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Thyroid function abnormalities and thyroid autoantibodies in Danish pregnant women

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Summary

Objective: Abnormal thyroid function in pregnant women is a matter of concern. Knowledge on the occurrence of known and unidentified thyroid function abnormalities in a large unselected cohort of pregnant women is warranted as part of the debate on benefits and risks of routine testing.

Design: Cohort study

Participants: 14,323 pregnant women in the North Denmark Region, who had a blood sample drawn as part of the prenatal screening program in early pregnancy (2011-2015).

Measurements: TSH, free thyroxine, thyroid peroxidase and thyroglobulin antibodies were measured in the stored blood samples using an automatic immunoassay (ADVIA Centaur XPT, Siemens Healthineers). Cohort-, method-, and week-specific reference ranges were used for classification of maternal thyroid function and a cut-off of 60 U/ml was used for thyroid autoantibodies. Information in Danish nationwide registers was used to identify diagnosed and treated maternal thyroid disease.

Results: Overall, 15.2% had thyroid function abnormalities in the early pregnancy and 14.9% were thyroid peroxidase and/or thyroglobulin antibody positive. Among women with known thyroid disease (n=365), the frequency of abnormal thyroid function was 45.7%, and 62.8% in women (n=172) who received current treatment in the pregnancy. When maternal thyroid disease was diagnosed in the years following pregnancy (n=313), 46.7% had abnormal thyroid function and 54.3% were thyroid peroxidase and/or thyroglobulin antibody positive in the early pregnancy.

Conclusion: Thyroid function abnormalities and thyroid autoantibodies were common in Danish pregnant women, particularly in women with known or later diagnosed thyroid disease, which raises concern about inadequately treated and unidentified abnormal thyroid function.

Keywords

Thyroid diseases, hyperthyroidism, hypothyroidism, pregnancy and autoimmunity

Introduction

Thyroid diseases are common endocrine disorders and contribute to the chronic disease burden in pregnant women.[1] In early pregnancy, thyroid hormones are of maternal origin,[2] and an adequate supply of maternal thyroid hormones are essential for the pregnancy as well as the developing fetus.[3] Thyroid diseases in women who are or may become pregnant are mainly of autoimmune origin,[4,5] and the presence of maternal thyroid autoantibodies is considered as a risk factor for pregnancy complications.[6,7]

Overt thyroid disease in pregnant women should be treated to prevent maternal and foetal complications.[6,7] However, studies from a number of countries have shown that women with known thyroid disease may not be adequately treated by the time they become pregnant.[8–12] On the other hand, the management of pregnant women with subclinical thyroid disease or isolated changes in free thyroxine (fT4) as well as women who are positive for thyroid peroxidase antibodies (TPO-Ab) and/or thyroglobulin antibodies (Tg-Ab) is not clear,[7] and evidence to recommend for or against routine testing of thyroid function in asymptomatic pregnant women remains insufficient.[6,7] As part of this debate, it is important to provide data on the occurrence of undetected and untreated thyroid function abnormalities in pregnant women.

Nationwide health registers in Denmark and other Nordic countries provide unique opportunities to identify pregnant women with unidentified thyroid function abnormalities, because information on known and later diagnosed thyroid disease can be obtained via linkage to hospital diagnoses and prescriptions of drugs. Among Danish women who were pregnant in the years 1997-2003,[8] a high frequency of thyroid function abnormalities in early pregnancy was observed. This accounted for both women with known thyroid disease and women diagnosed in the years following pregnancy. These findings raised concern about the management of thyroid disease in pregnant women, but more recent data were warranted.[8] Mandatory iodine fortification of salt was implemented in Denmark in the year 2000, which has raised the iodine intake.[13,14] This has changed the pattern of thyroid diseases in the population in general, especially in young individuals.[15–17] Furthermore, clinical routine may have changed during the last decade[18] and a re-evaluation was warranted.

This led us to retrospectively evaluate the frequency of thyroid function abnormalities in a recently established large cohort of pregnant women in the North Denmark Region, and to evaluate the frequency of thyroid autoantibodies (TPO-Ab and Tg-Ab).

Materials and methods

Study population

The study is a retrospective, descriptive cohort study, and the study population is part of the North Denmark Region Pregnancy Cohort located in West Denmark.[19] Denmark was previously iodine deficient with regional differences (moderate iodine deficiency in West and mild iodine deficiency in East). A

mandatory iodine fortification of salt was introduced in the year 2000 as has increased the iodine intake in the Danish population.[13,14] However, iodine intake in Danish pregnant women living in West Denmark was below the recommended when evaluated in 2012 (median urinary iodine concentration in iodine supplement users: 109 μg/l; non-users: 68 μg/l) and 84.1% of the women were iodine supplement users.[20]

In Denmark, all pregnant women are offered an early pregnancy prenatal screening for foetal chromosomal anomalies, which includes a blood sample drawn from the pregnant women at the first pregnancy visit in general practice. As previously described,[19] serum residues from all samples drawn as part of the prenatal screening program in the North Denmark Region were consecutively collected in the period from June 2011 to January 2015, and the woman's first blood sample in the first pregnancy in the study period was selected for the present study (n=14,323). All data were linked in Statistics Denmark and available in encrypted form so that no individuals could be identified by the researcher. The study was approved by the North Denmark Region Committee on Health Research Ethics (N-20150015) and the Danish Data Protection Agency (J.nr. 2008-58-0028).

