Hypothyroidism incidence in and around pregnancy: a Danish nationwide study

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Abstract

Objective: Immunological changes in and after a pregnancy may influence the onset of autoimmune diseases. An increased incidence of hyperthyroidism has been observed both in early pregnancy and postpartum, but it remains to be studied if the incidence of hypothyroidism varies in a similar way.

Design: Population-based cohort study using Danish nationwide registers.

Method: All women who gave birth to a singleton live-born child in Denmark from 1999 to 2008 ($n=403\,958$) were identified, and data on hospital diagnosis of hypothyroidism and redeemed prescriptions of thyroid hormone were extracted. The overall incidence rate (IR) of hypothyroidism during 1997–2010 and the IR in three-month intervals before, during and after the woman's first pregnancy in the study period were calculated and compared with the IR of hyperthyroidism.

Results: Altogether 5220 women were identified with onset of hypothyroidism from 1997 to 2010 (overall IR 92.3/100 000/year) and 1572 women developed hypothyroidism in the period from 2 years before to 2 years after birth of the first child in the study period. The incidence of hypothyroidism decreased during the pregnancy (incidence rate ratio (IRR) vs overall IR in the rest of the study period: first trimester: 0.89 (95% CI: 0.66–1.19), second trimester: 0.71 (0.52–0.97), third trimester: 0.29 (0.19–0.45)) and increased after birth with the highest level at 4–6 months postpartum (IRR 3.62 (2.85–4.60)).

Conclusion: These are the first population-based data on the incidence of hypothyroidism in and around pregnancy. The incidence declined during pregnancy followed by a sharp increase postpartum. Notably, hypothyroidism as opposed to hyperthyroidism showed no early pregnancy increase.

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Introduction

Autoimmune thyroid diseases result from non-physiological alterations in the immune system that either stimulate the thyroid gland to excessive production of thyroid hormone or damage the thyroid gland and compromise its ability to produce and secrete thyroid hormone (1). Pregnancy is a period of physiological changes in the immune system with a typical immune suppression during the pregnancy followed by an immune rebound after birth of the child (2).

These pregnancy-associated physiological changes in the maternal immune system may influence the onset of an autoimmune thyroid disease (2). One type of autoimmune thyroid disease associated with pregnancy is postpartum thyroiditis that may lead to both transient hyperthyroidism and hypothyroidism (3). However, we previously observed that the incidence of prolonged maternal hyperthyroidism in need of antithyroid drug therapy was high in the postpartum period, and also

in the early pregnancy, which is at variance with other diseases of autoimmune origin (e.g. rheumatoid arthritis and inflammatory bowel disease) (4).

We used data from the Danish nationwide registers to study the incidence of prolonged maternal hypothyroidism in and around pregnancy. We aimed to identify women with persistent, autoimmune hypothyroidism that was diagnosed for the first time in the period from 2 years before to 2 years after the birth of a child and to provide estimates on the incidence in three-month intervals in and around pregnancy. We *a priori* expected that the postpartum period would be a significant risk factor for the onset of hypothyroidism. This would be in accordance with the 'immune rebound hypothesis' previously proposed by Amino *et al.* (5) as well as the postpartum peak observed for hyperthyroidism (4) and the previous notion that some women with hypothyroidism apparently caused by postpartum thyroiditis are in need of permanent thyroid hormone replacement therapy (6). A pertinent question was how the incidence of hypothyroidism varied during the pregnancy and how this compared with the variation observed for hyperthyroidism.

Methods

Study population

We conducted a population-based cohort study using Danish nationwide registers and studied all women who gave birth to a singleton live-born child in Denmark from 1st January 1999, to 31st December 2008, and had no registration of multiple births. In Denmark, nationwide health data are systematically registered and a unique 10-digit identification number is provided at birth and used in all the registers. Information on all births in Denmark is available in the Danish Medical Birth Register (MBR) (7), and we identified the woman's first live birth in the study period and the 2 year period before and after this event. In addition, the MBR provided information on the woman's age, parity and smoking during the pregnancy. The Statistic Denmark had information on geographical residence, cohabitation and origin. The study was approved by the Danish Data Protection Agency.

