) had a second tumour; the clinical

characteristics of these patients are listed in Table 1. The TC patients with a second tumour were comparable to those without a second tumour for the male/female ratio, mean age and the distribution of histological types. The prevalence of a second tumour was not significantly related to age, stage at diagnosis, period of diagnosis, type of hospital or initial therapy. The cumulative incidence rate of subsequent tumours was 7% after 10 years and 21% after 20 years, respectively (Figure 1).

SIR's for all cancer and for the different cancer sites separatedly are shown in Table 2: TC patients had a not significantly increased risk of 42%, partly due to an excess of relatively rare tumours, such as pancreas cancer, leukaemia or melanoma of the skin. No cancer of the stomach, bladder or larynx, or NHL occurred (expected number 0.9, 0.5, 0.1 and 0.4, respectively).

The risk of developing a second tumour was determined separatedly for non-melanoma skin cancers: the number of TC patients with one or more non-melanoma skin cancer was 8 (1 male; 7 females), which accounted for a SIR of 2.0 (95%CI 0.6-3.4).

Differentiated thyroid cancer. Seventeen patients with differentiated TC (6.5%) had a second malignancy. Papillary TC patients had significantly increased risks for developing, leukaemia (SIR=16.7 (95%CI 2.0-60)) and prostate cancer (SIR=9.5 (95%CI 1.1-34)). These increased risks were not related to the use of ^{131}I ablation therapy. The cumulative incidence rate related to histological type or follow-up treatment are presented in Figure 2 and 3, respectively. We found relatively more second tumours in males (RR=1.2 (95%CI 0.4-3.6), in elder patients (45-59 yrs. vs. <45 yrs.: RR=3.2 (95%CI 0.8-12.1) and >60 yrs. vs. <45 yrs.: RR=4.4 (95%CI 1.4-14.0), respectively), in follicular TC (RR=1.8 (95%CI 0.7-4.9)) and in patients not treated with ^{131}I (RR=1.8 (95%CI 0.5-6.5); 3 of 83 patients treated with ^{131}I developed a second tumour).

Discussion

TC patients treated in general hospitals in Southeastern Netherlands had a, not statistically significant, increased risk for developing a second malignancy: the overall excess risk of about 40% is in accordance with the results from most other studies (see Table 3) (7-14). The risk of second tumours was not related to histological type of TC.

An association between TC and leukaemia was found by Brincker et al., Edmonds et al. and Teppo et al. and it was suggested that the increased risk of developing leukaemia was due to the therapeutic use of relatively high doses ^{131}I (12,17,20). Differentiated TC patients who underwent ^{131}I treatment in our region received in the majority of cases an ablation dose of 50 mCi. The use of such relatively low dose has not been related with the development of leukaemia (13,14,15,21). We showed that the papillary type of TC was associated with subsequent leukaemia, but that no association existed with ^{131}I ablation therapy. Probably papillary TC and leukaemia share the same riskfactors (e.g. previous external irradiation) (5,22).

It is unlikely that the detection of the majority of subsequent tumours is the result of close medical surveillance of the TC patients only, because it concerns relatively rare tumours who would not remain obscure. We suppose, however, that some etiological association might exist between TC and malignancies such as cancer of the urinary tract (kidney, bladder), pancreas, salivary gland or central nervous system (CNS) cancer, or melanoma. Arguments in favor for this association are: the spectrum of second tumours is more or less the same in the various studies (increased SIRs for urinay tract cancer were found in 6 studies (7,9-13), for

melanoma in 2 studies (11,14), for CNS cancer in 2 studies (8,10) and for pancreas cancer in one study (7)), some tumours are found before and after the diagnosis of TC (in our registry we found 2 women who developed breast cancer at the age of 32 and 48 years with subsequent TC after 2 and 5 years, respectively, and one women having salivary gland cancer at 43 years before the diagnosis of TC 15 years later) (23,24), the second tumours developed irrespective of ^{131}I treatment, and tissues accumulating ^{131}I share also other characteristics (25).
The number of observed breast cancer was higher than the expected number. An association between breast cancer and TC has been described previously by several authors (SIR 1.9-2.4) (7,9,12,23); others, however, were unable to confirm the association (10,11,13). TC and breast cancer might share some aetiological factors, such as genetic, hormonal and environmental (repeated diagnostic or therapeutic radiation) (4,5,23).
In conclusion, TC patients showed a slightly increased risk for developing a second tumour, largely due to relatively rare cancers. An aetiological association between TC and a spectrum of cancers such as breast, pancreas or urinary tract cancer or leukaemia may exist. ^{131}I treatment with relatively low doses is not related with the development of a subsequent tumour.

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Table 1. Clinical characteristics of 23 thyroid cancer patients with a second tumour following thyroid cancer.

	n
Gender:	
- male	10
- female	13
Mean age at diagnosis:	54.1 years
Histological type thyroid cancer:	
- papillary	9
- follicular	8
- medullary	1
- anaplastic	1
- other	4

Table 2. Second malignancies and standardised incidence ratio's (and 95% confidence intervals (SIR (95%CI)) among 343 thyroid cancer patients in Southeastern Netherlands, 1960-92, specified for organ sites.

cancer site	observed	expected	SIR (95%CI)
all sites*	23	16.22	1.42 (0.9-2.1)
oral cavity	1	0.06	15.43 (0.4-85.9)
colon/rectum	2	2.42	0.83 (0.1-3.0)
biliary tract	1	0.28	3.61 (0.1-20.1)
pancreas	2	0.39	5.12 (0.6-18.5)
respiratory tract	2	1.96	1.02 (0.1-3.7)
melanoma	2	0.34	5.86 (0.7-21.1)
breast	5	3.60	1.39 (0.5-3.2)
corpus uteri	2	0.57	3.54 (0.4-12.8)
prostate	3	0.66	4.57 (0.9-13.4)
kidney	1	0.40	2.48 (0.1-13.8)
leukaemia	2	0.31	6.55 (0.8-23.7)

*: non-melanoma skin cancer excluded.

Table 3. Comparison of studies on second malignancies following thyroid cancer.

	country	period	number	mean follow-up (yrs)	2nd tumours (%)	SIR (95% CI)
population based studies						
Tucker (1985)	USA (Conn.)	1935-82	2284	9	169 (7.4)	1.49 (1.3-1.7)
Osterlind (1985)	Denmark	1943-80	1935	5.6	78 (4.0)	0.96 (0.76-1.20)
Hrafnkelsson (1989)	Iceland	1955-84	383[P]	-	68 (17.8)	1.5 (1.1-1.9)
Hall (1990)	Sweden	1958-75	2968	12	283 (9.5)	1.18 (1.03-1.31)
Akslen (1992)	Norway	1955-85	3658	8.4	200 (5.5)	1.01 (0.88-1.16)
this study	The Netherlands	1960-92	343	7.6	23 (6.7)	1.42 (0.9-2.1)
referral centers						
Edmonds (1986)	UK	1949-82	258[1]	11.2	18 (7.0)	1.51 (p=0.049)
Hall (1991)	Sweden	1950-75	834[1]	-	99 (11.9)	1.43 (1.17-1.75)
			1121[2]	-	122 (10.9)	1.19 (0.98-1.42)
Dottorini (1995)	Italy (Varese)	1960-93	730[1]	7.4	24 (3.3)	1.19 (0.76-1.77)
			201[2]	10.3	7 (3.5)	0.95 (0.38-1.95)

P: papillary thyroid cancer only
1: treated with ^{131}I
2: not treated with ^{131}I.

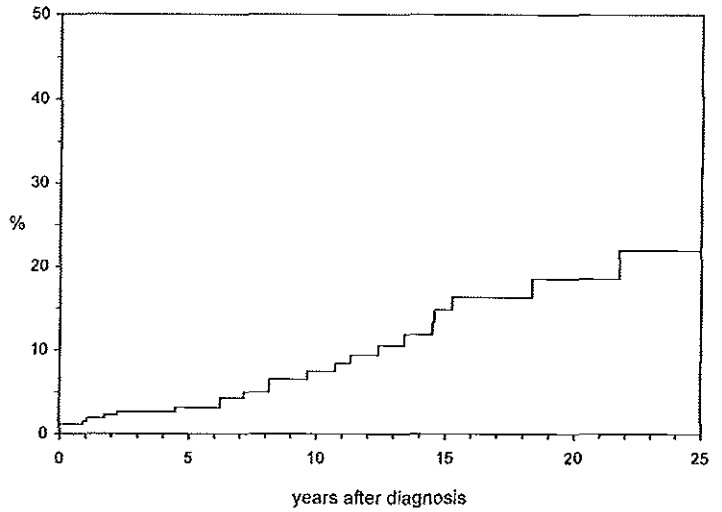

Figure 1. Cumulative incidence rate of a second tumour following thyroid cancer (all histological types; n=343).