Biochemical measurements

The blood samples collected in early pregnancy were stored at minus 80 degrees Celsius until the biochemical analyses of maternal thyroid function and thyroid autoantibodies. TSH, fT4, TPO-Ab and Tg-Ab were measured by an ADVIA Centaur XPT automatic immunoassay (Siemens Healthineers, Germany) from September 2015 to May 2016 at Department of Clinical Biochemistry, North Denmark Regional Hospital, Hjørring, Denmark, as described in detail previously.[19]

In the present study, maternal thyroid function was classified from the method- and pregnancy week-specific reference ranges previously established within the specific cohort using the biochemical measurements performed in 2015-2016 from a selected reference cohort, as previously described in detail.[19] Overt hyperthyroidism was defined by TSH <2.5th percentile and fT4 >97.5th percentile, and subclinical hyperthyroidism by TSH <2.5th percentile and fT4 within the reference ranges (5 women had suppressed TSH and fT4 slightly below the lower reference ranges and were classified with subclinical hyperthyroidism). Overt hypothyroidism was defined by TSH >97.5th percentile and fT4 <2.5th percentile, and subclinical hypothyroidism by TSH >97.5th percentile and fT4 within the reference ranges (6 women had elevated TSH and fT4 slightly above the upper reference ranges and were classified with subclinical hypothyroidism). Finally, isolated changes in maternal fT4 were defined by a fT4 concentration below the lower reference limit (hypothyroxinaemia) or above the upper reference limit (hyperthyroxinaemia) combined with a TSH within the reference range. For classification of maternal thyroid autoimmunity, cut-off values of 60 U/ml given by the manufacturer for both TPO-Ab and Tg-Ab were applied. Furthermore, a lower cut-off of 30 U/ml for TPO-Ab and 20 U/ml for Tg-Ab was used in a sub-analysis to evaluate more

subtle changes in maternal thyroid autoimmunity in line with previous Danish investigations of non-pregnant and pregnant women.[17,21]

Diagnosis and treatment

The study relied on a single blood sample from each pregnant woman drawn in the early pregnancy. However, information on hospital diagnoses and redeemed prescription of drugs in Danish nationwide registers from 1994 to 2017 was used to evaluate if the women had diagnosed and treated thyroid disease before, during or after the pregnancy with follow-up until December 31, 2017. Treatment of thyroid disease was identified via registrations of redeemed prescriptions of drugs used for the treatment of thyroid disease and coded according to the Anatomic Therapeutic Chemical (ATC) Classification System in the Danish National Prescription Register.[22] Diagnosis of thyroid disease (in- and outpatient visits) and thyroid surgery were identified via registrations in the Danish National Hospital Register[23] and coded according to the 10th International Classification of Disease (ICD-10).

The subtype of maternal thyroid disease was determined in a stepwise procedure. First, maternal thyroid disease was classified as *thyroid cancer* (n=18) if the woman had a diagnosis of thyroid cancer (ICD-10: DC739) at or after the date of thyroid surgery (ICD-10: KBAA20-KBAA60). Among the remaining women, maternal *hyperthyroidism* (n=301) was defined as any redeemed prescription of antithyroid drug (ATD) (ATC: H03B) and/or a hospital diagnosis of hyperthyroidism (ICD-10: DE05). Subsequently, maternal non-surgical *hypothyroidism* (n=273) was defined as any redeemed prescription of thyroid hormone (Levothyroxine (L-T4)) (ATC: H03A) and/or a hospital diagnosis of hypothyroidism (ICD-10: DE00, DE02, DE03, DE890) and no registration of thyroid surgery. The remaining women with surgical hypothyroidism and women with a hospital diagnosis of benign goiter (ICD-10: DE01 and DE04) were classified as *benign goiter* (n=77). Finally, few women (n=9) had only a hospital diagnosis of thyroiditis (ICD-10: DE06) or post-partum thyroiditis (ICD-10: DO905) and were classified with *other* maternal thyroid disease.

The onset of maternal thyroid disease was defined by the date of first redeemed thyroid drug prescription or by the date of first hospital diagnosis of thyroid disease, whichever came first. However, if the subtype of thyroid disease was cancer, the onset was defined as the first date of a thyroid cancer diagnosis. For women with onset of thyroid disease before the blood sampling in early pregnancy, current treatment was defined by redeemed prescriptions of drugs in the period from 3 months prior to pregnancy start until the date of blood sampling. A subgroup of women (n=30) were classified with previous hyperthyroidism but received LT-4 in the pregnancy. In this group, six women had a registration of previous thyroid surgery, but information on previous treatment with radioiodine was not available.

