Thyroid Dysfunction and Autoantibodies during Pregnancy as Predictive Factors of Pregnancy Complications and Maternal Morbidity in Later Life

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Context: Knowledge is scarce concerning the significance of thyroid dysfunction/antibodies during pregnancy in regard to pregnancy complications/later maternal morbidity.

Objective: The aim of this study was to evaluate the association between maternal thyroid dysfunction/antibodies during pregnancy and pregnancy complications or later maternal hypertension, diabetes, and thyroid disease.

Design and Setting: We studied a prospective population-based cohort, Northern Finland Birth Cohort 1986 (NFBC 1986), with follow-up of 20 yr. Medication and hospital discharge records were used to assess maternal morbidity to hypertension, diabetes, and thyroid diseases.

Participants: The study consisted of mothers of NFBC 1986 with early pregnancy serum samples for thyroid function and antibody analyses (n = 5805). Mothers were grouped and compared according to these test results.

Main Outcome Measures: We focused on preeclampsia and gestational diabetes during index pregnancy, later maternal hypertension, diabetes, and thyroid disease morbidity and total mortality.

Results: Thyroid dysfunction and antibodies were not associated with pregnancy complications. Overt hypothyroidism was associated with subsequent maternal thyroid disease [hazard ratio (HR) (95% confidence interval), 17.7 (7.8–40.6)] and diabetes [6.0 (2.2–16.4)]. Subclinical hypothyroidism [3.3 (1.6–6.9)], TPO-Ab-positivity [4.2 (2.3–7.4)], and TG-Ab-positivity [3.3 (1.9–6.0)] were also associated with later thyroid disease. No association was found between thyroid dysfunction/antibodies and hypertension or overall mortality.

Conclusions: Thyroid dysfunction and antibodies during pregnancy seem to predict later thyroid disease. Overt hypothyroidism poses risk of diabetes. ***(J Clin Endocrinol Metab* 95: 1084–1094, 2010)**

Pregnancy may serve as a glimpse into a woman's future health because gestation presents many challenges for various organ systems. Several changes are observed in maternal thyroid function during pregnancy, and failure to adapt to these physiological changes results in thyroid dysfunction (1), especially if complicated by the presence of thyroid antibodies (2). Therefore, thyroid dysfunction and/or antibodies are relatively common during gestation (3, 4), and they have been thought to represent a risk to maternal and fetal health during pregnancy, although the

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Abbreviations: BMI, Body mass index; CI, confidence interval; fT3, free T_3; fT4, free T_4; HR, hazard ratio; TG-Ab, thyroglobulin antibody; TPO-Ab, thyroid-peroxidase antibody.

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results from different studies are controversial (3–5). Up to now, thyroid dysfunction and/or antibodies have been thought to be associated with pregnancy complications such as placental abruption (4), gestational diabetes (6, 7), pregnancy-induced hypertension (8), and preeclampsia (7, 9), but these relationships have not been proved in all studies (3, 9). Studies in which these complications have been evaluated show differences in populations, definition of thyroid dysfunction, and background factors, which may explain why the results are noncongruent.

Elevated circulating levels of TSH and thyroid antibodies existing alone or together are clear risk factors of hypothyroidism in nonpregnant women during long-term follow-up (10). Although maternal thyroid function usually returns to its prepregnancy state after gestation (11), there may still be a risk of subsequent thyroid disease, especially if the pregnancy has been complicated with thyroid dysfunction. There is, however, only scarce knowledge of this risk up to now; in a small study over half of women with nontreated hypothyroidism during pregnancy developed later thyroid disease (12). Thyroid antibodies detected during pregnancy indicate an increased risk of postpartum thyroiditis and hence may increase the risk of permanent thyroid disease (13, 14).

The prevalence of thyroid diseases, hypertension, and diabetes increases with age. These conditions may coexist or even lead to one another (15, 16). Thyroid hormones have an effect on cardiovascular function (17), and thyroid dysfunction is associated with arrhythmias (18), hypertension (16), as well as ischemic heart disease (19). Hence, thyroid dysfunction and antibodies may be significant predictive factors even at a young age when considering cardiovascular diseases and mortality (19–21). Thyroid dysfunction is also associated with insulin resistance (15, 22, 23), thyroid antibodies are prevalent among diabetics (24–26), and therefore they may also be risk factors for diabetes. In addition, thyroid dysfunction and antibodies may be intervening or confounding factors when considering gestational diabetes and preeclampsia and their known association with later diabetes and hypertension (27). Up to now, it is not known whether thyroid dysfunction and antibodies observed during pregnancy are associated with a later risk of maternal cardiovascular diseases or diabetes.

The aim of this study was to find out whether thyroid dysfunction and/or antibodies detected in early pregnancy are associated with pregnancy complications or later morbidity of the mothers regarding thyroid diseases, hypertension, or diabetes during a 20-yr follow-up period.