Maternal hypothyroidism

We studied incident hypothyroidism diagnosed in the age of 15–45 years, which in Denmark predominantly is spontaneous, autoimmune hypothyroidism (8). For the

identification of maternal thyroid disease, information was available on hospital diagnosis of the disease, thyroid surgery procedure and redeemed prescriptions of thyroid medication. The Danish National Prescription Register (DNPR) (9) holds nationwide data on all redeemed prescriptions of drugs from Danish pharmacies since 1995 classified according to the Anatomical Therapeutic Chemical classification system (ATC). The Danish National Hospital Register (DNHR) (10) holds nationwide data on all inpatient visits to any Danish hospital since 1977 and all hospital inpatient and outpatient visits since 1995 classified according to the 8th revision of the International Classification of Disease (ICD-8) from 1977 to 1993 and the 10th revision (ICD-10) from 1994.

Women who redeemed prescriptions of antithyroid drugs (ATC H03B) were first identified and classified with hyperthyroidism, as described previously in detail (4). After this, incident cases of prolonged hypothyroidism were defined as women who redeemed a minimum of two prescriptions of thyroid hormone (ATC H03A) in the period from 1st January 1997 to 31st December 2010 and who redeemed prescriptions for a period of more than 2 years and had no hospital diagnosis of congenital or iatrogenic hypothyroidism. In addition, women classified with incident hypothyroidism had no previous redeemed prescription(s) of thyroid hormones, no hospital diagnosis of hypothyroidism (ICD-8: 243.99–244.09 and ICD-10 groups: E03 and E89.0) more than three months before the first redeemed prescription of ATD and no previous registration of thyroid surgery (ICD-8: 080.60–082.20 and ICD-10: BAA20–BAA60). The time of onset of hypothyroidism was defined by the date the first prescription of thyroid hormone was redeemed from a Danish pharmacy. Women identified with onset of hypothyroidism in the years 2008–2010 and who redeemed multiple prescriptions of thyroid hormone were included, although treatment beyond 2 years could not be ascertained (end of follow-up in 2010).

Statistical analysis

The incidence rate (IR) of maternal hypothyroidism from 1997 to 2010 was estimated as the number of women with onset of hypothyroidism divided by the total years of observation time and expressed per 100 000 women per year with 95% confidence interval (95% CI). The IR of maternal hypothyroidism was subsequently calculated in each three-month interval in and around the woman's first pregnancy in the study period. The incidence rate

ratio (IRR) with 95% CI was calculated by comparison with the IR in the rest of the period 1997–2010, using the method described previously in detail (4).

Additional analyses included a comparison with women identified with transient hypothyroidism (treatment for a period of less than 2 years) and sub-analyses of the association to maternal parity. Statistical analyses were performed using STATA version 11 (Statacorp). A level of significance of 5% was chosen.

Results

Main analyses

Altogether 403 958 women were included in the study and gave birth to a singleton live-born child in Denmark from 1999 to 2008. Among these, a total of 3679 women had previously been identified with hyperthyroidism. In this study, a total of 5220 women were identified with onset of hypothyroidism from 1997 to 2010 (median age at diagnosis 33.7 years (interquartile range

Table 1 Characteristics of mothers giving birth to a singleton live-born child in Denmark from 1999 to 2008 according to maternal onset of hypothyroidism from 1997 to 2010. Information was obtained at the time of the mother's first birth of a child in the study period.

	No incident hyperthyroidism or hypothyroidism 1997–2010		Incident hypothyroidism 1997–2010	
	<i>n</i>	%	<i>n</i>	%
Mothers	395 065		5220	
Age (years)				
≤30	240 868	61.0	2939	56.3
>30	154 197	39.0	2281	43.7
Parity*				
1	256 476	64.9	3087	59.1
≥2	138 589	35.1	2133	40.9
Cohabitation				
Married	201 317	51.0	3042	58.3
Not married	193 748	49.0	2178	41.7
Origin				
Born in Denmark	347 698	88.0	4443	85.1
Not born in Denmark	47 367	12.0	777	14.9
Residence				
West Denmark	208 394	52.7	2623	50.3
East Denmark	186 671	47.3	2597	49.7
Smoking in pregnancy [§]				
Yes	77 386	20.5	788	15.8
No	300 032	79.5	4193	84.2

*Previous live birth and stillbirth including index pregnancy; [§]Reported smoking or smoking cessation in the pregnancy. Mothers with missing value on smoking not included.