Statistical analyses

Results were reported as the number of women and the frequency of biochemical thyroid function abnormalities and thyroid autoantibody positive among all women, as well as in women with known or later diagnosed thyroid disease according to treatment and type of diagnosed thyroid disease. Furthermore, results were evaluated according to information on maternal characteristics, which was available from the Danish Medical Birth Register[24] (age, parity, pre-pregnancy body mass index (BMI), and smoking) and from Statistics Denmark (country of birth). Predictors of abnormal maternal thyroid function and thyroid autoimmunity were evaluated in univariate stratified analyses and in multivariate logistic regression models with dichotomous variables (odds ratio (OR) with 95% confidence interval (CI)). Statistical analyses were preformed using STATA version 15 (StataCorp, College Station, TX).

Results

Altogether 14,323 pregnant women in the North Denmark Region were included in the study. The women had a median age of 30 years (ranging from 16 to 51 years) and 88.3% were born in Denmark. Blood samples were drawn in median pregnancy week 10 (range: 4 to 20). A total of 678 (4.7%) women had registrations of thyroid disease in nationwide registers and were diagnosed before (n=365) or after (n=313) the blood sampling.

Overall findings

Overall, 15% of the women had TSH and/or fT4 outside the pregnancy week specific reference ranges and were classified with thyroid dysfunction (Table 1). All subtypes of thyroid dysfunction were observed, and hypothyroidism was the most frequent thyroid function abnormality (Table 1). Altogether, 47 women (0.3%) had TSH above 10 mIU/l. As expected, subclinical thyroid function abnormalities were more frequent than overt abnormalities, and 5% of the women had isolated changes in fT4. Considering thyroid autoimmunity, 15% of the women were positive for TPO-Ab and/or Tg-antibodies (Table 1) with 10% being TPO-Ab positive (irrespective of Tg-Ab status) and 10% being Tg-Ab positive (irrespective of TPO-Ab status).

When analyses were restricted to women who gave birth to a singleton live-born child (89.9%), the frequencies of biochemical thyroid function abnormality and thyroid autoimmunity in early pregnancy were comparable to the overall figures (thyroid dysfunction: 14.9%; TPO-Ab and/or Tg-Ab: 14.8%). Furthermore, the exclusion of women diagnosed with thyroid cancer (n=18) did not change results. Finally, when the cut-offs for thyroid autoantibodies were reduced to 30 U/ml for TPO-Ab and 20 U/ml for Tg-Ab the number of thyroid autoantibody positive women increased (TPO-Ab and/or Tg-Ab: 53.2%; Total TPO-Ab positive 45.7%; Total Tg-Ab positive 22.4%).

Women with diagnosed thyroid disease

The frequencies of thyroid function abnormalities and thyroid autoimmunity in early pregnancy were considerably higher among women with known or later diagnosed thyroid disease (Table 2 and 3) as compared with the overall findings. Thus, 167 of the 365 women with known thyroid disease had abnormal thyroid function in the early pregnancy and the frequency of thyroid autoimmunity was similarly high (Table 2). The highest frequency of thyroid function abnormalities was observed among women who received current treatment (Table 2). When stratified by subtype of disease and treatment in early pregnancy (Figure 1), the frequency of thyroid function abnormalities was high in women who received ATD (Figure 1A) and in women treated with L-T4 (Figure 1B). Notably, thyroid function abnormalities were also observed in women who were previously diagnosed with thyroid disease but received no current treatment in the pregnancy (Figure 1). A small subgroup of the women (n=15) were newly diagnosed with thyroid disease in the early pregnancy. The frequency of thyroid function abnormalities was high in this group (80%) and included both hyperthyroidism and hypothyroidism. However, the frequencies of thyroid function abnormalities among women with known disease were similar after the exclusion of this group (thyroid dysfunction: 44.3%; TPO-Ab and/or Tg-Ab: 58.0%).

Among women diagnosed with thyroid disease after the blood sampling, the frequency of thyroid function abnormalities in early pregnancy was similarly high and dominated by both overt and subclinical findings (Table 3). When stratified by subtype of disease (Figure 1), 36 (27.7%) of the 130 women with later diagnosis of hyperthyroidism had overt or subclinical hyperthyroidism as evaluated from the early pregnancy blood sample (Figure 1A). On the other hand, 74 (52.8%) of the 140 women with later diagnosis of hypothyroidism had hypothyroidism in early pregnancy (Figure 1B). Notably, 170 of the 313 women with later diagnosis of thyroid disease were positive for TPO-Ab and/or Tg-Ab in early pregnancy. The women were followed for a median of 4.2 years after the pregnancy for diagnosis of thyroid disease (range 2.3-6.5 years). When the follow-up period was restricted to 2 years, the number of women with onset of thyroid disease was lower (n=196), but the frequencies of biochemical thyroid dysfunction and thyroid autoimmunity were at a similar level (thyroid dysfunction 49.5%; TPO-Ab and/or Tg-Ab: 55.1%).