Subjects and Methods

Study population and data collection

The study population consists of the prospective Northern Finland Birth Cohort (NFBC) 1986. The cohort covers 99% of all births with calculated term between July 1, 1985, and June 30, 1986, drawn from the two northernmost provinces of Finland (9362 mothers, 9479 children) (28, 29). We included only the mothers with singleton pregnancies in the present study (n = 9247). The cohort has been followed up since the 12th week of gestation. Data collection was carried out during routine visits to maternal welfare clinics as well as via questionnaires. The first questionnaire, on demographic, biological, health behavioral, and socioeconomic characteristics of the mothers/families, covered the period up to the 24th gestational week, when the mothers were enrolled in the study if still pregnant. The second questionnaire covered maternal health and health behavior during pregnancy and the perinatal period. The mothers were assisted in completion of the questionnaire by nurses who ensured that all questions were answered. The third questionnaire contained items about pregnancy complications and diseases, delivery, and neonatal outcome and was completed in maternity hospitals by attending midwives. All women gave birth at hospitals. Data concerning mothers' background factors [*i.e.* age, body mass index (BMI), parity, obstetric history, and previous diseases] was obtained through the questionnaires as well as the data regarding pregnancy complications such as preeclampsia [blood pressure ≥140/90 mm Hg, and proteinuria (≥0.3 g/liter)], gestational hypertension (blood pressure ≥140/90 mm Hg without proteinuria), placental abruption, gestational diabetes (one or more abnormal values in oral glucose tolerance test), and excessive weight gain (calculated as prepregnancy weight − weight at last antenatal visit; excessive if result >20 kg). The perinatal outcome of this population has been previously published (5). The Ethics Committees of the University of Oulu and the National Institute of Health and Welfare approved this study. Informed consent was obtained from all subjects.

Serum samples and laboratory assays

The biochemical data were obtained via the Finnish Maternity Cohort, which is a biobank consisting of serum samples collected from all pregnant women in Finland and approved under Finnish law. The law allows use of the samples in studies promoting public health. The samples were stored at −25 C and thawed for the first time for the analyses of this study in 2006. The effects of freezing, thawing, and frozen storage on thyroid laboratory parameters have been reported previously (30). Quantitative analyses of thyroid hormones [TSH, free T_3 (fT3), and free T_4 (fT4)] and autoantibodies associated with autoimmune thyroiditis [thyroid-peroxidase antibody (TPO-Ab) and thyroglobulin antibody (TG-Ab)] were performed by way of chemiluminescent microparticle immunoassays, using an Architect i2000 automatic analyzer (Abbott Diagnostics, Abbott Park, IL). The lower limits of detection and intra- and interassay coefficients of variation were 0.0025 mIU/liter, 1.7 and 5.3% for TSH; 5.1 pmol/liter, 3.6 and 7.8% for fT4; 1.53 pmol/liter, 2.3 and 5.0% for fT3; 1.0 IU/ml, 2.5 and 9.8% for TPO-Ab; and 1.0 IU/ml, 2.7 and 8.2% for TG-Ab.

The number of serum samples analyzed was 5805 (61.2% of the whole cohort); only samples of a sufficient volume (≥1 ml) were included in this study. The excluded population did not differ significantly from those included. The mean gestational age at sampling was 11.0 wk (SD, 3.6), and only samples drawn before or at the 20th gestational week were accepted (98% of the samples). When the sample size was not sufficient for all analyses, thyroid hormone analyses were carried out primarily.

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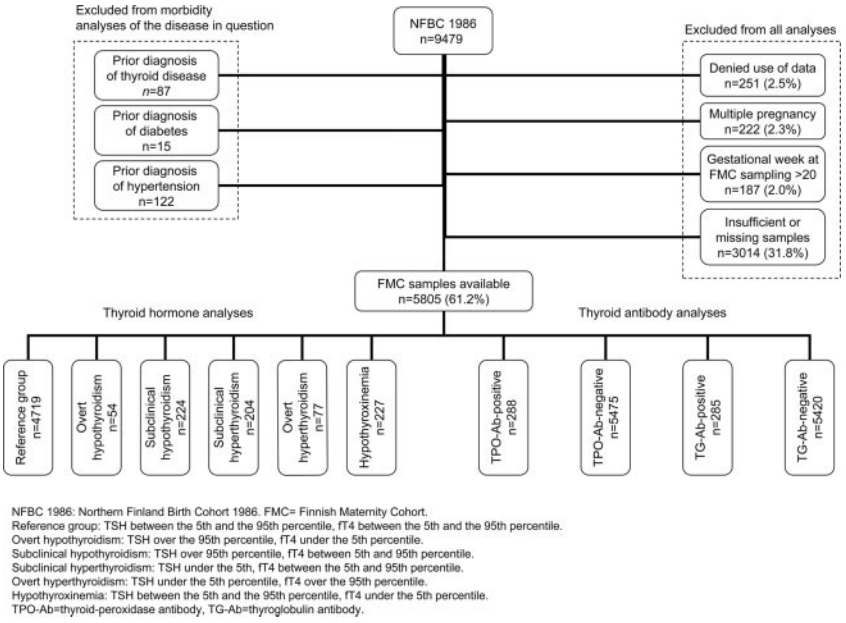

FIG. 1. Flow chart concerning the study population—the Northern Finland Birth Cohort (NFBC) 1986.

Categorization of the study population and outcomes

For association analyses, the data were categorized using percentiles of laboratory values because the reference values given by the manufacturer of the analyzer (Abbott) apply to a nonpregnant population, and these values may differ from those in a pregnant population (31). Our study is population-based and large enough to create our own reference values and to take into account the effect of freezing and storage (30).

The study population is shown in a flow chart (Fig. 1).

Concerning thyroid hormones, the mothers with serum concentrations of both TSH and fT4 between the 5th and 95th percentiles were considered to have normal thyroid function (reference group, n = 4719). Of these mothers, 100 were TPO-Ab-positive, 129 were TG-Ab-positive, and 63 had both antibodies positive.