Figure 1

Incidence rates (with 95% confidence interval) of maternal hypothyroidism in 3-month intervals before, during and after the first pregnancy leading to birth of a live-born child from 1999 to 2008 in a Danish nationwide study of 403 958 women. The dashed horizontal lines are the overall incidence rate of maternal hypothyroidism in women aged 15–45 years in the study period from 1997 to 2010 (92.3/100 000/year) with 95% confidence interval.

(IQR: 29.8–37.8 years), median duration of treatment for hypothyroidism in the observation period: 6.0 years (IQR 4.1–8.4 years)), leaving 395 065 women with no incident hypothyroidism or hyperthyroidism. All women were studied in relation to their first pregnancy in the study period. Maternal characteristics indicated that women with hypothyroidism were older, less frequently smoking and more often living in East Denmark (Table 1).

The overall IR of maternal hypothyroidism from 1997 to 2010 (horizontal line in Fig. 1) was 92.3/100 000/year (95% CI: 89.9–94.9) compared with that of 65.0/100 000/year for maternal hyperthyroidism. Among cases of incident hypothyroidism, altogether 1572 women had onset of disease in the 4-year period from 2 years before to 4 years after birth of the first child in the study period (median age at diagnosis 30.7 years (IQR: 27.8–34.1 years)). The IR of hypothyroidism in and around pregnancy declined during the pregnancy (Fig. 1) followed by a sharp increase after birth of the child that reached the highest level at 4–6 months postpartum (IRR first trimester vs the rest of the study period: 0.89 (95% CI: 0.66–1.19)), second trimester (0.71 (0.52–0.97)), third trimester (0.29 (0.19–0.45)) and 4–6 months postpartum (3.62 (2.85–4.60)).

The IR of maternal hypothyroidism was subsequently compared with that of hyperthyroidism (Fig. 2).

Figure 2

Relative frequency of incident maternal hypothyroidism and hyperthyroidism before, during and after the first pregnancy leading to birth of a live-born child from 1999 to 2008 in a Danish nationwide study of 403 958 women. The reference (set to 100%) is the overall incidence rate of disease in the study population from 1997 to 2010 (92.3/100 000/year for maternal hypothyroidism and 65.0/100 000/year for hyperthyroidism).

Both types of thyroid dysfunction showed a decline late in pregnancy, but only hyperthyroidism showed an early pregnancy increase. After birth of the child, both hypothyroidism and hyperthyroidism showed a sharp incidence increase, but the incidence peak was earlier for hypothyroidism and completed within 1 year postpartum (Fig. 2).

Additional analyses

An increased incidence of hypothyroidism postpartum was observed both among women who had given birth to their first child and also when the studied postpartum period was after the woman's second, third or later child birth. However, the IRR for postpartum onset was higher after a woman's first pregnancy (IRR for onset 4–6 months postpartum vs the rest of the study period: 4.41 (95% CI: 3.45–5.64)) than after a second or later pregnancy (IRR 2.52 (95% CI: 2.00–3.18)).

If analyses were restricted to women who only gave birth once during the study period to exclude a possible interference with subsequent pregnancies, these analyses gave a similar incidence pattern in and around pregnancy.