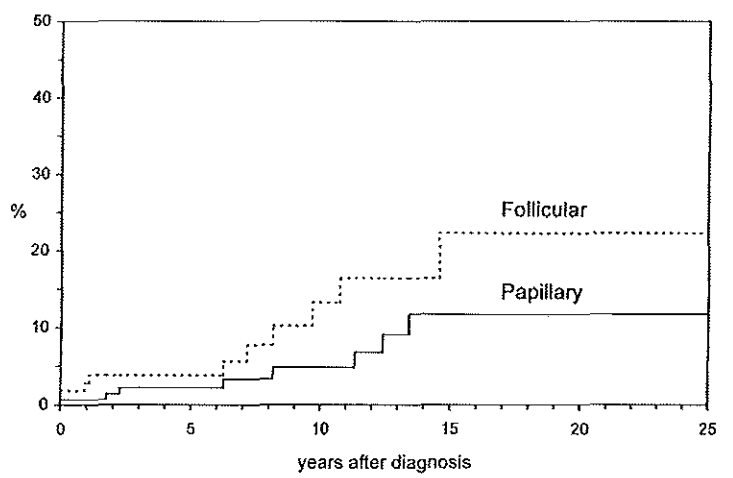

Figure 2. Cumulative incidence rate of a second cancer in 149 patients with papillary and 111 patients with follicular thyroid carcinoma.

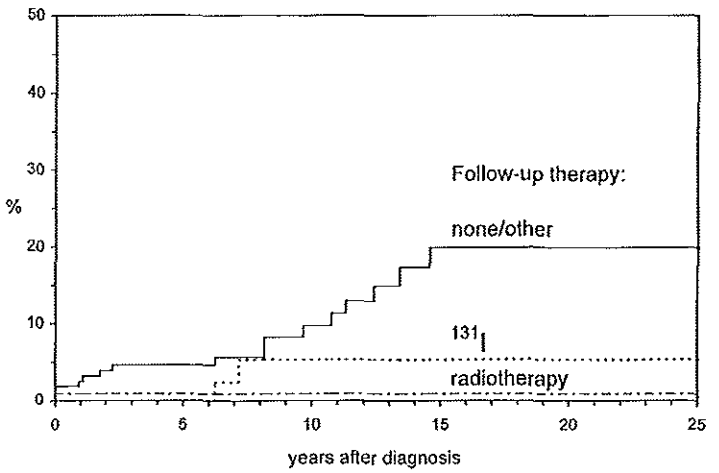

Figure 3. Cumulative incidence rate of a second cancer in 260 patients with differentiated thyroid carcinoma according to the follow-up therapy: external radiotherapy, Jodium-131 ablation therapy, or other or no follow-up treatment.

Chapter 4.

General discussion.

In this thesis, studies on postpartum thyroid dysfunction (PPTD) and thyroid cancer have been presented. These studies were all performed in the southeastern part of the Netherlands. In this chapter, the internal validity and generalizibility (external validity) of these studies are discussed, as well as their possible implications for public health policies and further research.

4.1. Validity and generalizibility of the results.

An important problem in the interpretation of study results in general concerns the validity of the data presented. Internal validity refers to questions concerning potential biases and confounding: do the data really measure what we want them to measure, are the data obtained from a selected population (selection bias), or are the results adjusted for possible confounding factors? Generalizibility (external validity) involves the question as to what extent the results can be generalized or extrapolated to other populations. Both internal validity and generalizibility in relation to the studies on PPTD and thyroid cancer are discussed in brief in the following.

Post partum thyroid dysfunction. In the PPTD studies we followed prospectively a cohort of 310 Caucasian women during pregnancy and in the first year after delivery. All women resided in the Kempen-region in the southeastern part of the province Noord-Brabant. Sampling or selection bias is unlikely since all consecutive pregnant women who came for their first visit to the local midwife or the obstetrical department of the St Joseph Hospital Veldhoven (together covering >90% of all pregnancies in the region) were asked to participate, and the mean age and the parity of the non-participating women were similar to that of the participants. Moreover, the prevalence of TPOAb of 10% was consistent with other studies in Caucasian women and the distribution of psychosocial variables was comparable to that in the general population in the southeastern part of Noord-Brabant (1-5). Recall or information bias was avoided by the prospective design of the study. Moreover, both the researcher and the participating women were blinded for the results of the thyroid function tests.

A confounding factor may be statistically significant related to the disease under study but is lacking a causative relation. Confounding arises when the different groups under study are not equal in a factor related with the disease other than the factor under study. Adjusting for confounding is possible by stratification or matching for putative confounding factors. In the studies described in the chapters 2.1, 2.3 and 2.4 we adjusted for confounders by performing multivariate analyses, e.g. in the multivariate analysis of the association between depression and the presence of TPOAb we introduced in the model the various determinants of depression known from the literature and the results from the thyroid function testing (see Chapter 2.3). In our study on the relation between cell mediated immunity disturbances and PPTD we matched for age and parity because these factors were supposed to have influence on the

development of PPTD.
Thyroid cancer. The completeness and reliability of the data registered by the Eindhoven Cancer Registry have been evaluated during 1981-83 (6,7). The area with a complete registration of all newly diagnosed cancers has been expanding since the early 60's from a region around the city of Eindhoven to a region which comprises 51 municipalities with about 1 million inhabitants. The registration can be considered as "complete" since the early 70's onwards for almost all cancer types, including throid cancer. The registration procedures remained the same since the 60's and the data were collected from multiple sources in the health care system (e.g. the patient's records in the hospitals, the regional pathologic institutes, the radiotherapy department in Eindhoven and by regular checks with oncological centres). As a consequence, selection bias does not exist since all detected thyroid cancer have most likely been registered.
An important problem in studying the trends in incidence is the indolent course of a considerable proportion of papillary and follicular thyroid cancer. This fact may lead to both under- and overestimation of the number of thyroid cancers. Overestimation might have been due to the detection of small asymptomatic papillary thyroid cancer in surgical specimens of patients operated for other thyroid disorders. Underestimation is due to the fact that up to onethird of thyroid glands contain occult papillary tumours and the prevalence of these occult thyroid cancers is unclear, in part because of the very low number of autopsies in the Netherlands.
It can be concluded that the results of the studies on PPTD and on thyroid cancer are valid and may be generalised to other populations in the Netherlands and western societies.