Maternal characteristics

The frequency of thyroid function abnormalities and thyroid autoimmunity differed according to maternal characteristics, and statistical significant predictors were observed in multivariate analyses (Table 4). Higher maternal age was a risk factor for biochemical hypothyroidism as well as thyroid autoimmunity. On the other hand, higher parity and non-Danish origin were risk factors for hyperthyroidism. Maternal smoking was

associated with a reduced risk of hypothyroidism and thyroid autoimmunity, whereas maternal BMI $\geq$ 30 kg/m^2 was a risk factor for maternal hypothyroidism and isolated abnormal fT4. Notably, higher maternal

BMI reduced the risk of hyperthyroidism, and this was most pronounced for BMI ≥ 30 kg/m^2, whereas the OR for BMI 25-30 kg/m^2 was 0.81 (0.65-1.01).

Discussion

Principal findings

In a large cohort of 14,323 pregnant women in the North Denmark Region, the frequency of thyroid function abnormalities and thyroid autoimmunity was high. The linkage between thyroid function measurements in blood samples from pregnant women and information in nationwide registers provided the unique opportunity to address thyroid function in women with known thyroid disease and in women first time diagnosed with thyroid disease in the years following the pregnancy. The frequency of thyroid function abnormalities in early pregnancy was even higher in these groups, which raise concern about inadequately treated as well as undetected and untreated thyroid disease in Danish pregnant women.

Previous investigations

Previous investigations on the frequency of thyroid function abnormalities in Danish pregnant women included women who were pregnant in the years 1997-2003 (nationwide study)[8] and in 2008 (East Denmark).[25] Studies of the general Danish population have shown, that the mandatory iodine fortification has been followed by an increase in the incidence of hyper- and hypothyroidism, particularly in young individuals, and it is debated whether this increase is explained by an increase in the occurrence of autoimmune thyroid disease.[15,16] Furthermore, the number of individuals with TPO-Ab and/or Tg-Ab has increased, most pronounced in young women and at low antibody levels.[17] With these changes in iodine intake during the last 20 years and a possible change in clinical routine for treating thyroid disease,[18] follow-up on the occurrence of thyroid disease in pregnant women and specification of subtypes of disease was warranted.

The present study was conducted in West Denmark more than 10-years after the implementation of iodine fortification of salt, and the frequency of thyroid function abnormalities in pregnant women was 15% and parallel to previous Danish investigations.[8,25] However, methodological differences make it difficult to compare results of the different studies, and the cross-sectional design from a single measurement of thyroid function in early pregnancy should be acknowledged.

The presence of thyroid autoantibodies are related to a process of autoimmune destruction of thyroid tissue.[26] Still, thyroid disease may not be present.[27] Considering the occurrence of thyroid autoimmunity, a recent study from East Denmark showed a marked increase in the presence of both TPO-Ab and Tg-Ab in Danish pregnant women after the iodine fortification of salt, and it was dominated by an increase in low autoantibody titers.[21] These findings were comparable to the figures on thyroid autoimmunity that we now report from West Denmark, also when different cut-offs for thyroid autoantibodies were applied. In

general, the frequency of thyroid autoantibodies in pregnant women varies worldwide and across populations with different iodine intake. Thus, the prevalence of TPO-Ab positive women was recently reported to range from 4.7 to 15.2% and Tg-Ab positive women from 4.2 to 12.7%.[28]

Women with known thyroid disease

Overt thyroid disease in pregnant women should be adequately treated to prevent maternal and foetal complications.[7] Preconception counselling and early detection of a pregnancy is recommended when the mother suffers from both hyper- and hypothyroidism.[7] Optimally a pregnancy should be planned and the women should be informed to contact the responsible physician as soon as a pregnancy is detected.[7] For women treated with ATD, the choice of drug is of importance considering the risk of birth defects.[29] In women treated with L-T4, the focus is on the need to increase the dose from the early pregnancy.[7]

We observed a very high frequency of early pregnancy thyroid function abnormalities in women with known thyroid disease, which was dominated by a high frequency of both overt and subclinical abnormalities. Similar figures have been observed in different countries[9–12] and are also in line with the findings in the nationwide study of pregnant women in Denmark with data collected nearly 20 years ago.[8] These findings raise important concerns about the management of thyroid disease in pregnant women. However, some clinical aspects should be considered in the interpretation of the results. According to clinical guidance overtreatment with ATD should be avoided to prevent foetal hypothyroidism, and it is recommended to keep maternal thyroxine in the upper part of the reference range or slightly above the upper level during treatment.[7] This may to some extent explain our findings of biochemical subclinical hyperthyroidism among nearly 30% of women with known hyperthyroidism treated with ATD. On the other hand, the target for TSH in pregnancy among women treated for hypothyroidism with L-T4 is in the lower half of the reference range.[7] Thus, our finding of biochemical hypothyroidism in 50% of Danish pregnant women in current treatment with L-T4 is a serious concern and stresses a need to improve the management of women with known hypothyroidism. Such improvements should include awareness among general practitioners, endocrinologists, and the patients. In Denmark, hypothyroidism in pregnant women is managed by endocrinologists, and timely referral from general practice, preconception counselling as well as early pregnancy detection are important aspects.