A subgroup of women were not included in the main analyses because their registration of redeemed prescriptions indicated that replacement therapy had

Figure 3

Incidence rates (IR) of maternal hypothyroidism in 3-month intervals after the birth of a live-born child from 1999 to 2008 in a Danish nationwide study of 403 958 women. The dashed horizontal lines are the overall incidence rate of persistent hypothyroidism from 1997 to 2010 (92.3/100 000/year) and transient hypothyroidism from 1997 to 2009 (18.3/100 000/year). Women who only redeemed one prescription of thyroid hormone in the last year of the study period (year 2010) were not included due to uncertainty on whether the treatment was transient or persistent. *95% CI of the 3-month interval IR and the 95% CI of the overall IR were not overlapping.

been withdrawn within 2 years ($n=1052$). The overall IR of such transient hypothyroidism that might have been caused by autoimmune thyroiditis from 1997 to 2009 was 18.3/100 000/year (95% CI: 17.5–19.8). Postpartum onset of transient hypothyroidism was less frequently observed than permanent hypothyroidism. However, it showed a similar pattern postpartum with an incidence peak confined to 1 year after birth, reaching the highest level at 4–6 months postpartum (Fig. 3).

Discussion

Principal findings

In this Danish population-based study, the incidence of hypothyroidism showed a gradual decline during pregnancy. This variation was followed by an increase in the first year after birth of the child, which peaked at 4–6 months postpartum. The incidence pattern was similar to that of hyperthyroidism in late pregnancy and postpartum, but the early pregnancy incidence peak of hyperthyroidism was not observed for hypothyroidism.

Autoimmune hypothyroidism

This study aimed to describe the incidence of prolonged maternal hypothyroidism in and around pregnancy. We had no results of thyroid function testing or thyroid autoantibodies, but indicators of persistent hypothyroidism were available from the registration of redeemed prescriptions of thyroid hormone for a period of more than 2 years. The use of the Danish nationwide registrations provided the opportunity to study a large number of women and to estimate the incidence of hypothyroidism in short time intervals in and around pregnancy.

The definition of disease from redeemed prescriptions provided no information on the underlying subtype of hypothyroidism. However, the additional data on hospital diagnosis of disease made it possible in most cases to exclude women with a diagnosis of congenital or iatrogenic hypothyroidism. In Denmark, the predominant type of hypothyroidism is spontaneous, autoimmune hypothyroidism, which in a population-based study with individual review of newly diagnosed cases of overt hypothyroidism was found to be present in 85% of the cases (8). Postpartum thyroid dysfunction of autoimmune origin was the second most common subtype (~5%), whereas the types of non-autoimmune origin (congenital, iatrogenic, subacute thyroiditis, drug associated) were rare (8).

Thyroid autoantibodies associated with autoimmune hypothyroidism are thyroid-peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab), which are directed against the thyroid gland. Such antibodies are prevalent in the population in general (almost 20% in the Danish population (11)) and considerably more frequent in individuals suffering from autoimmune hypothyroidism (spontaneous or postpartum) (3, 8).

Hypothyroidism in pregnancy

The incidence of maternal hypothyroidism in pregnancy was low with a gradual decline during the pregnancy, which is in agreement with a general suppression of the maternal immune system during pregnancy and the decrease in thyroid autoimmunity (2). TPO-Ab and Tg-Ab decrease during pregnancy with a nadir in the third trimester (12, 13, 14, 15).

Maternal hypothyroidism showed no early pregnancy incidence peak. This disparity between hypothyroidism and hyperthyroidism and the similar lack of an early pregnancy peak in other autoimmune diseases (rheumatoid arthritis, inflammatory bowel

disease) support the hypothesis that the mechanism for the development of hyperthyroidism in early pregnancy is not related to a general phenomenon in autoimmune diseases (4).

Serum human chorionic gonadotropin (hCG) levels increase in the first trimester of pregnancy and stimulate the thyroid gland. This may lead to the development of gestational hyperthyroidism, which is a non-autoimmune transient disorder. As discussed previously (4), individual review of case registrations indicated that the women identified with incident hyperthyroidism in early pregnancy most likely suffered from Graves' disease. One possible mechanism is that the hCG-mediated increase in the production of thyroid hormone in early pregnancy triggers the onset of Graves' disease in susceptible individuals (16). Likewise, this mechanism may trigger early pregnancy relapse in women with known hyperthyroidism in remission before pregnancy (17).