4.2. Thyroid dysfunction in gestation and postpartum.
We found indications for the existence of two forms of PPTD (see Chapter 2.1 and 2.2):
1. an autoimmune form of PPTD characterized by symptoms and signs of hypothyroidism (and hardly of hyperthyroidism) and/or depression, the presence of TPOAb and disturbances of cell mediated immunity similar to that in autoimmune endocrine (thyroid) disease. Onethird of the women with this form of PPTD needed (transient) thyroid hormone replacement therapy; they appear to be at risk for a relapse of PPTD at a rate of 40% after a following pregnancy and for developing permanent hypothyroidism at a rate of 5% per year (8,9). Also, these women had an increased risk for having or developing depression (Chapter 2.3). Therefore, a long-term follow-up of these women should be considered;
2. a non-autoimmune form of PPTD characterized by transient hyperthyroidism alone with mild or absent symptomatology. This form did not have the characteristic humoral or cell mediated immune disturbances of AITD. The etiology was obscure in the majority of the cases and we believe that follow-up of thyroid function is not indicated as all women remained euthyroid during follow-up.
The results of our and of others studies indicate that the autoimmune form of PPTD represents an exacerbation of a chronic autoimmune process and that PPTD is part of the spectrum of autoimmune thyroid diseases (AITDs) (10,11). Arguments in favour of this view are: the familial predisposition, the linkage with HLA-DR3, -DR4 and DR5, the association with other autoimmune endocrine diseases (such as type-I diabetes mellitus and pernicious anemia), the strong association with TPOAb and the presence of persistent cell mediated immune alterations during pregnancy and after delivery (see Chapter 1.2).
T helper-1 cell mediated processes are considered to be one of the most important pathogenetic

mechanisms in destructive endocrine diseases, including AITDs (12). A direct pathogenetic role of TPOAb in the destructive thyroiditis is questionable. The results of our study presented in Chapter 2.2 are compatible with this view: the percentage activated T cells was increased at all time points during the study in TPOAb positive who truly developed PPTD. The fact that the chronic autoimmune process did not evolve into clinically overt disease during pregnancy might be due to yet not fully developed effector phases, or to a suppression of the destructive T helper-1 mechanisms via the suggested shift from predominant T helper-1- to predominant T helper-2-driven immune response during pregnancy (15).
TPOAb+ women had alterations in various other CMI functions as well from the first trimester of pregnancy onwards, indicating that the autoimmune process was already present at that moment at the level of the immunoregulatory cells. In particular the lowered fMLP-induced monocyte polarization and persistently lowered NK cell numbers are compatible with the state of chronic AITD, and are consistent with CMI abnormalities found in other endocrine autoimmune diseases (13,14).

The use of a strict biochemical definition (both an abnormal TSH and fT4) resulted in an incidence of PPTD of 5.2% in our study (Chapter 2.1). This incidence is similar to that found in studies with the same case definition, i.e. an incidence of PPTD in Caucasian women of 4-7% (1,2). The annual number of women with PPTD in the Netherlands can thus be estimated as 9,500 - 14,000 (incidence 5-7%; number of newborns 190,000-200,000) (2). When subclinical thyroid dysfunction (abnormal TSH alone) was taken into account, the incidence of thyroid dysfunction in the postpartum inclined to 12.4% (half of them TPOAb+). From these women with (sub-)clinical thyroid dysfunction after delivery 19.4% also had a thyroid dysfunction in the first trimester of pregnancy, mainly subclinical hypothyroidism (Chapter 2.1). It might be important to identify these women because of the risk of low fT4 levels during pregnancy for child intellectual and motor development (see Chapter 2.4) and the risk of depression and permanent hypothyroidism in the woman's future life (Chapter 2.1 and 2.3) (8,9,16).

High prevalence rates of depression according to RDC of 13-24% were found both during pregnancy and in the first year after delivery (Chapter 2.3). Harris et al. found in a study of postpartum women comparable prevalences (17); Pop and O'Hara, however, found lower prevalences in the second half of pregnancy and after delivery (18,19). Our results are comparable with the view that depression is not specifically related to the postpartum state ("postpartum depression" as a clinical entity) but is a continuum. Thus the concept of "postpartum depression" as a separate clinical entity need to be revised. Arguments in favor for this view are: depression has a high prevalence in pregnancy and in the postpartum year, but also in non-pregnant women (20). The most consistent risk factor was the occurence of major life events and our data are in accordance with data from the literature (18).
The pathogenesis of depression is multifactorial and several psychosocial and biologic determinants are involved. The implications of our study for the prediction and treatment of depression are:
- women who have suffered from depression in the postpartum period are at risk for developing depression in future life because of the high recurrence rate of depression;
- TPOAbs are an independent risk factor for depression and therefore TPOAb+ women need

a long-term follow-up not only for regular evaluation of their thyroid function but also for the diagnosis of a possible depression. The excess risk that can be attributed to a risk factor in the population (in case of the study presented in Chapter 2.3: TPOAb as a risk factor for depression) can be determined by calculating the population attributable risk (PAR = $R-R_0/R$; R = risk in the whole study group; R_0 risk in the unexposed group = percentage depression in the TPOAb negative group). PARs calculated for depression attributable to TPOAb were 4% at 12 and 32 weeks gestation and 13, 6, 3, 1 and 0% at 4, 12, 20, 28 and 36 weeks postpartum, respectively. These results indicate that the contribution of depression associated with TPOAb is limited. However, it might be important to identify these women because it might be hypothesed that treatment with thyroxine or antidepressivants is beneficial.

Several risk factors for PPTD have been described previously (see Chapter 1.2). However, these risk factors have been studied at an univariate level without correction for possible interactions, although in some studies cases and controls were matched for age and parity. The study described in Chapter 2.1 was the first in which a multivariate analysis was performed to determine independent risk factors.
Apart from the wellknown risk factor TPOAb (RR=27.2), we found smoking and bottle feeding independently related with PPTD: women who had ever smoked and women who did not start breastfeeding had significantly increased risks (RR=3.1 and RR=11.1, respectively).
A relation between smoking and PPTD was also found by Fung et al., but others could not confirm the relation (21,22). This discrepancy can be explained by differences in study design (only current smokers or also ex-smokers in analysis) or a different distribution of smokers in the population. Smoking during pregnancy has been related with obstetrical complications and low birth-weight infants and disturbances of child development (23). We add a new argument to the active campaign to prevent smoking in young women who might become pregnant: the possible prevention of an exacerbation of AITD in the postpartum period.
We also found that breast feeding might have a protective effect (Chapter 2.1). The mechanism of this presumed protective effect is unknown, but it might be suggested that some immunomodulating process associated with the pregnant state (see also Chapter 2.2) remains operative during lactation. Also from this point of view it might be important to stimulate women to start breast feeding after delivery.

Maternal hypothyroidism in gestation has been associated with disturbances of mental and motor development of the child. Women with (subclinical) AITD (as determined by the presence of TPOAb) are at risk for developing hypothyroidism during pregnancy, especially when residing in iodine-deficient regions (16,24). In a study of preschool children, Pop et al. found that children from mothers positive for TPOAb in the third trimester of pregnancy showed an impaired development compared to children from mothers negative for TPOAb (3). The differences between the two groups persisted after correction for maternal thyroid function and mood disturbances, and other psychosocial and child related variables related to child development. However, information on the maternal thyroid function in early pregnancy was not available and other environmental and psychosocial factors who might have affected the child's development were not studied. The study described in Chapter 2.3 was performed to confirm the results from Pop et al. and to include information on thyroid function and TPOAb status in early pregnancy because the fetal thyroid does not produce thyroid hormones in the

first trimester, and the developing brain might well be dependent upon maternal thyroid hormone supply during the early stage of pregnancy (3,25). Child development was assessed within ten months after delivery to avoid bias from environmental and psychosocial factors supposed to interact with child development. We have shown that after correction for psychosocial and medical factors low and low-normal fT4 concentrations at 12 weeks gestation correlated with lower scores on the Bayley Psychomotor Developmental Index (PDI) scale at 10 months of age. The results of this study indicated that even in our region with sufficient iodine-intake low fT4 concentrations in early pregnancy do exist and that these low fT4 concentrations might have a negative effect on child development. Prolonged follow-up studies of children from mothers with low fT4 and/or TPOAb during pregnancy are needed to evaluate whether the arrear in development is temporarily or permanent.

One of the main objectives of the studies described in the chapters 2.1 and 2.2 was to evaluate if the prediction of PPTD could be improved by taking into account the time of TPOAb testing, the combination with other anamnestic determinants, and/or CMI parameters related with AITD. We found that the sensitivity of TPOAb testing alone was highest at 12 weeks gestation (67%) and that the positive predictive value depended upon the cut-off point of TPOAb testing (Chapter 2.1). Our results are comparable with those from other studies (sensitivity 60-80%; positive predicitive value 40-60%) (1,2,21,26). The combination of the results of TPOAb testing with the independent risk factors smoking and bottle feeding has limited additional value for predicting PPTD: the positive predictive value increased slightly; on the other hand, the already low sensitivity decreased. CMI parameters alone or in combination with TPOAb did not yield higher sensitivities or positive predictive values for identifying women at risk for PPTD.