The subjects with thyroid dysfunction were divided into five groups with respect to thyroid hormone levels:

1) Overt hypothyroidism, with TSH levels above the 95th percentile and fT4 levels below the 5th percentile (n = 54). Of these mothers, 17 were TPO-Ab-positive, eight were TG-Ab-positive, and seven had both antibodies positive.
2) Subclinical hypothyroidism, with TSH levels above the 95th percentile and fT4 levels between the 5th and 95th percentiles (n = 224). Of these mothers, 45 were TPO-Ab-positive, 18 were TG-Ab-positive, and 27 had both antibodies positive.
3) Subclinical hyperthyroidism, with TSH levels below the 5th percentile and fT4 levels between the 5th and 95th percentiles (n = 204). Of these mothers, one was TPO-Ab-positive, and five were TG-Ab-positive.
4) Overt hyperthyroidism, with TSH levels below the 5th percentile and fT4 levels above the 95th percentile (n = 77). Of these mothers, one was TPO-Ab-positive, five were TG-Ab-positive, and one had both antibodies positive.
5) Hypothyroxinemia, with TSH levels between the 5th and 95th percentiles and fT4 levels below the 5th percentile (n = 227). Of these mothers, 201 had fT3 values between the 5th and 95th percentiles, 24 had fT3 values below the 5th percentile, and two had fT3 values above the 95th percentile. In addition, 10 mothers were TPO-Ab-positive, six were TG-Ab-positive, and five had both antibodies positive.

Thyroid dysfunction groups were compared with the reference group in the analyses after including or excluding those with positive antibodies from the groups.

With respect to thyroid antibodies, mothers were TPO-Ab- or TG-Ab-positive if the antibody concentration was above the 95th percentile. This high cutoff level was used instead of the assay manufacturer's reference values because the samples in this study were from pregnant women and after frozen storage (30). The 5th and 95th percentiles as well as geometric means and 95% confidence intervals (CIs) of all laboratory data are presented in Table 1. The mothers positive for thyroid antibodies were compared with antibody-negative mothers after including or excluding those with thyroid dysfunction from the groups.

Register-based data

Three register-based data sets were used in this study to evaluate the health of the mothers after their index pregnancy, the follow-up time being 20 yr. First, data from the Social Insurance Institute of Finland comprises information on diagnosed diseases with medication and reimbursement of medical expenses (32). Second, the national Finnish Hospital Discharge Register includes information on diagnoses at discharge from all hospital wards or outpatient clinics, using the International Classification of Diseases. The register has accuracy of 83 to 95% (33, 34). Third, the Population Register Data and Registry for Causes of Death contains information on causes of death, covering all deaths in Finland. Data from these registers were obtained for the period 1985–2006. Data from the national Hospital Discharge Register was complete from 2000 onward. The register-based data were combined with the NFBC 1986 data by using indi-

TABLE 1. Biochemical characteristics of samples analyzed

	n	Geometric mean	95% CI	5th percentile	95th percentile
TSH (mU/liter)	5779	1.06	1.03–1.08	0.19	3.6
fT4 (pmol/liter)	5726	15.3	15.3–15.4	11.96	20.5
fT3 (pmol/liter)	5737	5.13	5.10–5.15	3.85	6.63
TPO-Ab (IU/ml)	5763	6.23	6.03–6.44	2.0	167.7
TG-Ab (IU/ml)	5705	12.5	12.3–12.7	6.4	47.7

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vidual social security numbers, which are given to all Finns. This was carried out by personnel uninvolved in this study, and the researchers had no access to identifiable data concerning the participants.

Receiving reimbursement for medication to treat diabetes, hypertension, or thyroid disease or having discharge diagnoses of the diseases was considered verification of these diseases. Mothers with diagnoses of these diseases before pregnancy were excluded from analyses of the disease in question but not from analyses of other diseases. (For instance, mothers with a diagnosis of diabetes before pregnancy were excluded from diabetes analyses, but not from thyroid disease or hypertension analyses.)

Statistical methods

Differences between groups were evaluated by using ANOVA, Student's *t* test, and Fisher's exact test. Logistic regression analysis was used to analyze the association between maternal thyroid parameters and pregnancy complications. Cox's regression analysis was applied to assess the effects of maternal thyroid parameters on later morbidity and was adjusted further for covariates (maternal age, parity, and BMI, and presence of gestational diabetes or gestational hypertension/preeclampsia). Statistical analyses were performed using SPSS v. 15.0 software (SPSS Inc., Chicago IL).

Results

Demographic data and previous diseases

The demographic data of the mothers in the different study groups are presented in Table 2. There were significant differences in background factors when thyroid dysfunction groups were compared with reference group and when antibody-positive mothers were compared with antibody-negative mothers. Almost all study groups had significant history of previous thyroid diseases. The mothers with subclinical hypothyroidism more often had history of chronic hypertension. No differences were observed in the rates of diabetes between the groups. These results are presented in Table 3.