Women with later diagnosis of thyroid disease

A unique methodology in the present study was the possibility to identify women who had no known thyroid disease at the time of pregnancy, but were diagnosed in the years following the pregnancy. This was possible via linkage to information in Danish nationwide registers. We observed a high frequency of thyroid function abnormalities in the early pregnancy in this group of women. This was in line with the previous Danish nationwide investigation that applied the same methodology for data linkage, but used

another thyroid function assay and blood samples that had been drawn in years around the implementation of iodine fortification and stored for a longer period prior to analys.[8] The findings, in two independent Danish cohorts, raise concern about the presence of undetected and untreated thyroid function abnormalities in pregnant women. The evaluation was based on a single measurement of thyroid function in both cohorts and repeated sampling would have been warranted. However, the specific high frequency of thyroid function abnormalities as well as thyroid autoimmunity among women who were diagnosed with thyroid disease in the years following the pregnancy suggest that the abnormalities were likely to persist. The findings are important contributions to the ongoing debate on benefits and risk of routine testing of thyroid function in pregnant women.[30] Notably, the frequency of maternal overt hypothyroidism observed in the present and other studies was considerably higher than congenital hypothyroidism which might favour routine testing.[30] Other aspects of this debate include the optimal timing of maternal thyroid function testing in pregnancy, and our results do not add to the discussion on the potential benefits of preconception testing. Finally, the subsequent consideration is whether the abnormalities affect the outcome of a pregnancy. The adverse outcomes of untreated maternal overt thyroid function abnormalities are evident.[7] On the other hand, results of previous investigations are not consistent regarding the role of smaller deviations in maternal thyroid function.[28,31,32] Thus, additional studies on the outcomes of different types and severity of maternal thyroid function abnormalities are warranted.

Methodological comments

A strength of the present study was the large and unselected study population of pregnant women and the possibility to measure thyroid function as well as thyroid autoantibodies. The blood samples were collected as part of the prenatal screening program for chromosomal anomalies and the participation rate in this program is high (>90%),[33] which reduces the risk of selection bias.

The validity of the Danish nationwide registers is considered high.[22,23] The diagnosis of thyroid disease in the DNHR revealed misclassification in less than 2% of 900 cases.[34] However, the DNHR do not reflect completeness regarding diseases treated solely in general practice, but the combined use of hospital diagnoses and redeemed prescriptions of drugs further improves the completeness regarding classification of disease in the general Danish population.[23]

The blood samples were stored at minus 80 degrees Celsius until the measurement of maternal thyroid function parameters and thyroid autoantibodies. Previous studies have shown that thyroid function parameters as well as thyroid autoantibodies are stable for more than 20 years when stored at minus 25 degrees Celcius.[35] We measured TSH and fT4 using an automated immunoassay. Measurement of free thyroid hormones using an indirect method is prone to alternations in binding proteins, which may be method dependent and may challenge the comparison between results of different assays.[36,37] However, we used method- and pregnancy week specific reference ranges established within the cohort[19] to classify

maternal thyroid function. We measured TPO-Ab and Tg-Ab, but not TSH-receptor antibodies, which limited the possibility to distinguish between hyperthyroidism of Graves' disease and gestational hyperthyroidism.

The study was based on routinely collected blood samples that were stored in a biobank. The linkage to Danish nationwide registers provided information on maternal thyroid disease and other covariates, however, no information was available on maternal use of iodine supplementation in pregnancy and urine samples were not collected for measurement of urinary iodine concentration. Such data would be warranted to evaluate results in relation to population iodine status and iodine fortification.

In line with other reports[38] we observed that maternal characteristics predicted the presence of different thyroid function abnormalities. Such characteristics are important to consider in outcome studies, since they may also associate with the outcomes of pregnancy or child development as well as introduce confounding.

Perspectives

The present study demonstrates a high frequency of thyroid function abnormalities in a large cohort of Danish pregnant women. The findings raise concern about inadequately treated and even untreated maternal thyroid disease in early pregnancy and call for a focus on optimal management and control of thyroid disease in women with known thyroid disease. Finally, results add data to the debate on routine testing of thyroid disease in pregnant women to identify undiagnosed disease, and call for studies evaluating the outcome of undetected and untreated thyroid function abnormalities in pregnant women.

Conflict of interest

Nothing to declare.