Screening can be defined as "the systematic application of a test or inquiry to identify individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action, among persons who have not sought medical attention or account of symptoms of that disorder" (27). A screening programme should be an organized public health activity and is justified only when the tested individuals might benefit from the proposed intervention. Examples of screening programmes in the Netherlands are the national programmes for breast and cervix cancer screening, the screening of all newborns for phenylketonuria and congenital hypothyroidism and the screening of all pregnant women in the first trimester of pregnancy for bloodgroup/Rhesus, Hepatitis B surface antigen and syphilis.
Whether a screening programme for all pregnant women for TPOAb in order to identify those at risk for PPTD (and related disorders) is worthwhile remains debatable. Some promote screening because of the risk of abortion, the risk of developing hypothyroidism in gestation or in future life, or the risk of PPTD and/or depression (10,16,24,28,29). Others state that because of the low predictive value of TPOAb and the absence of severe clinical symptoms of PPTD a screening programme is not justified (30,31). However, screening for (subclinical) hypothyroidism and identification of those at risk for hypothyroidism may be worthwhile in some defined risk groups (e.g. pregnant women with type-I diabetes mellitus or women with unexplained infertility) (32). Danese et al., Meier et al. and Weetman stated that TPOAb and/or TSH testing to screen for (subclinical) hypothyroidism in women over 35-40 years may be cost effective: the costs per quality-adjusted life year were about 9,200 US Dollars and were

comparable with that for breast cancer screening and much lower than that for cervical cancer screening (32-35).
The studies described in Chapters 2.1, 2.2, 2.3 and 2.4 indicate that TPOAb screening of all pregnant women in the first trimester of pregnancy might be considered worthwhile for several reasons:
- the detection of women at risk for hypothyroidism/low fT4 in gestation is important to identify those at risk for obstetrical complications and/or impairment of child development (Chapters 2.1 and 2.4);
- the identification of TPOAb+ women is of clinical interest because these women are in particular at risk for thyroid dysfunction in gestation, in the postpartum period and/or future life and, to a lesser extent, for depression (Chapters 2.1, 2.2 and 2.3).
The most suitable screening test is clearly TPOAb testing which should be performed in the first trimester of pregnancy and, if positive, followed by a fT4 assay (Chapter 2.4). It might be worthwhile to determine the number of activated T cells in TPOAb+ women to predict PPTD development (Chapter 2.2). In future studies this diagnostic approach and possible therapeutic interventions (e.g. L-thyroxine during or even before pregnancy) should be evaluated. Also, a cost-benefit analysis of screening for TPOAb during pregnancy should be performed. In such an analysis the costs of screening and treatment should be compared to the benefits of the (possible) prevention of obestetrical complications, symptomatology of PPTD, depression and the earlier detection of hypothyroidism, and the possible prevention of disturbances of child development.

4.3. Thyroid cancer.
In Chapter 3.1 the (trend in) incidence of thyroid cancer was described. The incidence in southeastern Netherlands was similar to that in the surrounding countries (see Table 1 in Chapter 1.3). In the 80's the incidence of papillary thyroid cancer (particular in women) peaked and returned to the baseline level in the early 90's (7). In studies from Akslen et al. in Norway and Zheng et al. in Connecticut, USA, an increase of the incidence of papillary thyroid cancer among males and females was found and in both studies a strong birth cohort effect occurred with the highest incidence rates in the cohorts born between 1910 and 1945 (and decreasing incidence rates in the cohorts born since 1945) (36,37). The increase of the incidence correlated with the introduction and widespread use of external radiation treatment for various benign conditions in childhood in these birth cohorts with highest incidences (37,38). It is unlikely that the peak in incidence was due to earlier diagnosis only, i.e. after the introduction of fine needle aspiration biopsy or close medical surveillance because the mean age at diagnosis remained the same for all histological types during the period 1960-1992 (e.g. the mean age at diagnosis for papillary thyroid cancer was stable about 43 years) (B. Hansen, personal communication) (36).

The consensus conference on the management of differentiated thyroid cancer in the Netherlands (1987) discussed guidelines for the diagnostic strategy and for surgical and additional ^{131}I therapy (39,40). The proposed guidelines were based on recent literature and discussions in workshops with participants from different countries. However, controversy remained on the extent of surgical therapy.
In 1993, the Dutch Health Council report on the quality and allocation of care in oncology

stated that oncological care should be organised in such a way that each patient receives the best possible care by the standards that apply at the time (41). Also, the report recommended that for thyroid cancer some form of concentration of tasks should be considered depending upon the regional infrastructure.
In the studies presented in the Chapters 3.1 and 3.2 we have evaluated retrospectively topics concerning the treatment of thyroid cancer patients in southeastern Netherlands. We showed that patients were treated in all hospitals in the region (approximately 2-4 per year) and that an increasing proportion was first seen by an internist (in the majority of cases an internist with endocrinological interest). Also, we showed that an increasing proportion of patients (in particular those with differentiated thyroid cancer) underwent more extended forms of surgery (total thyroidectomy with/without regional lymph node dissection) and that ^{131}I ablation therapy has been administered increasingly. Lastly, we showed that the prognosis of thyroid cancer patients treated in the region was similar to that of patients treated in large referral centres. Overall, it can be concluded that thyroid cancer patients in the area under study received state-of-the-art therapy. However, the number of patients per hospital is low and we were unable to evaluate postoperative complications such as hypoparathyroidism and recurrent nerve lesions (whose prevalence depends on the experience of the surgeon) (42,43). Moreover, the number of thyroid operations (for benign and malignant conditions) has decreased (43a). It might be suggested to stimulate regional cooperation by developing regional guidelines for diagnostic procedures and treatment. The outcomes of the various surgical strategies and their complications should be studied systematically in order to improve the prognosis even further.

Prognostic factors for thyroid cancer have been studied manifold. The study of prognostic factors is important for pre-operative selection of patients who might benefit most from treatment (44). In the studies described in the Chapters 3.1 and 3.2 we found histological type, sex, age at diagnosis and stage of disease related with survival. The results of these univariate analyses were consistent with the findings from other studies: females, younger patients, those with stage I-II disease and those with papillary or follicular thyroid cancer are doing better (45,46,47).
In Chapter 3.2 we described a multivariate analysis of prognostic factors for differentiated thyroid cancer only. Our study was unique in two aspects: we studied the effect of treatment on prognosis in an unselected population and we studied the effects of the various prognostic variables within the first 5 years after diagnosis and after 5 years separatedly. We found that the extent of surgical therapy was not related to prognosis and that ^{131}I therapy had a favourable effect on prognosis in the first 5 years only, and that the effects of the prognostic factors age, sex, histological type and extent of disease were different in the two 5-year period. These findings may explain the differences in outcome between studies with different follow-up periods and strengthen the need to study the results of the different surgical strategies and additional ^{131}I treatment. Such a study to clarify which surgical strategy and follow-up treatment is preferable should be performed at the supraregional or national level and should last for a period of one or more decades.

The study on the prevalence of serious comorbid conditions (Chapter 3.3) and the incidence of second tumours (Chapter 3.4) is important for several reasons:
- the presence of one or more comorbid conditions may have an independent negative prognostic

value and may limit the therapeutic alternatives;
- to illustrate the complexity of care when co-morbidity does exist and the impact on follow-up when an increased risk of developing subsequent malignancies is present;
- co-morbid conditions and subsequent tumours may point at aetiological notions.
In the study on co-morbidity in patients with thyroid cancer (Chapter 3.3) it was shown that the choice of surgical treatment, and therefore probably prognosis, was influenced by the presence of one or more comorbid conditions in patients ≥60 years. The same was found in studies of other cancer types (48). The association between previous hematological malignancies or tuberculosis and thyroid cancer is a confirmation of the wellknown association between the exposure to external radiation for diagnostic or therapeutic purposes (38). Another explanation is the close medical surveillance of these patients.

Although thyroid cancer is a rare type of cancer, it is important to describe its epidemiology. Rare tumours, especially those who appear at a younger age, can act as indicators for environmental factors thought to have effect on the initiation of that tumours. Examples are the studies on the relation between thyroid cancer and the exposure to external radiation and/or ^{131}I in populations in Japan and the Pacific Ocean and, recently, in the Chernobyl region (38). Also, studies on co-morbidity and on second tumours (see Chapters 3.3 and 3.4) are relevant in this respect.