Pregnancy complications

Thyroid dysfunction or antibodies were not associated with preeclampsia, gestational diabetes, placental abruption, or excessive maternal weight gain (Table 3). However, TG-Ab-positive mothers had higher prevalence of gestational hypertension compared with TG-Ab-negative mothers, the odds ratio (95% CI) being 1.8 (1.02–3.1) unadjusted and 1.8 (1.01–3.11) after adjusting for maternal age and parity. This association was no longer significant when excluding those with thyroid dysfunction from the analyses. Maternal BMI was an independent risk factor for gestational hypertension. No differences were seen in the rates of gestational hypertension between thyroid dysfunction groups and reference group or between TPO-Ab-positive and -negative mothers (Table 3). The results did not change when excluding the antibody-positive from thyroid dysfunction analyses or when excluding those with thyroid dysfunction from TPO-antibody analyses.

Maternal morbidity after index pregnancy in the course of 20 yr

The mean age of the mothers was 28.2 yr (SD, 5.4; range, 15.9–47.2) at the time of their index pregnancies, and therefore their mean age at the end of the follow-up period was approximately 48 yr.

Thyroid disease morbidity

During follow-up, thyroid disease was observed in 192 mothers (3.3%), of whom 107 had normal thyroid function during pregnancy (reference group). The mean age of the women at the time of diagnosis was 41.1 yr (SD, 7.9; range, 23.2–61.1). In the reference group, 18.7% of the antibody-positive mothers developed thyroid disease during follow-up compared with 5.8% of the antibody-negative mothers (Table 4).

The thyroid diseases observed during follow-up were mostly hypothyroid diseases with different etiologies; most were of acquired/idiopathic origin (n = 75), some were the result of radiotherapy (n = 15), only one was confirmed to be of autoimmune origin, and one was the result of goiter. Nine cases of thyroid carcinoma were observed during the follow-up period.

The unadjusted and adjusted hazard ratios (HRs) with 95% CIs, regarding thyroid disease in later life among mothers with thyroid dysfunction or antibodies during pregnancy, are presented in Table 5. The rates of antibody positivity detected in thyroid dysfunction groups are presented in Table 4.

The most important risk factor for subsequent thyroid disease was overt hypothyroidism, with more than a 17-fold independent risk and over 20-fold risk when antibodies were present (Table 5). However, antibody positivity among women with overt hypothyroidism did not differ between those who had subsequent thyroid disease and those who had no disease during follow-up (Table 4).

TPO-Ab positivity predicted later thyroid disease with a 4.2-fold independent risk, but the risk was over 8-fold if TPO-Ab positivity was complicated with any thyroid dysfunction during pregnancy (Table 5).

Subclinical hypothyroidism was also associated with an increased (3.3-fold) risk of later thyroid disease, and the risk was over 8-fold if antibodies were present (Table 5). Those who had later thyroid disease more often had thyroid antibodies (Table 4).

TG-Ab positivity was not as high a risk factor for thyroid diseases as TPO-antibody positivity, but the risk associated with TG-Ab positivity was higher if thyroid dysfunction was present (Table 5).

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TABLE 2. Demographic characteristics of NFBC 1986 mothers during their index pregnancy

	Reference group	Overt hypothyroidism	Subclinical hypothyroidism	Subclinical hyperthyroidism	Overt hyperthyroidism	Hypothyroxinemia	TPO-Ab-positive	TPO-Ab-negative	TG-Ab-positive	TG-Ab-negative
n	4719	54	224	204	77	227	288	5475	285	5420
Age (yr)	28.0 (5.3)	28.7 (5.1)	28.6 (5.8)	29.5 (5.5)[a]	28.9 (5.8)	29.4 (6.0)[a]	28.6 (5.1)	28.2 (5.4)	29.1 (5.4)[a]	28.1 (5.4)
Gestational week at screening	10.7 (2.8)	10.9 (3.3)	10.9 (2.8)	10.5 (2.2)	10.4 (2.2)	11.4 (3.1)[a]	10.3 (2.4)	10.8 (2.8)	10.4 (2.7)	10.7 (2.8)
BMI (kg/m^2)	22.1 (3.4)	22.5 (3.8)	22.6 (3.7)[a]	22.5 (3.5)	22.0 (2.9)	23.0 (3.8)[a]	22.7 (4.0)[a]	22.2 (3.4)	22.7 (4.0)[a]	22.2 (3.4)
Nulliparous	1628 (34.5%)	12 (22.2%)	69 (30.8%)	45 (22.1%)[a]	17 (22.1%)[a]	69 (30.7%)	81 (28.1%)	1842 (33.6%)	73 (25.6%)[a]	1828 (33.7%)
Parity (min-max)	1.3 (0–15)	1.5 (0–7)	1.6 (0–13)[a]	1.9 (0–12)[a]	2.1 (0–12)[a]	2.0 (0–14)	1.3 (0–13)	1.4 (0–15)	1.7 (0–13)[a]	1.4 (0–15)
Smokers	1307 (27.7%)	3 (5.6%)[a]	40 (17.9%)[a]	31 (15.2%)[a]	17 (21.1%)	74 (32.6%)	74 (25.7%)	1486 (27.1%)	45 (15.8%)[a]	1491 (27.5%)
Alcohol use during pregnancy	271 (5.7%)	3 (5.6%)	11 (4.9%)	10 (4.9%)	3 (3.9%)	18 (7.9%)	16 (5.6%)	310 (5.7%)	15 (5.3%)	310 (5.7%)
Education level										
Elementary school	1058 (22.4%)	13 (24.1%)	66 (29.5%)[a]	53 (26.0%)	20 (26.0%)	52 (22.9%)	71 (24.7%)	1257 (23.0%)	70 (24.6%)	1246 (23.0%)
Vocational school	2505 (53.1%)	22 (40.7%)	95 (42.4%)[a]	105 (51.3%)	39 (50.6%)	123 (54.2%)	155 (53.8%)	2870 (52.4%)	140 (49.1%)	2854 (52.7%)
Upper secondary school	244 (5.2%)	5 (9.3%)	14 (6.3%)	9 (4.4%)	3 (3.9%)	12 (5.3%)	12 (4.2%)	289 (5.3%)	15 (5.3%)	282 (5.2%)
University	344 (7.3%)	7 (13.0%)	17 (7.6%)	19 (9.3%)	5 (6.5%)	10 (4.4%)	20 (6.9%)	358 (6.5%)	22 (7.7%)	379 (7.0%)