Data availability statement

Research data cannot be shared due to regulatory restrictions that apply to the availability of data generated and analysed during this study to preserve patient confidentiality and according to the GDPR regulations.

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Table 1 Frequency of biochemical thyroid function abnormalities and thyroid autoimmunity in the total cohort (n=14,323)

	n	%
Thyroid dysfunction[a]	**2178**	**15.2**
Hyperthyroidism	**557**	**3.9**
Overt	230	1.6
Subclinical	327	2.3
Hypothyroidism	**905**	**6.3**
Overt	140	1.0
Subclinical	765	5.3
Abnormal fT4	**716**	**5.0**
Hyperthyroxinemia	258	1.8
Hypothyroxinemia	458	3.2
Thyroid autoimmunity[b]	**2129**	**14.9**
Total TPO-Ab positive	1558	10.9
Only TPO-Ab positive	**634**	**4.4**
Total Tg-Ab positive	1495	10.4
Only Tg-Ab positive	**571**	**4.0**
TPO-Ab and Tg-Ab positive	**924**	**6.5**

[a] Abnormal TSH and/or fT4

[b] TPO-Ab >60 U/ml and/or Tg-Ab >60 U/ml

Abbreviations: fT4, free thyroxine; Tg-Ab, thyroglobulin antibodies; TPO-Ab, thyroid peroxidase antibodies

Table 2 Frequency of biochemical thyroid function abnormalities and thyroid autoimmunity in women with diagnosis of thyroid disease prior to blood sampling in early pregnancy

	All women with known disease (n=365)		**No medical treatment in early pregnancy (n=193)**		**Medical treatment in early pregnancy (n=172)**	
	n	%	n	%	n	%
Thyroid dysfunction[a]	**167**	**45.7**	**59**	**30.6**	**108**	**62.8**
Hyperthyroidism	**41**	**11.2**	**16**	**8.2**	**25**	**14.5**
Overt	14	3.8	3	1.6	11	6.4
Subclinical	27	7.4	13	6.6	14	8.1
Hypothyroidism	**107**	**29.3**	**37**	**19.2**	**70**	**40.7**
Overt	22	6.0	10	5.2	12	7.0
Subclinical	85	23.3	27	14.0	58	33.7
Abnormal fT4	**19**	**5.2**	**6**	**3.2**	**13**	**7.6**
Hyperthyroxinemia	13	3.6	3	1.6	10	5.8
Hypothyroxinemia	6	1.6	3	1.6	3	1.8
Thyroid autoimmunity[b]	**213**	**58.3**	**87**	**45.0**	**126**	**73.3**
Total TPO-Ab positive	189	51.8	74	38.3	115	66.9
Only TPO-Ab positive	**61**	**16.7**	**22**	**11.4**	**39**	**22.7**
Total Tg-Ab positive	152	41.6	65	33.6	87	50.6
Only Tg-Ab positive	**24**	**6.5**	**13**	**6.7**	**11**	**6.4**
TPO-Ab and Tg-Ab positive	**128**	**35.1**	**52**	**26.9**	**76**	**44.2**

[a] Abnormal TSH and/or fT4

[b] TPO-Ab >60 U/ml and/or Tg-Ab >60 U/ml

Abbreviations: fT4, free thyroxine; Tg-Ab, thyroglobulin antibodies; TPO-Ab, thyroid peroxidase antibodies

Table 3 Frequency of biochemical thyroid function abnormalities and thyroid autoimmunity in women diagnosed with thyroid disease after the blood sampling in early pregnancy (n=313)

	n	%
Thyroid dysfunction[a]	**146**	**46.7**
Hyperthyroidism	**42**	**13.4**
Overt	25	8.0
Subclinical	17	5.4
Hypothyroidism	**81**	**25.9**
Overt	24	7.7
Subclinical	57	18.2
Abnormal fT4	**23**	**7.4**
Hyperthyroxinemia	14	4.5
Hypothyroxinemia	9	2.9
Thyroid autoimmunity[b]	**170**	**54.3**
Total TPO-Ab positive	145	46.3
Only TPO-Ab positive	**39**	**12.5**
Total Tg-Ab positive	131	41.8
Only Tg-Ab positive	**25**	**8.0**
TPO-Ab and Tg-Ab positive	**106**	**33.8**

[a] Abnormal TSH and/or fT4

[b] TPO-Ab >60 U/ml and/or Tg-Ab >60 U/ml

Abbreviations: fT4, free thyroxine; Tg-Ab, thyroglobulin antibodies; TPO-Ab, thyroid peroxidase antibodies