4.4 Thyroid diseases and public health.
Apart from the national screening programma for congenital hypothyroidism, thyroid diseases are not considered to be of great importance for public health policies in the Netherlands. A chapter on thyroid diseases is lacking in both the first and the second edition of the Dutch "Public health status and forecasts" published in 1993 and 1997 (49-53). Based on the findings of these reports policy recommendations are being formulated regarding health care planning, prevention and screening programmes and future research. Furthermore, the estimated costs of endocrine disorders other than diabetes mellitus are limited: 0.6% of the total health care budget in the Netherlands (54). However, these total costs were higher than that for AIDS or lung or breast cancer, and the costs of endocrine disorders will increase with the ageing of the population.
In the foregoing chapters we discussed items showing that thyroid diseases, and in particular AITD and thyroid cancer, should be considered as a public health problem of considerable interest. Arguments for this point of view are:
- the considerable number of new patients with hypothyroidism largely as the result of AITD is 2,250-4,500 per year, based on the results of the Whickham Survey and Dutch sentinel-studies (55,56,57);
- the estimated number of patients using thyroid replacement therapy is 150,000-200,000: the number of patients treated with L-thyroxine is about 15 per general practice (58);
- many hypothyroid cases continue to be unrecognised and remain untreated;
- the association between TPOAb, AITD and depression, the latter being considered as one of the most important public health problems in the Netherlands because of the high prevalence in the population (53). We found that a proportion of depression in pregnant and postpartum women could be attributed to the biologic determinant TPOAb (Chapter 2.3). Perhaps all depressed patients should be tested for their thyroid function and TPOAb status in order to

identify those with (subclinical) AITD and therefore might benefit form L-thyroxine treatment;
- the number of thyroid cancer patients diagnosed and treated since 1970 and still alive is relatively high (about 2,700 in the Netherlands (7)) because of the very good prognosis for the majority of thyroid cancer patients. These patients need specialized care (experienced surgeons and in onethird of the cases ^{131}I ablation therapy; see Chapter 3.2) and long-term surveillance, not only for the detection of recurrences, but also for the evaluation of thyroid replacement therapy and the risk of developing a second tumour (Chapter 3.4) (59).
- thyroid cancer is one of the tumours who should be considered to be registered at a national level because of its low incidence and the complexity of diagnostic procedures and the complexity of care and the need for a long-term follow-up (6).

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Chapter 5.

Summary.
This thesis focuses on epidemiological and pathogenetic aspects of thyroid dysfunction in gestation and in the postpartum period ("postpartum thyroid dysfunction", PPTD) and the epidemiology and pattern of care of thyroid cancer. The questions for the studies in this thesis concentrated on the possibility to predict the outbreak, severity and/or course of the aforementioned thyroid disorders.

In the first part of Chapter 1 the epidemiology of thyroid diseases in the Netherlands was reviewed to be able to put our data in perspective.
A brief description of PPTD and related disorders is presented in Chapter 1.2. Within the scope of this thesis we defined PPTD as any form of clinical thyroid dysfunction (abnormal TSH and abnormal fT4) occurring in the first year after delivery. The incidence of PPTD is 4-8%. PPTD is thought to be part of the spectrum of autoimmune thyroid diseases (AITDs) in the majority of the cases and is strongly associated with the presence of thyroid peroxidase antibodies (TPOAb) during pregnancy and postpartum. PPTD is characterized by hyperthyroidism (with less or no complaints) followed by hypothyroidism (with complaints such as fatigue or weight gain) and finally recovery. PPTD and/or TPOAb have also been associated with depression in the postpartum period. Women positive for TPOAb have a relative risk (RR) of 20-80 for developing PPTD. However, the positive predictive value of TPOAb is limited (40-60%) and therefore screening of all pregnant women to detect those at risk for PPTD remains controversial.
The epidemiology and management of thyroid cancer is reviewed in Chapter 1.3. Thyroid cancer is a rare cancer type in the Netherlands (0.5% of all new cancers) and its incidence is similar to that in the surrounding countries. The only well established risk factor is exposure to external radiation. The prognosis is very good for papillary and follicular cancer, but extremely poor for anaplastic thyroid cancer. Fine needle aspiration biopsy is the test of choice for pre-operative selection of patients and surgery is the initial treatment of choice. ^{131}I ablation is recommended for all differentiated thyroid cancer patients with remnant thyroid tissue.

For the studies on PPTD, depression and its relation with TPOAb and/or thyroid dysfunction, and child development, we followed prospectively a representative cohort of pregnant women residing in the region Kempenland.
In Chapter 2.1 we evaluated if the positive predictive value of TPOAb could be enhanced by taking into account the time of testing or by combining TPOAb with other putative determinants of PPTD. The long-term prognosis of women with PPTD was also studied. We found that the incidence of gestational thyrotoxicosis was 2.1% and of PPTD 5.2%. We confirmed TPOAb

as the most prominent risk factor (RR 27.2) and found smoking habits (RR 3.1) and bottle feeding (RR 11.1) independently related with PPTD. We found that a maximum of twothird of PPTD cases can be predicted from the presence of TPOAb, and the most appropriate time for testing is in the first trimester of pregnancy. The combination of TPOAb testing with anamnestic determinants did not increase the predictive value substantially.
Another approach to improve the predictive value was described in Chapter 2.2: cell mediated immunity parameters who are disturbed in various autoimmune states were studied prospectively in pregnancies followed by PPTD and matched controls in order to determine the usefulness of these parameters in the prediction of PPTD. TPOAb positive women (irrespective of development of PPTD) showed several cell mediated immunity abnormalities such as persistently lower percentages natural killer cells and a lowered monocyte polarization towards chemoattractants consistent with other autoimmune endocrine diseases. An increased percentage of activated T cells in gestation or postpartum discriminated between those TPOAb positive women who did develop PPTD and those who did not. Women at risk for PPTD were most accurate identified by TPOAb testing followed by repeated activated T cell measurement. The findings in Chapters 2.1 and 2.2 are suggestive for the existence of two forms of PPTD: an autoimmune (TPOAb positive) form and a non-autoimmune form who are different in pathogenesis, symptomatology and long-term prognosis.
There appears to exist an intriguing association between the presence of TPOAb as a marker for (subclinical) AITD and depression, e.g. postpartum depression. In Chapter 2.3 we studied the relationship between TPOAb and depression (according to the RDC criteria) during pregnancy and in the 1st year postpartum, also in relation with other determinants of depression, and we studied whether TPOAb positivity in pregnancy predicts depression after delivery. After correction for the possible effects of other determinants for depression (such as educational level, major life events, previous depression, pregnancy related factors and thyroid dysfunction) we found TPOAb and depression significantly related at 12 weeks gestation and 4 and 12 weeks postpartum. Also, TPOAb positivity at 12 weeks gestation was related with an increased risk for developing depression in the postpartum period, about 1 year later (OR=2.8; 95%CI 1.7-4.5). Our findings confirmed the association of TPOAb (as a marker for AITD) and depression and might indicate that AITDs and depression share (in part) a common etiology.
In Chapter 2.4 we present a study on the association between low fT4 levels in early pregnancy and impaired psychomotor development in infancy. Children of women with low or low-normal fT4 in the first trimester of pregnancy showed lower scores on the Dutch version of the Bayley Psychomotor Developmental Index. The detrimental effect of low fT4 appeared to be dose-related. After correction for other determinants who might have affected child development, such as demographic, psycho-social factors and TPOAb positivity, the association continued to exist. It was concluded that low-normal fT4 levels in early pregnancy even in an iodine-sufficient region might have a negative impact on child psychomotor development and that therefore screening of women in early pregnancy for low fT4 and TPOAb should be considered.