Values are expressed as mean (SD) or number (percent). Reference group: TSH between the 5th and 95th percentiles; fT4 between the 5th and 95th percentiles. Overt hypothyroidism: TSH above the 95th percentile, fT4 below the 5th percentile. Subclinical hypothyroidism: TSH above the 95th percentile; fT4 between the 5th and 95th percentiles. Subclinical hyperthyroidism: TSH below the 5th percentile; fT4 between the 5th and 95th percentiles. Overt hyperthyroidism: TSH below the 5th percentile; fT4 above the 95th percentile. Hypothyroxinemia: TSH between the 5th and 95th percentiles; fT4 below the 5th percentile.

[a] $P < 0.05$ when comparing thyroid dysfunction groups together or separately with the reference group or comparing the antibody-positive group with the antibody-negative group.

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TABLE 3. The pregnancy complications and previous diseases observed among mothers with thyroid dysfunction or antibodies during pregnancy

	Reference group	Overt hypothyroidism	Subclinical hypothyroidism	Subclinical hyperthyroidism	Overt hyperthyroidism	Hypothyroxinemia	TPO-Ab-positive	TPO-Ab-negative	TG-Ab-positive	TG-Ab-negative
n	4719	54	224	204	77	227	288	5475	285	5420
Gestational hypertension	139 (3.0)	2 (3.8)	7 (3.3)	7 (3.5)	2 (2.7)	7 (3.3)	7 (2.5)	161 (3.0)	14 (5.1)[a]	153 (2.9)
Preeclampsia	89 (1.9)	1 (1.9)	8 (3.8)	7 (3.5)	2 (2.7)	3 (1.4)	6 (2.2)	108 (2.0)	3 (1.1)	111 (2.1)
Gestational diabetes mellitus	47 (1.0)	0	0	1 (0.5)	1 (1.3)	0	0	50 (1.0)	2 (0.7)	48 (0.9)
Placental abruptions	24 (0.5)	0	1 (0.5)	2 (1.0)	0	1 (0.5)	1 (0.4)	28 (0.5)	3 (1.1)	26 (0.5)
Maternal weight gain >20 kg during pregnancy	430 (9.8)	5 (10.0)	22 (10.5)	13 (6.7)	5 (6.7)	18 (8.7)	31 (11.4)	477 (9.3)	30 (11.3)	477 (9.4)
Previous diseases										
Thyroid diseases	41 (0.9)	2 (3.7)	14 (6.2)[a]	5 (2.5)[a]	3 (3.9)[a]	4 (1.8)	12 (4.2)[a]	42 (0.8)	7 (2.5)[a]	47 (0.9)
Type 1 diabetes	10 (0.2)	0	2 (0.9)	0	0	0	1 (0.3)	11 (0.2)	0	12 (0.2)
Chronic hypertension	87 (1.9)	2 (3.7)	11 (4.9)[a]	2 (1.0)	2 (2.6)	8 (3.5)	8 (2.8)	113 (2.1)	8 (2.8)	112 (2.1)

Values are expressed as number (percent). Reference group: TSH between the 5th and 95th percentiles; fT4 between the 5th and 95th percentiles. Overt hypothyroidism: TSH above the 95th percentile; fT4 below the 5th percentile. Subclinical hypothyroidism: TSH above the 95th percentile; fT4 between the 5th and 95th percentiles. Subclinical hyperthyroidism: TSH below the 5th percentile; fT4 between the 5th and 95th percentiles. Overt hyperthyroidism: TSH below the 5th percentile; fT4 above the 95th percentile. Hypothyroxinemia: TSH between the 5th and 95th percentiles; fT4 below the 5th percentile.

[a] $P < 0.05$ when comparing thyroid dysfunction groups together or separately with the reference group or comparing the antibody-positive group with the antibody-negative group.

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TABLE 4. The antibody positivity among mothers with thyroid dysfunction during pregnancy grouped according to thyroid disease morbidity during follow-up

	Thyroid disease observed during follow-up		No thyroid disease during follow-up		
	Total diseased	Antibody positive	Total not diseased	Antibody positive	*P* value
Reference group	107 (2.3)	20 (18.7)	4551 (97.7)	264 (5.8)	<0.001
Overt hypothyroidism	19 (38.0)	13 (68.4)	31 (62.0)	17 (54.8)	0.39
Subclinical hypothyroidism	36 (17.3)	28 (77.8)	172 (82.7)	59 (34.3)	<0.001
Subclinical hyperthyroidism	9 (4.5)	2 (22.2)	189 (95.5)	3 (1.6)	0.02
Overt hyperthyroidism	3 (4.1)	1 (33.3)	70 (95.9)	5 (7.1)	0.23
Hypothyroxinemia	12 (5.4)	4 (33.3)	211 (94.6)	16 (7.6)	0.02