Table 4 Predictors of biochemical thyroid function and thyroid autoimmunity

	Crude OR[a]	95% CI	Adjusted OR[ab]	95% CI
Maternal age (ref.: < 35 years)				
Hyperthyroidism	1.35	1.09-1.68	1.18	0.94-1.48
Hypothyroidism	1.24	1.03-1.48	1.28	1.06-1.54
Isolated abnormal fT4	1.00	0.81-1.24	0.97	0.78-1.22
Thyroid autoimmunity[c]	1.41	1.25-1.59	1.37	1.21-1.56
Maternal parity (ref.: nulliparous)				
Hyperthyroidism	1.65	1.37-1.97	1.58	1.31-1.91
Hypothyroidism	0.87	0.76-1.01	0.82	0.71-0.96
Isolated abnormal fT4	1.01	0.86-1.18	1.01	0.85-1.18
Thyroid autoimmunity[c]	1.14	1.04-1.26	1.07	0.97-1.18
Maternal origin (ref.: born in Denmark)				
Hyperthyroidism	1.62	1.28-2.05	1.50	1.18-1.90
Hypothyroidism	1.06	0.85-1.32	1.07	0.85-1.33
Isolated abnormal fT4	0.95	0.74-1.22	0.99	0.77-1.27
Thyroid autoimmunity[c]	1.13	0.98-1.31	1.10	0.95-1.27
Maternal smoking (ref.: non-smoking)				
Hyperthyroidism	0.90	0.67-1.20	0.97	0.73-1.30
Hypothyroidism	0.65	0.50-0.84	0.64	0.49-0.83
Isolated abnormal fT4	1.08	0.85-1.37	1.05	0.83-1.34
Thyroid autoimmunity[c]	0.70	0.59-0.82	0.71	0.60-0.84
Maternal pre-pregnancy BMI (ref.: < 30 kg/m^2)				
Hyperthyroidism	0.48	0.35-0.66	0.49	0.35-0.67
Hypothyroidism	1.41	1.18-1.68	1.44	1.21-1.73
Isolated abnormal fT4	1.42	1.17-1.72	1.39	1.14-1.70
Thyroid autoimmunity[c]	0.98	0.86-1.12	1.00	0.87-1.14

Abbreviations: BMI, body mass index; CI, confidence interval; fT4, free thyroxine; OR, odds ratio; ref., reference group

[a] The reference group for the dependent variables hyperthyroidism, hypothyroidism, isolated abnormal and fT4 was all women with TSH and fT4 within the pregnancy week specific reference ranges, and for thyroid autoimmunity it was thyroid autoantibody negative women.

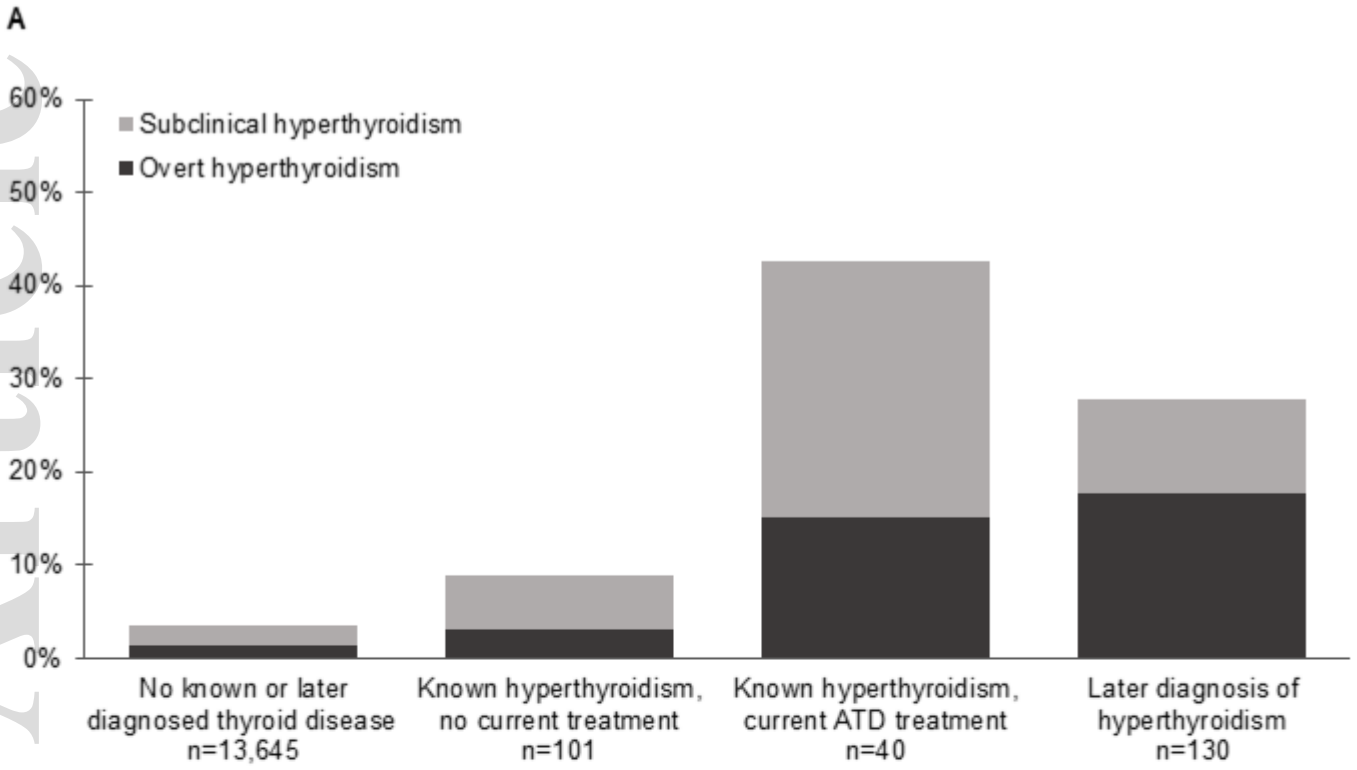
[b] Adjusted model included all predictors mentioned in the table.