The studies on thyroid cancer presented in this thesis were all based on data derived from the Eindhoven Cancer Registry. These data were studied retrospectively for patients registered since 1960.
The studies in Chapters 3.1 and 3.2 describe the trends in incidence and prognosis, and the

trends in treatment, for all thyroid cancer and for differentiated thyroid cancer separatedly. The incidence of thyroid cancer increased from 1.4 to 3.0/100,000/year for females and remained unchanged for males (1.1/100,000/year). The proportion differentiated thyroid cancer increased, whereas the proportion anaplastic thyroid cancer decreased. These findings were comparable to that in the surrounding countries. The prognosis of thyroid cancer patients in Southeastern Netherlands was good and similar to that of patients treated in large referral centres: relative 5 and 10 year survival rates were 80 and 75%, respectively; after 10 years of follow-up no excess mortality occurred.
In all hospitals in the region thyroid cancer patients were treated and patients received increasingly more extended forms of surgery. The treatment for differentiated thyroid cancer appeared to be as recommended by the Dutch consensus conference in 1987 and it was concluded that patients with differentiated thyroid cancer in Southeastern Netherlands received state-of-the-art treatment.
In Chapter 3.2 a multivariate analysis of prognostic factors for differentiated thyroid cancer is presented as well. Our findings were consistent with other studies: females, younger patients, patients with stage I-II disease and patients with the papillary type of tumour did better. However, we found that the effects of the various prognostic factors were different in the first 5 year and after 5 years, and that the extent of surgical therapy did not influence the prognosis and that ^{131}I had a favourable effect within the first 5 years only.
In a study on co-morbidity (Chapter 3.3) the prevalence of comorbid conditions in thyroid cancer patients diagnosed in 1993-96 is described. The number of comorbid conditions did affect the choice for surgical treatment in elder patients. Also, an association between previous hematological malignancies and tuberculosis and later thyroid cancer was found. We were unable to study the possible effect on prognosis because of the short follow-up period.
Second tumours after the diagnosis of thyroid cancer are described in Chapter 3.4. Thyroid cancer patients exhibited a non significantly increased risk of developing a subsequent tumour of 40%, which was in accordance of the results of other studies. For papillary thyroid cancer separatedly, increased risks for developing leukaemia and prostate cancer were found and these increased risks were not related with ^{131}I therapy. It is suggested that some etiological association between thyroid cancer and a spectrum of other cancers does exist.

In the general discussion (Chapter 4) the conclusion and some critical remarks on the studies are finally given. The validity and generalizibility of the results of the studies are discussed (Chapter 4.1): it was concluded that both the studies on thyroid dysfunction and related topics, and the studies on thyroid cancer were valid and representative. The implications of our studies for medical practice, and in particular screening, are discussed in Chapter 4.2. Because of the relative high incidence of PPTD, the association with obstetrical complications and impairment of child psychomotor development, the increased risk of developing permanent hypothyroidism and the association with depression, TPOAb screening of all pregnant women should be considered. For thyroid cancer, it should be considered to study the incidence and the results of the different treatment strategies at the supraregional or national level because of the low incidence and the complexitiy of diagnostic procedures and therapy. To our opinion, thyroid diseases, such as AITD (including PPTD) and thyroid cancer, should be considered as important items for future public health policy in the Netherlands.

Chapter 6.

Samenvatting.
Dit proefschrift beschrijft met name epidemiologische en pathogenetische aspecten van schildklierfunktiestoornissen in de zwangerschap en de postpartum periode ("postpartum schildklierfunktiestoornis"; PPS) en de epidemiologie en behandelingspatronen van schildklierkanker. De onderzoeksvragen voor de studies in dit proefschrift richtten zich op de mogelijkheden om het uitbreken, de ernst en/of het verloop van bovengenoemde schildklierziekten te voorspellen.

Om de resultaten van de studies in perspectief te plaatsen, werd het eerste deel van Hoofdstuk 1 gewijd aan een overzicht van de epidemiologie van schildklierziekten in Nederland.
Een korte beschrijving van PPS en daaraan gerelateerde aandoeningen wordt gegeven in Hoofdstuk 1.2. PPS werd voor dit proefschrift gedefinieerd als iedere vorm van een klinische schildklierfunktiestoornis (zowel afwijkend TSH als afwijkend fT4) optredend in het eerste jaar na de bevalling. De incidentie van PPS is 4-8%. Verondersteld wordt dat de meerderheid van de gevallen van PPS deel uitmaakt van het spectrum van autoimmuun schildklierziekten. Er is een associatie met de aanwezigheid van antistoffen tegen schildklierperoxidase (TPOAb) in serum gedurende de zwangerschap en postpartum. Het klinisch beeld van PPS bestaat uit een periode van hyperthyreoidie (met geen of weinig klachten) gevolgd door hypothyreoidie (met klachten als vermoeidheid of gewichtstoename) en tenslotte volledig herstel. PPS en TPOAb zijn beiden geassocieerd met depressie in de postpartum periode. Vrouwen die seropositief zijn voor TPOAb hebben een relatief risico (RR) van 20-80 voor het ontwikkelen van PPS. De positief voorspellende waarde van TPOAb is echter beperkt (40-60%) en daarom blijft de screening van alle zwangeren om degenen die een verhoogd risico hebben op PPS te identificeren discutabel.
Een overzicht van de epidemiologie en de diagnostiek en behandeling van schildklierkanker wordt gegeven in Hoofdstuk 1.3. Schildklierkanker is zeldzaam in Nederland (0,5% van alle nieuw gediagnostiseerde kankers) en de incidentie is vergelijkbaar met die in de omringende landen. Blootstelling aan radioactieve straling is de enige goed beschreven risicofactor. De prognose voor patiënten met papillair of folliculair schildkliercarcinoom is bijzonder goed; voor die met anaplastisch schildkliercarcinoom extreem slecht. Voor pre-operatieve selectie van patiënten heeft dunne-naald-aspiratie-biopsie de voorkeur; chirurgische behandeling is in eerste instantie aangewezen. Ablatietherapie met radioactief Jodium (^{131}I) is aanbevolen voor alle patiënten met gedifferentieerd (papillair of folliculair) schildkliercarcinoom met resten van schildklierweefsel na operatie.

Om PPS, de relatie tussen TPOAb en/of schildklierfunktiestoornissen en depressie en vroegkinderlijke ontwikkeling te bestuderen, werd een representatief cohort van zwangere vrouwen afkomstig uit de regio Kempenland prospectief gevolgd.
In Hoofdstuk 2.1 onderzochten wij of de positief voorspellende waarde van TPOAb verbeterd zou kunnen worden door rekening te houden met het tijdstip van testen of door het resultaat van de TPOAb-test te combineren met andere (mogelijke) determinanten van PPS. Tevens werd de lange-termijn prognose van vrouwen die PPS doormaakten bestudeerd. De door ons gevonden incidentie van zwangerschapsthyrotoxicose was 2,1%, die van PPS 5,2%. TPOAb waren ook in onze studie de meest belangrijke risicofactor voor PPS (RR 27,2); het roken/gerookt hebben van sigaretten (RR 3,1) en het geven van flesvoeding (RR 11,1) waren eveneens onafhankelijk gerelateerd met PPS. Wij vonden dat maximaal tweederde van de gevallen van PPS voorspeld kan worden met behulp van TPOAb; het meest geschikte moment voor testen is in het eerste trimester van de zwangerschap. Het combineren van het resultaat van de TPOAb-test met anamnestische determinanten verhoogde de positief voorspellende waarde slechts in geringe mate.
Een andere benadering om de voorspellende waarde te verbeteren is beschreven in Hoofdstuk 2.2: de parameters van de cellulaire immuniteit die gestoord zijn bij verschillende autoimmuun ziekten werden prospectief bestudeerd bij zwangeren die later PPS doormaakten en in gematchte controles om de bruikbaarheid van deze parameters voor de predictie van PPS te bestuderen. TPOAb positieve vrouwen (onafhankelijk van de ontwikkeling van PPS) vertoonden verschillende cellulair immuun gemedieerde abnormaliteiten zoals voortdurend verlaagde percentages "natural killer" cellen en een verlaagde chemoattractant-gestimuleerde monocyten polarisatie. Deze abnormaliteiten zijn vergelijkbaar met die bij andere endocriene autoimmuun ziekten. Een verhoogd percentage geactiveerde T cellen in de zwangerschap of postpartum discrimineerde tussen die TPOAb positieve vrouwen die PPS ontwikkelden en die dat niet deden. Vrouwen die "at risk" waren voor PPS werden het beste geidentificeerd door eerst te testen op de aanwezigheid van TPOAb en daarna het percentage geactiveerde T cellen bij herhaling te bepalen.
De resultaten van de studies beschreven in de Hoofdstukken 2.1 en 2.2 zijn suggestief voor het bestaan van twee vormen van PPS: een autoimmuun (TPOAb positieve) vorm en een niet-autoimmune vorm. De twee vormen zijn verschillend in pathogenese, symptomatologie en lange-termijn prognose.
Er is een intrigerende associatie tussen de aanwezigheid van TPOAb (een "marker" voor (subklinische) autoimmuun schildklierziekten) en depressie (zoals postpartum depressie). In Hoofdstuk 2.3 bestudeerden wij de relatie tussen TPOAb en depressie (vastgesteld met behulp van de RDC criteria) gedurende de zwangerschap en in het eerste jaar na de bevalling. In deze studie werden ook andere determinanten van depressie betrokken. Tevens werd bestudeerd of TPOAb positiviteit tijdens de zwangerschap voorspellende waarde had voor depressie na de bevalling. Na correctie voor de mogelijke invloed van andere determinanten (zoals opleidingsniveau, stressvolle levensgebeurtenissen, een eerdere depressie, zwangerschapscomplicaties en schildklierfunktiestoornissen) bleken TPOAb en depressie significant gerelateerd bij 12 weken zwangerschap en 4 en 12 weken postpartum. De aanwezigheid van TPOAb bij 12 weken zwangerschap was tevens geassocieerd met een verhoogd risico op het ontwikkelen van depressie na de bevalling, ongeveer 1 jaar later (OR= 2,8; 95% betrouwbaarheidsinterval 1,7-4,5). Onze resultaten bevestigden de associatie van