Data are expressed as number (percent). *P* value was obtained using Fisher's exact test when comparing the antibody-positivity between those with disease or no disease during follow-up in each thyroid dysfunction group or among the reference group. Reference group: TSH between the 5th and 95th percentiles; fT4 between the 5th and 95th percentiles. Overt hypothyroidism: TSH above the 95th percentile; fT4 below the 5th percentile. Subclinical hypothyroidism: TSH above the 95th percentile; fT4 between the 5th and 95th percentiles. Subclinical hyperthyroidism: TSH below the 5th percentile; fT4 between the 5th and 95th percentiles. Overt hyperthyroidism: TSH below the 5th percentile; fT4 above the 95th percentile. Hypothyroxinemia: TSH between the 5th and 95th percentiles; fT4 below the 5th percentile. Antibody positivity was defined as when TPO-Ab or TG-Ab or both were positive.

Hypothyroxinemia did not predict later thyroid diseases independently, but if it was associated with thyroid antibodies, the risk for later thyroid diseases was increased (Tables 4 and 5). Subclinical and overt hyperthyroidism during pregnancy did not significantly increase the risk of later thyroid disease (Table 5).

Diabetic morbidity

Diabetes was observed in 82 (1.4%) mothers during follow-up, of whom 61 belonged to the reference group. The women's mean age at the time of diagnosis was 46.7 yr (SD, 7.3; range, 30.0–63.3). The HRs and CIs regarding diabetes in later life among mothers with thyroid dysfunction or antibodies during pregnancy are presented in Table 5. Overt hypothyroidism during pregnancy was associated with a 6-fold increased risk of later diabetic morbidity (Table 5). Three out of four of these mothers with diabetes were thyroid antibody-positive. Other thyroid dysfunctions or antibodies detected during pregnancy did not have a significant effect on diabetic morbidity during follow-up (Table 5). The association between overt hypothyroidism and diabetes diminished after excluding those with positive antibodies from the thyroid dysfunction analyses. Other results did not change when excluding those with positive thyroid antibodies from thyroid dysfunction analyses or those with thyroid dysfunction from antibody analyses.

Hypertension

Hypertension was observed in 483 (8.3%) mothers during follow-up, of whom 392 belonged to the reference group. The mean age of the women at the time of diagnosis was 44.4 yr (SD, 7.0; range, 24.2–66.7). The HRs and CIs are presented in Table 5.

No statistically significant differences were observed in hypertension morbidity when comparing thyroid dysfunction groups with the reference group or antibody-positive mothers with antibody-negative mothers (Table 5). The results did not change when excluding those with antibodies from thyroid dysfunction analyses or when excluding those with thyroid dysfunction from antibody analyses.

Mortality among mothers with thyroid dysfunction or antibodies during pregnancy

Of the whole study population, 92 women (1.6%) died during follow-up. Of these, 74 belonged to the reference group. No association was seen between mortality and thyroid dysfunction or antibodies during pregnancy (data not shown).

Discussion

This study shows for the first time in a large population that hypothyroidism and thyroid antibodies detected in early pregnancy predict subsequent morbidity to thyroid diseases. In addition, overt hypothyroidism seems to be associated with later diabetes morbidity. We found no association between thyroid dysfunction or antibodies and pregnancy complications.

To our knowledge, this is the first large study in which long-term morbidity of mothers with thyroid dysfunction or antibodies during early pregnancy has been evaluated. For reliable follow-up studies, well-documented population-based cohort data are required. Our study is a large, prospective population-based cohort study with extensive data from the index pregnancies and serum samples from

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TABLE 5. The unadjusted and adjusted HR (95% CI) of diabetes, hypertension, and thyroid disease morbidity among women with thyroid dysfunction or antibodies during pregnancy