Hypothyroidism postpartum

We observed a high incidence of maternal hypothyroidism in the postpartum period. Hypothyroidism incidence peaked earlier than that observed for hyperthyroidism and was confined to 1 year after birth in line with the 'immune rebound hypothesis' (5). In this model (5), the authors suggested that rebound of cellular immunity may exacerbate autoimmune hypothyroidism, whereas the later rebound of humoral immunity may trigger the development of autoimmune hyperthyroidism.

Hypothyroidism in the postpartum period is mainly of autoimmune origin (8). When thyroid dysfunction is detected within 1 year after birth of a child in a woman with no previous diagnosis of thyroid disease, it is classified as postpartum thyroiditis, except if the diagnosis is Graves' disease (3). Postpartum thyroiditis is an autoimmune and common clinical manifestation, which is associated with the presence of TPO-Ab and/or Tg-Ab and can present in various clinical types (e.g. subtle changes in thyroid function that are not clinically detected, isolated thyrotoxicosis or hypothyroidism, or a biphasic course with a thyrotoxic phase followed by hypothyroidism (3)). In a Danish study of 66 TPO-Ab-positive women, 55% developed postpartum thyroid dysfunction and 50% of these individuals showed a biphasic course (15).

Thyrotoxicosis in postpartum thyroiditis is typically transient and should not be treated with antithyroid drugs (18, 19). As discussed previously (4), the challenge in such patients is to distinguish transient thyrotoxicosis

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in postpartum thyroiditis from the hyperthyroidism of Graves' disease. Considering hypothyroidism, this can be transient in the postpartum period, but some women are in need of permanent thyroid hormone replacement therapy (6). We studied women diagnosed and treated for hypothyroidism for the first time in the postpartum period and who redeemed prescriptions of thyroid hormone for a period of more than 2 years. Thus, the cases we identified were persistent hypothyroidism, but the findings were similar when we subsequently evaluated the postpartum incidence variation in women considered to have transient hypothyroidism.

We observed a high incidence of hypothyroidism in the postpartum period not only among women who had given birth for the first time, but also among multiparous women. In a Danish population-based case-control study (20), the number of previous live births and induced abortions were considerable risk factors for the development of autoimmune hypothyroidism after the postpartum period in women diagnosed up to the age of 55 years, but not in postmenopausal women. The proposed mechanism was that repeated pregnancy exposure may accelerate the development of disease in women susceptible to the development of autoimmune hypothyroidism (20). Other studies evaluating the association between parity and the development of autoimmune thyroid disease have shown inconsistent results (21, 22, 23, 24, 25, 26, 27). Some studies corroborated an association with parity (25, 26), whereas others did not (21, 22, 23, 24, 27), but study designs and populations were heterogeneous.

Methodological comments

The women studied in this register-based design were selected because they had given birth to a singleton live-born child and women with multiple births were excluded from the study. Thus, the study did not provide data on the incidence of maternal hypothyroidism in and around multiple pregnancies or in case of pregnancy losses.

Women identified with hypothyroidism all redeemed prescriptions of thyroid hormone and had no registration of hyperthyroidism. Thus, women with asymptomatic changes in thyroid function not seen by a doctor and women with no need for medical treatment were not identified. Furthermore, if a woman with a biphasic postpartum thyroiditis (transient hyperthyroidism followed by hypothyroidism) had been diagnosed with hyperthyroidism in a Danish hospital or inappropriately treated with ATD, she would not have been classified with hypothyroidism. These considerations possibly explain

why persistent hypothyroidism was more frequent than transient hypothyroidism in this study. 'Onset' of maternal hypothyroidism was defined by the time the first prescription of thyroid hormone was redeemed. The validity of the DNPR is in general considered high (9), and we included a 2-year period after the initiation of the register to exclude prevalent cases.

Conclusion

The incidence of maternal hypothyroidism in and around a pregnancy was in agreement with the physiological suppression of immune system during the pregnancy followed by an immune rebound after birth. The incidence pattern for hypothyroidism and hyperthyroidism in and around pregnancy was similar in late pregnancy and postpartum but showed a notable difference in the early pregnancy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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