TPOAb (als "marker" voor autoimmuun schildklierziekten) met depressie en zijn suggestief voor een mogelijke (gedeeltelijke) gezamenlijke etiologie van depressie en autoimmuun schildklierziekten.
In Hoofdstuk 2.4 wordt een studie gepresenteerd over de associatie tussen laag fT4 in serum in de vroege zwangerschap en een gestoorde psychomotore ontwikkeling van het kind. Kinderen van vrouwen met een verlaagd of laag-normaal fT4 in het eerste trimester van de zwangerschap vertoonden lagere scores op de Nederlandse versie van de "Bayley Psychomotor Developmental Index". Het nadelige effect van laag fT4 leek dosis-gerelateerd: bij lagere fT4 waarden was er tevens een lagere score op de ontwikkelingsschalen. Ook na correctie voor andere determinanten van psychomotore ontwikkeling, zoals demografische en psychosociale factoren en de aanwezigheid van TPOAb tijdens de zwangerschap, bleef de associatie bestaan. Geconcludeerd kan dan ook worden dat lage fT4 waarden in de vroege zwangerschap ook in een Jodium-sufficiente regio een negatieve invloed kunnen hebben op de psychomotore ontwikkeling van het kind en dat daarom screening op laag fT4 en TPOAb in het eerste trimester overwogen dient te worden.

De studies over schildklierkanker in dit proefschrift zijn gebaseerd op gegevens verkregen van de kankerregistratie van het Integraal Kankercentrum Zuid (IKZ) te Eindhoven. De gegevens van patiënten geregistreerd sinds 1960 werden retrospectief bestudeerd.
In de Hoofdstukken 3.1 en 3.2 worden de trends in de incidentie en de prognose, en de trends in behandeling, beschreven voor de gehele groep patiënten en voor patiënten met gedifferentieerd schildkliercarcinoom afzonderlijk. De incidentie van schildklierkanker nam toe bij vrouwen van 1,4 tot 3,0/100.000/jaar en bleef constant bij mannen (1,1/100.000/jaar). Het percentage gedifferentieerde schildkliercarcinomen nam toe; het percentage anaplastisch schildkliercarcinoom nam af. Deze resultaten waren vergelijkbaar met die in de omringende landen. De prognose voor patiënten met schildklierkanker in Zuidoost Nederland was goed en gelijk aan die van patiënten behandeld in grote referentie ziekenhuizen: de relatieve 5- en 10-jaars overlevingskansen waren respectievelijk 80 en 75%; na een follow-up periode van 10 jaar trad er geen extra sterfte meer op.
In alle ziekenhuizen in de regio werden schildklierkankerpatiënten behandeld en deze patiënten ondergingen in toenemende mate uitgebreidere vormen van chirurgie. De behandeling van patiënten met gedifferentieerd schildkliercarcinoom bleek zoals aanbevolen door de Nederlandse consensus-bijeenkomst in 1987 en geconcludeerd kan worden dat patiënten met gedifferentieerd schildkliercarcinoom in Zuidoost Nederland behandeld werden volgens de meest recente opvattingen.
In Hoofdstuk 3.2 werd tevens een multivariate analyse van prognostische factoren voor gedifferentieerd schildklierkanker beschreven. Onze resultaten waren vergelijkbaar met die van andere studies: vrouwen, jongere patiënten, patiënten met TNM stadium I-II en patiënten met een papillaire tumor hadden een betere prognose. Tevens vonden wij echter dat de effecten van de verschillende prognostische factoren in de eerste 5 jaar en in de periode vanaf 5 jaar verschillend waren, en dat de uitgebreidheid van de chirurgische behandeling geen effect had op de prognose en dat ^{131}I nabehandeling alleen een gunstig effect had in de eerste 5 jaar.
De prevalentie van co-morbiditeit bij nieuwe patiënten met schildklierkanker in de periode 1993-96 werd beschreven in Hoofdstuk 3.3. De keuze om chirurgisch te behandelen werd bij oudere patiënten beinvloed door het aantal van bijkomende aandoeningen. Tevens werden er

aanwijzingen gevonden voor een relatie van schildklierkanker met een voorafgaande hematologische maligniteit en tuberculose. Het effect van co-morbiditeit op de prognose kon niet bestudeerd worden vanwege de korte follow-up periode.
Het voorkomen van tweede tumoren na schildklierkanker werd beschreven in Hoofdstuk 3.4. Schildklierkankerpatiënten vertoonden een statistisch niet-significant verhoogd risico van 40% op het ontwikkelen van een tweede tumor, hetgeen in overeenstemming was met de resultaten van andere studies. Voor papillair schildklierkanker afzonderlijk was er een verhoogd risico op de ontwikkeling van leukemie en prostaatkanker; dit verhoogde risico was niet gerelateerd met ^{131}I nabehandeling. Mogelijk is er een etiologische associatie tussen schildklierkanker en een spectrum van andere maligniteiten.

In het laatste Hoofdstuk (4.4) worden de conclusies en enkele kanttekeningen bij de studies besproken. De validiteit en de generaliseerbaarheid van de resultaten van de studies worden besproken (Hoofdstuk 4.1): geconcludeerd kan worden dat zowel de studies over PPS en gerelateerde onderwerpen als de studies over schildklierkanker als valide en representatief beschouwd kunnen worden. De implicaties van de studies voor de praktijk, en dan met name voor screening, worden besproken in Hoofdstuk 4.2. Argumenten voor het aanbieden van een TPOAb test aan alle zwangeren zijn de relatief hoge incidentie van PPS, de associatie met obstetrische complicaties, de negatieve gevolgen voor de psychomotore ontwikkeling van het kind, het grote risico op het ontwikkelen van een permanente hypothyreoidie en de associatie met depressie. Vanwege de lage incidentie en de complexiteit van de diagnostiek en therapie verdient het aanbeveling om de incidentie en de resultaten van de verschillende behandelingsopties van schildklierkanker op supraregionaal of nationaal niveau te evalueren. Tenslotte: schildklierziekten, zoals autoimmuun schildklierziekten (inclusief PPS) en schildklierkanker, dienen beschouwd te worden als relevante onderwerpen voor het toekomstige gezondheidsbeleid in Nederland.

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Appendix.

Southeastern Netherlands and the Kempen.