	No. diseased/ total (%)	*P* value	HR (95% CI) for diabetes	Adjusted HR (95% CI) for diabetes[a]	Adjusted HR (95% CI) for diabetes[b]
Diabetes morbidity					
Reference group	61/4708 (1.3%)				
Overt hypothyroidism	4/54 (7.4%)	0.006	6.0 (2.2–16.4)	7.1 (2.5–19.7)	7.4 (2.6–20.6)
Subclinical hypothyroidism	6/222 (2.7%)	0.124	2.1 (0.9–4.8)	1.5 (0.6–3.8)	1.7 (0.7–4.1)
Subclinical hyperthyroidism	4/204 (2.0%)	0.346	1.5 (0.6–4.2)	1.2 (0.4–3.4)	1.0 (0.3–3.1)
Overt hyperthyroidism	0/77 (0%)	0.627	NA	NA	NA
Hypothyroxinemia	5/227 (2.2%)	0.229	1.7 (0.7–4.3)	0.9 (0.3–2.5)	1.0 (0.4–2.8)
TPO-Ab negative	75/5463 (1.4%)				
TPO-Ab positive	5/287 (1.7%)	0.599	1.3 (0.5–3.1)	0.9 (0.4–2.3)	1.0 (0.4–2.4)
TG-Ab negative	76/5407 (1.4%)				
TG-Ab positive	3/285 (1.1%)	0.798	0.7 (0.2–2.4)	0.5 (0.2–1.8)	0.6 (0.2–1.8)
			HR (95% CI) for hypertension	**Adjusted HR (95% CI) for hypertension[a]**	**Adjusted HR (95% CI) for hypertension[c]**
Hypertension morbidity					
Reference group	392/4632 (8.5%)				
Overt hypothyroidism	4/52 (7.7%)	1.000	0.9 (0.3–2.4)	0.9 (0.3–2.3)	0.8 (0.3–2.0)
Subclinical hypothyroidism	20/213 (9.4%)	0.615	1.1 (0.7–1.7)	1.0 (0.7–1.6)	1.0 (0.6–1.6)
Subclinical hyperthyroidism	15/202 (7.4%)	0.698	0.9 (0.5–1.5)	0.8 (0.5–1.3)	0.7 (0.4–1.2)
Overt hyperthyroidism	3/75 (4.0%)	0.209	0.5 (0.1–1.4)	0.5 (0.1–1.4)	0.4 (0.1–1.4)
Hypothyroxinemia	18/219 (8.2%)	1.000	0.96 (0.6–1.5)	0.8 (0.5–1.3)	0.4 (0.5–1.3)
TPO-Ab negative	453/5362 (8.4%)				
TPO-Ab positive	21/280 (7.5%)	0.659	0.9 (0.6–1.4)	0.8 (0.5–1.3)	0.8 (0.5–1.2)
TG-Ab negative	445/5308 (8.4%)				
TG-Ab positive	28/277 (10.1%)	0.318	1.2 (0.8–1.8)	1.1 (0.7–1.6)	1.0 (0.4–1.5)
			HR (95% CI) for thyroid disease	**Adjusted HR (95% CI) for thyroid disease[a]**	
Thyroid disease morbidity					
Antibody-positive excluded					
Reference group	87/4287 (2.0%)				
Overt hypothyroidism	6/20 (30.0%)	<0.001	17.7 (7.8–40.6)	18.0 (7.9–41.4)	
Subclinical hypothyroidism	8/113 (6.6%)	0.004	3.3 (1.6–6.9)	2.5 (1.1–5.4)	
Subclinical hyperthyroidism	7/186 (3.6%)	0.118	1.9 (0.9–4.0)	1.5 (0.7–3.3)	
Overt hyperthyroidism	2/65 (3.0%)	0.390	1.5 (0.4–6.2)	1.3 (0.3–5.4)	
Hypothyroxinemia	8/195 (3.9%)	0.071	2.0 (0.98–4.2)	1.5 (0.7–3.2)	
Antibody-positive included					
Reference group	107/4668 (2.3%)				
Overt hypothyroidism	19/51 (37.3%)	<0.001	20.2 (12.4–33.0)	21.5 (13.1–35.3)	
Subclinical hypothyroidism	36/209 (17.2%)	<0.001	8.2 (5.6–11.9)	7.5 (5.1–11.0)	
Subclinical hyperthyroidism	9/199 (4.5%)	0.054	2.0 (1.02–4.0)	1.7 (0.9–3.4)	
Overt hyperthyroidism	3/73 (4.1%)	0.239	1.8 (0.6–5.8)	1.7 (0.5–5.3)	
Hypothyroxinemia	12/223 (5.4%)	0.011	2.4 (1.3–4.3)	1.9 (1.03–3.5)	
Thyroid dysfunction excluded					
TPO-Ab negative	94/4409 (2.1%)				
TPO-Ab positive	13/141 (8.4%)	<0.001	4.2 (2.3–7.4)	3.7 (2.0–6.8)	
TG-Ab negative	94/4376 (2.1%)				
TG-Ab positive	13/177 (6.8%)	<0.001	3.3 (1.9–6.0)	2.6 (1.4–4.8)	
Thyroid dysfunction included					
TPO-Ab negative	137/5425 (2.5%)				
TPO-Ab positive	54/274 (19.7%)	<0.001	8.6 (6.2–11.7)	8.3 (6.0–11.4)	
TG-Ab negative	150/5365 (2.8%)				
TG-Ab positive	39/276 (14.1%)	<0.001	5.4 (3.8–7.7)	4.8 (3.4–6.9)	

Reference group: TSH and fT4 between 5th and 95th percentiles. Overt hypothyroidism: TSH above 95th percentile; fT4 below 5th percentile. Subclinical hypothyroidism: TSH above 95th percentile; fT4 between 5th and 95th percentiles. Subclinical hyperthyroidism: TSH below 5th percentile; fT4 between 5th and 95th percentiles. Overt hyperthyroidism: TSH below 5th percentile; fT4 above 95th percentile. Hypothyroxinemia: TSH between 5th and 95th percentiles; fT4 below 5th percentile. *P* value was obtained from Fisher's exact test when comparing individual thyroid dysfunction group to reference group or comparing antibody-positive group to antibody-negative group. HR represents hazard ratio when comparing individual thyroid dysfunction group to reference group or antibody-positive group to antibody-negative group. NA, Not applicable.

[a] Adjusted for maternal age, parity, and BMI.

[b] Adjusted for maternal age, parity, BMI, and gestational diabetes.

[c] Adjusted for maternal age, parity, BMI, and gestational hypertension/preeclampsia status.

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early pregnancy. Mortality and morbidity are reliably documented in Finland using valid national registers. Thus, the results of this study can be considered to be robust. In addition, iodine deficiency does not exist in Finland; therefore, cases of thyroid dysfunction or disease arise from other factors. There is iodine supplementation and even the pregnant population has sufficient iodine intake (35–37).