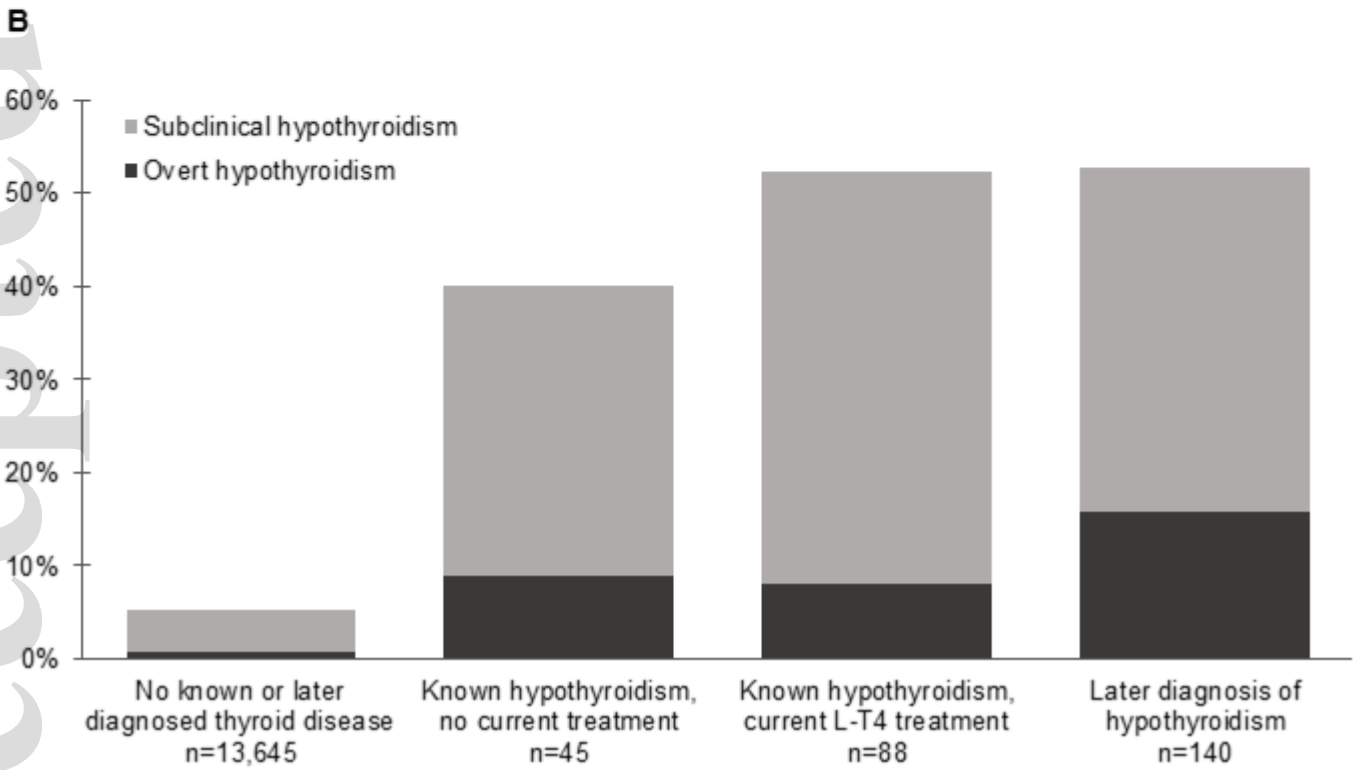
[c] TPO-Ab >60 U/ml and/or Tg-Ab >60 U/ml

Legends to figures

Figure 1

Frequencies of biochemical hyperthyroidism (**A**) and hypothyroidism (**B**) among women with diagnosed hyperthyroidism (**A**) and hypothyroidism (**B**), and stratified by current treatment (antithyroid drug (ATD) and Levothyroxine (L-T4)) in early pregnancy as well as onset of disease. Women with known hyperthyroidism who received current treatment with L-T4 (n=30) as well as women who received current L-T4 after previous thyroid surgery of benign goiter or cancer (n=14) were not shown.





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