The studies reported in this thesis were all performed in the southeastern part of The Netherlands. Therefore, a brief description of the characteristics of this region is given.
For the studies on postpartum thyroid dysfunction (PPTD), a representative cohort of 310 Caucasian women residing in the region Kempenland/Veldhoven/Valkenswaard (the "Kempen-region") was followed prospectively during pregnancy and in the first year after delivery. The region consists of seven municipalities south of the town of Eindhoven and had 155,000 inhabitants in 1996 (1).
The high fertility rate of 3 in the 60's has dropped to 1.5 per women in the 90's, illustrating the secularization of the largely Roman-Catholic population; in the Kempen-region, 1,900-2,000 children are being born annually (1). About twothird of all pregnant women attend to the local midwives and onethird to a gynaecologist in one of the regional hospitals, in the majority of cases the St Joseph Hospital Veldhoven. As a consequence of the dropped fertility rate and increasing life-expectancy, there is a pronounced ageing of the regional population: the number of people over 55 years increases annually with 2% (1,2).
The region served by the Eindhoven Cancer Registry (part of the Comprehensive Cancer Centre South, Eindhoven) comprises an area of about 2,500 km^2 in the southeastern part of the province Noord-Brabant and the northern part of the province Limburg (2). The number of newly diagnosed cancers is about 11,000 per year (2). Both the incidence of lung cancer in males and breast cancer in females belong to the highest when compared to other western countries (3,4). The region has about 1 million inhabitants (7% of the total Dutch population) and is representative for the caucasian population in The Netherlands.
The number of community hospitals in the region covered by the Eindhoven Cancer Registry has been declining from 11 to 8, due to hospital mergers in the late 80's. The Department of Radiotherapy in Eindhoven serves since the late 50's as the regional centre for patients referred for treatment with external radiotherapy or treatment with radioactive iodine (^{131}I) for benign or malignant thyroid diseases. The completeness and accuracy of the data registered by the Eindhoven Cancer Registry was evaluated in 1980-83 and it was concluded that the completeness of the data for most tumours could be assumed from the early 70's onwards (5).
The average population density is about 400 persons/km^2, conform to the national average. About 45% of the population lives in urban, 45% in suburban and 10% in rural municipalities.
The southeastern part of The Netherlands is one of the most industrialized regions of the country. The rapidly growing industries generate electronic and high tech products, cars and trucks, textiles and food products. The tobacco processing industry was traditionally important in the Eindhoven area; nowadays the Dutch tobacco industry is concentrated in the Kempen-region and is one of the worlds greatest producers of cigars. Zinc factories, situated along the border with Belgium since 1900, caused a marked pollution of the soil with cadmium. An intensive pig and poultry breeding industry has developed during the last 30 years, which now contributes considerably to acid rain and the rising nitrate content in the groundwater, which also contains increasing amounts of agrochemicals (the latter probably related to the development of thyroid tumours (6)). Since the 60's there were rising and relatively high concentrations of ozone, lead, nitrogen monoxide and sulphur dioxide, orginating from surrounding industrialized regions and an marked increase of transport by trucks and cars.

The daily iodine intake is sufficient in southeastern Netherlands (7,8). In the 40's and 50's, however, the prevalence of goiter due to deficient iodine intake was extremely high, especially in the Kempen-region (prevalence >60%) (9).

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Dankwoord.

Aan de totstandkoming van (de artikelen opgenomen in) dit proefschrift hebben velen een bijdrage geleverd.
Mijn beide promotores ben ik dank verschuldigd: Wilmar Wiersinga voor zijn kritische, uitdagende en prikkelende discussies en commentaren en het in een breder perspectief plaatsen van het probleem schildklierziekten, en Hemmo Drexhage voor het leren kritisch te kijken naar de brij van informatie en gegevens om daar de relevante resultaten uit te halen en die dan overzichtelijk te presenteren.
Victor Pop, mijn co-promotor, fungeerde als "turbo" achter het veldwerk. Zijn positieve en voortvarende aanpak zorgden voor vaart in het hele project.
Bijzondere waardering is op z'n plaats voor Jan-Willem Coebergh. Als supervisor tijdens de opleiding tot sociaal-geneeskundige, tak AGZ, hebben we veel discussies gehad over de gezondheidszorg en de betekenis van de sociale geneeskunde en de epidemiologie voor de volksgezondheid. Daarnaast heeft Jan-Willem het mogelijk gemaakt binnen de kankerregistratie van het IKZ onderzoek te doen.
Maarten van Son dank ik voor de relativerende gesprekken bij de start van het onderzoek.
Het onderzoek naar de schildklierfunktiestoornissen en depressie in en na de zwangerschap en het vervolgonderzoek bij de kinderen was niet mogelijk geweest zonder de medewerking van de deelnemende vrouwen en de verloskundigen in Veldhoven, Valkenswaard en Hapert/ Hoogeloon en de medewerkers van de afdeling Gynecologie/verloskunde van het St Joseph Ziekenhuis te Veldhoven.
Ruim 2100 maal is er een schildklierfunktie bepaald en ruim 900 maal is er een lymfocyten-scheiding verricht. Dit alles was niet mogelijk zonder de hulp van de medewerkers van de Klinische laboratoria (hoofd: Huib Vader) van het Sint Joseph Ziekenhuis Veldhoven. Op het Laboratorium voor immunologie van de Erasmusuniversiteit heeft Meeny de Haan het grootste deel van de immunologische bepalingen verricht.
Het bestuur en de directie van het IKZ te Eindhoven en de medewerkers van de kankerregistratie wil ik danken voor de mogelijkheden die mij geboden zijn om van de gegevens van de kankerregistratie gebruik te kunnen maken. Veel hulp en steun heb ik gehad van Louis van der Heijden, Bettina Hansen, Maryska Jansen en Willem Klokman bij het verzamelen van de gegevens en het opbouwen en analyseren van het bestand met patiënten met schildklierkanker.
Aan de artikelen in dit proefschrift hebben 20 mede-auteurs afkomstig van 5 universiteiten (8 vakgroepen), 5 ziekenhuizen en de kankerregistratie van het IKZ te Eindhoven meegewerkt: allen dank ik voor de opbouwende commentaren bij de (vele) concepten van artikelen.
Het bestuur en de directie van de GGD dank ik voor de mogelijkheden die mij geboden zijn om naast het dagelijkse werk buiten de deur van de GGD te kijken en onderzoek te doen. Alle medewerkers van de afdeling AGZ/VGZ in Valkenswaard dank ik voor hun geduld. Eindelijk weten ze nu ook wat er met "die 300 vrouwen van Hans" is gebeurd.

Mijn ouders dank ik voor de mogelijkheden die mij gegeven zijn. Ik weet dat jullie trots zijn.
Pieter, Juliëtte en Maarten: het wachten is voorbij, papa heeft weer alle tijd. Tenslotte: "En Janneke is ook heel trots". Uit: Jip en Janneke, Annie M.G. Schmidt.

Curriculum vitae.

De schrijver van dit proefschrift werd geboren op 28 oktober 1956 te Breda. In 1975 behaalde hij het eindexamen Atheneum B aan het Onze Lieve Vrouw Lyceum te Breda, waarna hij geneeskunde studeerde aan de Katholieke Universiteit Nijmegen. Gedurende de studie was hij 2 jaar bestuurslid van de studentenroeivereniging Phocas. Het artsexamen werd behaald in 1983. Aansluitend werd de militaire dienstplicht vervuld op de afdeling Interne Geneeskunde van het Militair Hospitaal "A. Mathysen" te Utrecht. In de periode 1984-1987 werkte hij achtereenvolgens als arts-assistent op de afdelingen Cardiologie van het Elisabeth's Gasthuis te Haarlem, het Franciscus Ziekenhuis te Roosendaal en het De Weverziekenhuis te Heerlen. Tegelijkertijd werd een korte periode gewerkt als toegevoegd onderzoeker bij de vakgroep Economie van de gezondheidszorg van de Rijksuniversiteit Maastricht. Vanaf augustus 1987 is de schrijver werkzaam bij de GGD regio Geldrop-Valkenswaard, thans de GGD Zuidoost-Brabant. In 1992 werd hij geregistreerd als sociaal-geneeskundige, tak AGZ; in 1991 werd tevens de registratie als forensisch geneeskundige verkregen.
De schrijver is gehuwd met Janneke Romeijnders; samen hebben ze drie kinderen: Pieter, Juliëtte en Maarten.