The present results show that both overt and subclinical hypothyroidism and thyroid antibodies observed in early pregnancy predict later thyroid disease morbidity of the mother. The risks persisted even after adjusting for background factors. Vanderpump *et al.* showed in a large population-based study that high TSH levels with or without thyroid antibodies are indicators of thyroid disease morbidity during a long-term follow-up period of 20 yr (10). The presence of thyroid antibodies during pregnancy may lead to postpartum thyroiditis (14), and therefore they represent a risk factor of permanent thyroid disease in later life (13). In addition, Haddow *et al.* (12) have previously shown in a small study that untreated hypothyroidism during pregnancy predicts later thyroid diseases. Our results are in accordance with these results.

A new finding in this study is that a hypothyroid condition during pregnancy is a major risk factor for later thyroid disease morbidity. This risk is increased if hypothyroidism during pregnancy is complicated by the presence of antibodies. Thyroid hypofunction during pregnancy probably becomes manifest after failure to adapt to pregnancy-induced demands on the thyroid (1) or because of the effects of thyroid antibodies (2), and the conditions observed during pregnancy reflect poor thyroid function. Therefore, it is logical that hypothyroidism observed in early pregnancy is a risk factor for later thyroid diseases.

Both TPO-Ab and TG-Ab were independent risk factors for subsequent thyroid diseases, and the risk was greater if associated with thyroid dysfunction. Those with hypothyroxinemia during pregnancy also had increased risk for later thyroid diseases, but only if the condition was associated with antibodies. We consider that the cases of hypothyroxinemia in our population arose as a result of poor adaptation to increased thyroid-binding globulin levels or increased demands of the pregnancy, and not from iodine insufficiency.

A hyperthyroid state during early pregnancy was not associated with later thyroid disease morbidity. Hyperthyroidism during early pregnancy may be a result of human chorionic gonadotropin stimulation (1) and can even be considered a normal phenomenon to a certain extent. Suppressed TSH levels have also been detected in pregnancy when circulating human chorionic gonadotropin levels reach a peak (1).

Both insulin-dependent diabetes and type 2 diabetes are associated with thyroid autoantibodies (24, 38), and hypothyroidism is also associated with insulin resistance (15). Our results show a similar association because overt hypothyroidism during pregnancy was a significant risk factor for later diabetes morbidity, the risk being 6-fold. The risk persisted even after adjusting for known risk factors of diabetes, such as maternal age, BMI, parity, and the presence of gestational diabetes. Antibodies may have a key role in the relationship between overt hypothyroidism and diabetes, because three out of four women who had overt hypothyroidism during pregnancy, and later diabetes, showed positivity to one or both antibodies. Therefore, there may be several mechanisms underlying the relationship between overt hypothyroidism and diabetes, including a possible autoimmune component and insulin resistance.

Hypertension is a major health concern that is associated with both overt hypo- and hyperthyroidism (17) and also with subclinical thyroid diseases to a lesser extent (39). Even subtle changes in TSH levels lead to a rise in blood pressure (40, 41). In contrast, thyroid dysfunction or antibodies during pregnancy were not associated with later hypertension. Our study population was relatively young regarding hypertension, the mean age being 48 yr at the end of the follow-up period. The incidence of hypertension in women increases after the menopause (42), and because of the relatively young age of our population, we can presume that most of the women had not yet reached menopause. In addition, it is common clinical practice to follow and treat mild cases of hypertension in primary health care by way of lifestyle changes. Therefore, we may be lacking information on hypertension morbidity when considering mild, non-hospital or non-medically treated cases.

Overall mortality was not higher among subjects with thyroid dysfunction or antibodies during pregnancy. Thyroid dysfunction is associated with cardiovascular mortality in populations under 65 yr of age (19). Our negative finding can be explained by the young age of our population and the rarity of cases of death during follow-up.

Previously, thyroid dysfunction and/or antibodies have been associated with a number of pregnancy complications. A few large studies have been conducted concerning this association, with contradictory results (3, 4, 6, 7, 9). Subclinical hypothyroidism has been associated with placental abruption in one study only (4), but this was not seen in our study. In addition, mothers undergoing T_4 treatment are thought to have an increased risk of preeclampsia (7, 9), but this relationship has not been seen in thyroid dysfunction groups (3, 4,

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6). Gestational diabetes is more common among those receiving T_4 treatment (7, 9), but mothers with hypothyroxinemia have also been thought to have an increased risk (6). In our study, no association was seen between thyroid dysfunction and antibodies in early pregnancy and preeclampsia or gestational diabetes. However, slightly higher prevalence of gestational hypertension was seen among TG-Ab-positive with and without thyroid dysfunction, but the association diminished when those TG-Ab-positive mothers with thyroid dysfunction were excluded. Therefore, this association might not be true and also might be obscured by maternal BMI, which is affected by maternal thyroid function (43). Maternal BMI also presented increased risk for gestational hypertension.

In conclusion, overt and subclinical hypothyroidism and thyroid antibodies detected in early pregnancy seem to predict later thyroid disease morbidity of the mother. In addition, overt hypothyroidism was associated with diabetes morbidity. These findings would suggest that routine assay of thyroid hormones and especially antibodies during pregnancy could be warranted. However, in our study thyroid dysfunction or antibodies detected in early pregnancy did not increase the risk of pregnancy complications.

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